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Advantages and limits of hemorrhoidal dearterialization in the treatment of symptomatic hemorrhoids

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Abstract

In the last two decades, hemorrhoidal dearterialization has become universally accepted as a treatment option for symptomatic hemorrhoids. The rationale for this procedure is based on the assumption that arterial blood overflow is mainly responsible for dilatation of the hemorrhoidal plexus due to the absence of capillary

interposition between the arterial and venous systems within the anal canal. Dearterialization, with either suture ligation (Doppler-guided hemorrhoid artery ligation/transanal hemorrhoidal dearterialization) or laser (hemorrhoidal laser procedure), may be successfully performed alone or with mucopexy. Although the added value of Doppler-guidance in association with dearterialization has recently been challenged, this imaging method still plays an important role in localizing hemorrhoidal arteries and, therefore, minimizing the effect of anatomic variation among patients. However, it is important to employ the correct Doppler transducer. Some Doppler transducers may not easily detect superficial arteries due to inadequate frequency settings. All techniques of dearterialization have the advantage of preserving the anatomy and physiology of the anal canal, when compared to other surgical treatments for hemorrhoids. This advantage cannot be underestimated as impaired anal function, including fecal incontinence and other defecation disorders, may occur following surgical treatment for hemorrhoids. Furthermore, this potentially devastating problem can occur in patients of all ages, including younger patients.

Key words: Dearterialization; Laser dearterialization; Hemorrhoids; Mucopexy

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Core tip: This editorial analyzes the techniques of dearterialization for hemorrhoids. The advantages and pitfalls of the various techniques of dearterialization are reported, with specific attention given to the role of Doppler ultrasound and technical tips on the various procedures. Finally, the author reports the efficacy of dearterialization based on data in the literature as well as personal experience in this field.

Giamundo P. Advantages and limits of hemorrhoidal dearterialization in the treatment of symptomatic hemorrhoids. *World J*

INTRODUCTION

The surgical treatment of hemorrhoids has evolved over the last three decades. Significant postoperative pain as well as changes to the anatomy of the anal canal leading to impaired defecation has led surgeons to adopt new procedures that are less invasive than traditional surgical hemorrhoidal excision.

A variety of surgical procedures are currently available for the treatment of hemorrhoids, however no single technique has been universally accepted as superior. Theoretically, surgical procedures should be tailored to individual patients. In reality, the choice of the surgical technique is often based upon the surgeon's preference or the availability of specialized equipment.

Hemorrhoidal disease has a multifactorial etiology and theories on its actual pathogenesis are still being debated. Symptoms related to hemorrhoidal disease may vary substantially among patients. An accurate preoperative evaluation is therefore mandatory and extremely useful in selecting the most appropriate surgical approach. Rectal mucosal prolapse is one among many potential anatomical alterations related to hemorrhoidal disease that impairs a patient's quality of life. In addition, bleeding, pruritus, pain, soiling, and recurrent thrombosis of piles cannot be underestimated.

The Goligher classification^[1] is commonly used to grade the severity of hemorrhoids and, consequently, indicates the modality of surgical treatment. However, the grade of prolapse and hemorrhoidal symptoms are often poorly correlated^[2]. Tolerance to hemorrhoidal symptoms varies among patients. Therefore the surgeon should be prepared to consider not only the anatomical aspects of the anal canal but also the patient's characteristics and symptoms. In particular, successful treatment should focus on the cure of symptoms affecting the patient's quality of life. In this regard, studies related to surgical treatment of hemorrhoids should include a thorough evaluation of the patient's quality of life as it represents one crucial aspect of successful therapy.

With this in mind, the current trend is to give preference to less invasive procedures with the aim of minimizing postoperative pain, providing relief of symptoms, and reducing the risk of anatomical alterations and dysfunction of the anal canal.

In the last two decades, hemorrhoidal artery ligation (HAL) has become universally accepted for the treatment of hemorrhoids. The rationale for this procedure is based on the assumption that arterial blood overflow is mainly responsible for dilatation of the hemorrhoidal plexus due to the absence of capillary interposition between the arterial and venous systems within the anal canal. This has been clearly demonstrated in anatomical studies^[3,4].

Both the mean caliber and blood flow of the arterial branches of the superior rectal artery (SRA) were found to be significantly higher in patients with hemorrhoids than in a control group^[5]. Closure of the terminal branches of the SRA is therefore expected to shrink the hemorrhoidal piles and alleviate symptoms, and even possibly reduce hemorrhoidal prolapse. Closure of the terminal branches of the SRA can also be performed in combination with plication of the prolapsing mucosa in cases of large and symptomatic prolapse [transanal hemorrhoidal dearterialization (THD) + mucopexy].

A systematic review of 17 case series that included 1996 patients reported satisfactory overall results in grade II and III hemorrhoids with mean recurrence rates of 11% for prolapse, 9% for pain at defecation, and 10% for bleeding at an average of 1-year follow-up after Doppler-guided hemorrhoidal dearterialization^[6]. In another recent review^[7], 2904 patients from 28 studies were included in the final analyses. Overall recurrence rates varied among studies with a pooled rate of 17.5% and an overall reintervention rate of 6.4%. In both of these systematic reviews, it was concluded that Doppler-guided hemorrhoidal dearterialization can be safely considered for primary treatment of grade II and III hemorrhoids. Grade IV hemorrhoids, however, had the highest recurrence rate at long-term follow-up. It is interesting to note that not all patients included in these reviews underwent a mucopexy in addition to dearterialization.

A recent multicenter trial including 803 patients who underwent Doppler-guided THD reported an overall success rate of 90.7% after a mean follow-up of 11.1 + 9.2 mo. These authors also reported a recurrence of hemorrhoidal prolapse, bleeding, or both in 6.3%, 2.4% and 0.6% of patients, respectively^[8].

The advantage of HAL/THD when compared to excisional methods is the absence of anal wounds, which significantly reduces the patient's postoperative pain and discomfort. In addition, preservation of the anal anatomy and physiology cannot be underestimated^[9]. In this regard, it must be stressed that one of the primary causes of fecal incontinence is anorectal surgery^[10].

The anticipated reduction of postoperative pain and alleviation of symptoms makes these procedures the most favored by patients. Early and mid-term results have shown high success and patient satisfaction rates^[11]. When compared to other non-excisional procedures for hemorrhoids such as stapled hemorrhoidopexy (PPH), dearterialization may have the added advantage of reducing the incidence of serious or life-threatening complications^[12]. Despite these advantages, long-term results may be associated with higher recurrence rates compared to conventional hemorrhoidectomy^[13]. In addition to the advantages of shorter-term decreased pain and quicker return to daily activities, patients should be informed of this potential eventuality, especially in case of 4th degree hemorrhoids.

Recent studies have called into question the true value of Doppler-assisted localization of the terminal

branches of the SRA in the HAL/THD procedures^[14]. According to this theory, the efficacy of artery ligation in all six of the odd-numbered clock positions around the anus (1, 3, 5, 7, 9 and 11 o'clock in the lithotomy position) followed by mucopexy would be equal to the same operation performed with Doppler-assistance. This would then suggest that there is no real need for the costly Doppler instruments. Conversely, it has been demonstrated that one-third of the population has at least one artery in an even-numbered clock position, and for this reason Doppler-assisted localization is important in correctly locating the arteries^[15].

Some studies have shown good overall success rates when hemorrhoidopexy is performed without dearterialization^[16]. Skepticism over the true value of dearterialization might therefore be justified. However, hemorrhoidopexy, beyond the treatment of mucosal prolapse, can most likely be considered an empiric form of de-arterialization, although the closure of underlying arteries cannot be proven by Doppler ultrasound. In fact, the running sutures placed on the redundant mucosa may include the underlying arteries. In this regard, there are some important issues regarding the anatomy of the anal canal and the type of Doppler device used for HAL/THD that need to be addressed.

Aigner *et al*^[3] and Schuurman *et al*^[4] have described in detail the vascular pattern of the anal canal. At approximately 2-3 cm above the dentate line, the terminal branches of the superior rectal arteries become superficial (2 mm deep) and thin (0.6-2 mm). These terminal branches may be directly responsible for blood overflow into the hemorrhoidal piles due to the lack of capillary interposition between the arterial system and the hemorrhoidal plexus. However, the Doppler transducers used by the majority of DGHAL and THD equipment operate at 7-8 MHz. At these frequency settings, Doppler probes can only detect deep arteries that may not directly contribute to the hemorrhoidal pile overflow.

In addition, in commonly used equipment, suture ligation is placed approximately 1 cm above the point where the arterial pulse is located by Doppler ultrasound, which may not succeed in closing the artery.

In this regard, dearterialization with laser [hemorrhoidal laser procedure (HeLP)] seems to be more precise and effective^[17]. This procedure uses a 20 MHz Doppler-transducer, which is more accurate in detecting superficial arteries at approximately 2 cm above the dentate line. In addition, diode laser energy delivered at 980 nm of wavelength causes shrinkage of the mucosa and submucosa to a depth of 4 mm, which can easily include the underlying superficial arteries. The efficacy of arterial shrinkage is in fact improved by the selective action of laser energy on hemoglobin at that specific wavelength. Furthermore, in the HeLP procedure, the laser fiber is placed in contact with the mucosa exactly at the same point where the Doppler signal locates the artery. By doing so, the risk of missing the artery is minimized.

Laser treatment may also have the added advantage of closing a larger number of arteries (12 instead of 6) and being less invasive than artery ligation, therefore requiring neither anesthesia nor sedation^[18]. However, one pitfall associated with this procedure is the low success rate of curing severe mucosal prolapse. In fact, the standard HeLP procedure does not address the issue of prolapsed mucosa. Nevertheless, in cases of concomitant severe and symptomatic prolapse, a mucopexy can easily be incorporated into the same procedure, following the laser treatment (HeLP + rectoanal repair)^[19].

The number of arteries closed as well as the level at which the arteries are located might also play a significant role in the clinical success of techniques that employ dearterialization. In order to optimize the results of THD, Ratto *et al*^[20] modified their technique of dearterialization by performing a "distal" ligation, rather than the original technique of closing the arteries approximately 4-5 cm above the dentate line, located by Doppler signal.

The terminal branches of the SRA multiply and become more superficial as they get closer to the dentate line. This explains the fact that 20 MHz Doppler probes, as seen in the HeLP procedure^[16], can easily identify and locate at least 12 arteries, compared to only 6 as has been previously described in other procedures employing different Doppler probes.

IN SUMMARY

The techniques of dearterialization for symptomatic hemorrhoids seem to have maintained the encouraging early results, despite a progressive increase in long-term recurrence rates that have been reported in some studies, especially for grade III and IV hemorrhoids. The rationale for this procedure seems to be valid, as demonstrated not only by anatomical studies but also by clinically successful results reported in numerous series in the literature, even when no additional mucopexy is performed.

Dearterialization, either with suture ligation (DGHAL/THD) or laser (HeLP), may be successfully performed alone or in association with mucopexy, when necessary.

Mucopexy improves resolution of short- and long-term symptoms when significant prolapse altering the patient's quality of life is present in grade III hemorrhoids. Dearterialization plus mucopexy should be indicated only in very selected cases of grade IV hemorrhoids. Mucopexy alone can be performed when prolapse is the only symptom, but this procedure may fail to control bleeding and recurrent acute symptoms in the long-term.

Although the added value of Doppler-guidance in association with dearterialization has recently been challenged, this imaging method still plays an important role in localizing hemorrhoidal arteries, and minimizing the effect of anatomic variation among patients.

Some Doppler transducers may not easily detect

superficial arteries due to inadequate frequency settings (7-8 MHz). In HAL/THD procedures, dearterialization may be empirically effective in that the arteries may be successfully closed because the width of the suture ligation would close a larger quantity of tissue, thus incorporating the underlying arteries regardless of Doppler-guidance. Unfortunately, these results may not be easily reproducible.

Finally, all techniques of dearterialization have the advantage of preserving the anatomy and physiology of the anal canal, when compared to other surgical treatments for hemorrhoids. This advantage cannot be underestimated as impaired anal function, including fecal incontinence and other defecation disorders, may occur following surgical treatment for hemorrhoids. Furthermore, this potentially devastating problem can occur in patients of all ages, including younger patients.

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2016 Laparoscopic Surgery: Global view

Laparoscopic liver resection: Experience based guidelines

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Abstract

Laparoscopic liver resection (LLR) has been progressively developed along the past two decades. Despite initial skepticism, improved operative results made laparoscopic approach incorporated to surgical practice and operations increased in frequency and complexity. Evidence supporting LLR comes from case-series, comparative studies and meta-analysis. Despite lack of level 1 evidence, the body of literature is stronger and existing data confirms the safety, feasibility and benefits of laparoscopic approach when compared to open resection. Indications for LLR do not differ from those for open surgery. They include benign and malignant (both primary and metastatic) tumors and living donor liver harvesting. Currently, resection of lesions located on anterolateral segments and left lateral sectionectomy are performed systematically by laparoscopy in hepatobiliary specialized centers. Resection of lesions located on posterosuperior segments (1, 4a, 7, 8) and major liver resections were shown to be feasible but remain technically demanding procedures, which should be reserved to experienced surgeons. Hand-assisted and laparoscopy-assisted procedures appeared to increase the indications of minimally invasive liver surgery and are useful strategies applied to difficult and major resections. LLR proved to be safe for malignant lesions and offers some short-term advantages over open resection. Oncological results including resection margin status and long-term survival were not inferior to open resection. At present, surgical community expects high quality studies to base the already perceived better outcomes achieved by laparoscopy in major centers' practice. Continuous surgical training, as well as new technologies should augment the application of lap-

aroscopic liver surgery. Future applicability of new technologies such as robot assistance and image-guided surgery is still under investigation.

Key words: Minimally invasive surgery; Laparoscopic surgery; Hand-assisted laparoscopy; Liver neoplasm; Liver cirrhosis; Living donor; Liver; Hepatectomy; Liver transplantation

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Core tip: Liver surgery was one of the last frontiers reached by minimally invasive surgery. Surgical technique and specialized equipment evolved to overcome technical limitations, making laparoscopic liver resections (LLR) safe and feasible. Surgeons developed skills in a stepwise approach, beginning with low complexity operations for benign diseases and reaching high-complexity surgeries for malignant cases and living donor organ harvesting. Despite a cautious slow start laparoscopic liver surgery has been incorporated to practice. On the following pages the successful history of LLR is depicted, along with an updated panel of its current role and expected achievements.

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INTRODUCTION

In the last two decades, minimally invasive liver surgery (MILS) underwent a major evolution. Willing to explore the possibility of laparoscopic liver resection (LLR), specialized centers with solid background on hepatic and laparoscopic surgery took the first steps^[1,2].

Initial development of MILS was slow, withheld by three main barriers. The first limit to overcome was technical, hence the translation of conventional techniques to the laparoscopic approach was needed. For instance, organ mobilization, manual palpation, vascular dissection, vascular control and parenchymal transection were steps universally applied to open liver resection (OLR) that had to be adapted to laparoscopy. The second barrier consisted of anticipated intraoperative hazards, such as massive bleeding and the theoretical increased risk of gas embolism secondary to pneumoperitoneum. The third step toward acceptance of LLR concerned about oncological outcomes such as adequate margins, port site seeding and long-term survival^[1,3-5].

The first wedge resection was reported by Reich *et al*^[6] (1991). Since then, improvements in surgical techniques associated with technological advances significantly expanded the complexity and safety of

MILS. The first laparoscopic anatomic hepatectomy was reported in 1996 simultaneously by Azagra *et al*^[7] and Kaneko *et al*^[8]. The first laparoscopic major hepatectomy in 1997 by Hüscher *et al*^[9]. In 2000, Cherqui *et al*^[11] and Descottes *et al*^[12] published the first structured case-series with results favoring laparoscopic liver operations. Many other small single center or multicenter case series emerged on the following years, with promising good results^[10-12].

By the year 2007 Koffron *et al*^[13] published the first major series showing operative results on 300 consecutive patients. On the following year a landmark meeting produced the Louisville Statement^[14], the first expert consensus conference on laparoscopic liver surgery. In 2009 a comprehensive review on published series accounted that 2804 LLR had been performed worldwide^[15]. Of note, previous publications reported mainly on resected benign lesions and this review showed, for the first time, a predominance of malignant cases.

The years 2010 witnessed many reports on safety and feasibility of laparoscopic operations^[16-18] including complex procedures such as major hepatectomies and graft harvesting for living donor liver transplantation (LDLT)^[19,20]. Clinically significant events of carbon dioxide (CO₂) embolism were extremely rare^[21,22] and no port seeding or peritoneal implant could be attributed to laparoscopy, dismissing many of the initial worries on LLR^[23,24].

Evidence supporting MILS comes from case-series, comparative studies and meta-analyses. Only recently, a prospective randomized study was published comparing the results of LLR with the OLR^[25]. There are prospective studies in course and their results are expected to provide the best scientific evidence to the already perceived superiority of MILS^[26,27]. Despite the lack of evidence level 1, existing data confirms the safety, feasibility and benefits of MILS. Also, many comparative series indicated the role of laparoscopy in disease specific settings, such as benign diseases^[12,17,25,28-33], hepatocellular carcinoma (HCC)^[34-49] and colorectal liver metastases (CRLM)^[50-58]. Recently, the 2nd International Consensus Conference (2nd ICC) on LLR in Japan demonstrated the progress and dissemination of the method worldwide^[59].

TERMINOLOGY AND DEFINITIONS

Extent and complexity of resection

LLR should be classified according to the complexity of the operation and the technique of minimally invasive access^[14]. Referring to complexity categories, laparoscopic operations might consist of: (1) small wedge resections; (2) resections of the left lateral section (segments 2 and 3) or anterior segments (segments 4b, 5 and 6); and (3) hemihepatectomies, trisectionectomies and resections of the difficult postero-superior segments (segments 1, 4a, 7 and 8). The first two categories are classified as "minor resections". The Louisville

Table 1 Laparoscopic liver resection learning curve key points

Knowledge of caudal view anatomy
Training in cadaveric and/or animal model
Clinical training should follow an increasing order of procedure difficulty (Difficult Scoring System for LLR ^[78] can be used to point difficulty levels)
Minor anterolateral resections
Minor anatomical resections (start with LLS)
Difficult resections
Major resections
Graft harvesting for LDLT
HALS and hybrid resections can be used in the early experience to overcome the learning curve

LLR: Laparoscopic liver resection; LLS: Left lateral sectionectomy; LDLT: Living donor liver transplantation; HALS: Hand-assisted liver surgery.

Statement^[14] defined the third group of operations as “major hepatectomies”, unlike the classical concept of open surgery, in which major resections are defined as operations resecting 3 or more contiguous liver segments^[60]. Subsequently, other authors have shown that resection of lesions located in the posterior and superior segments require greater technical proficiency and have higher complication rates than anterolateral resections. These operative results justify the “upgrade” of difficult resections to major resections due to their technical complexity^[61,62]. In a recent study, Di Fabio *et al.*^[62] evaluated the outcomes of the “traditional” major hepatectomies (hemi-hepatectomy, trisectionectomies) compared to laparoscopic “postero-superior” resections and concluded that the creation of two subcategories of laparoscopic major hepatectomy seems appropriate to reflect differences in intraoperative and postoperative outcomes between those two sets of patients. In the 2nd ICC the classical definition was used (minor resection: ≤ 2 segments, major resections > 2 segments)^[59]. In this review, we employ the term “major resection” for hemi-hepatectomies and trisectionectomies and the term “difficult resections” for resections of the postero-superior segments (segments 1, 4a, 7 and 8).

Types and techniques of LLR

LLR can be categorized in three different approaches^[14]: (1) Pure LLR (PLLR): the entire resection is performed through laparoscopic ports and an auxiliary incision is used only for specimen extraction; (2) Hand-assisted laparoscopy surgery (HALS): The operation is carried out with elective placement of an auxiliary hand-port, which also aids specimen extraction. If a pure laparoscopic procedure demands the insertion of a hand-port in order to overcome difficulties and to complete the procedure, this should be considered a “conversion from pure laparoscopy to hand-assisted hepatectomy”. The third type of minimally invasive liver resection is (3) Hybrid hepatectomy (also termed laparoscopy-assisted hepatectomy): The operation begins with laparoscopic liver mobilization (with or without hand-assistance), followed by an elective mini-laparotomy for a conventional approach to vascular pedicles (if

necessary) and parenchymal transection.

Along the development of MILS the pure laparoscopic approach was the overall preferred method, especially in European centers^[63-66]. The hybrid and hand-assisted methods are adopted more liberally to perform complex resections in United States and Japan, although there is a trending shift towards PLLR in Japan^[67-70].

LEARNING CURVE

To overcome the difficulties associated with minimally invasive hepatic resections the training of surgeons is essential in order to safely spread the benefits of laparoscopic liver surgery^[71-73].

A consensual observation in many papers on LLR is that laparoscopic hepatectomies should be performed by surgeons with extensive training in hepatobiliary and advanced laparoscopic surgery^[14,74]. Thence, fellowships in specialized centers should offer high-level training in order to accomplish competence in both domains. The key points related to the training with LLR are summarized in Table 1.

A major change in MILS is the way surgeons approach the liver, as the classic open frontal view is modified. In laparoscopy, due to the insertion of the optical equipment in or near the umbilicus, a caudal approach is forcefully undertaken. In the caudal view the surgeon sees the well-known anatomy from a different perspective^[64]. Basic technical skills acquisition can occur through practicing in cadaveric or animal model^[75] and further clinical training should follow an increasing order of procedure difficulty^[14,73,76]. Case selection is essential in early clinical experience; first cases should involve lesions prone to small wedge resections located on the anterolateral segments (segments 2, 3, 4b, 5 and 6). Anatomic resections can be started with left lateral sectionectomy (LLS), which is a patterned straightforward segmental resection that requires liver mobilization, pedicle treatment and parenchymal transection^[33,71,76,77]. It is safer to move on to complex resections after the surgeon has acquired proficiency in minor resections (Table 1)^[73].

In order to better understand the difficulty associated with each kind of operation, a recent paper proposed a scoring index for LLR^[78]. This scoring system incorporates factors such as tumor size and location; proximity to major vessels; liver function and extent of liver resection. Resections are graded from 1 to 10, being score 1 for peripheral wedge resection; 4 for LLS; 7 for hemihepatectomy and 10 stands for extremely difficult resections. This interesting index offers a numeric score of progressive difficulty that can help learners to evaluate their progress. This scoring system can be used as a guide in training and progressive skill acquisition.

Learning curve analysis is somewhat a preoccupation linked to laparoscopic operations. When a laparoscopic operation is proposed, it is usually compared with its conventional counterpart in order to assess results

and to establish the number of operations required for technical competence. To our knowledge there is no data on open hepatectomy learning curve, and Rau *et al.*^[79] published the first mention of a LLR learning curve in 1998. Cherqui's group published a seminal paper on the subject and their analysis revealed that 60 cases were needed in order to achieve optimal results^[72]. Of notice, the use and duration of Pringle maneuver, and use of HALS decreased over time. This indicates that pedicle clamping and HALS play an important role during the learning curve. Likewise, hybrid resections can also be used in the early experience to overcome the learning curve^[13,70,80].

Other series have indicated a smaller number in order to obtain expertise. A recent Chinese paper observed a variable number on cases needed to achieve competence, according to the complexity of the operation. Their caseload ranged between 15 to 43 operations^[81].

Other authors have made some interesting conjoined analysis, looking beyond the numbers, also considering the effect of expert training. Hasegawa *et al.*^[58] made an analysis on their experience with 24 cases of LLS divided in 3 eras; initially a senior surgeon performed the first 8 operations with no technical standardization. In the second era a senior surgeon operated on 8 cases with a standardized technique. The third group of 8 patients underwent operations performed by junior surgeons under senior guidance. Comparative analysis showed better results of the second and third eras in comparison to the first period and, most important, results did not differ between the second and third periods.

Other authors studied the learning curve for complex and major hepatic resections^[73,82]. Nomi *et al.*^[83] studied 173 patients that underwent major LLR in a high-volume center using the cumulative sum method. The learning curve identified three phases: Phase 1 (45 initial patients), phase 2 (30 intermediate patients) and phase 3 (the subsequent 98 patients). These data suggests that the learning phase of major LLR included 45 to 75 patients^[83].

INDICATIONS AND LIMITATIONS OF LLR

Laparoscopic access offers some benefits over conventional operations^[66,84]. The magnified view of the operating field allows meticulous haemostasis. During parenchymal transection, most of the blood loss derives from the hepatic veins and laparoscopy offers the possibility of parenchymal transection under positive pressure, resulting in less bleeding. However, minimally invasive liver operations has some drawbacks, such as lack of tactile feedback, restricted manoeuvres and difficult visualization of the posterior and superior segments of the liver^[85].

Nowadays, LLR is utilized in a small percentage of liver resections (5%-30%) in most centers, although some very skillful surgeons have reported higher rates, reaching from 50% to 80%^[59,64,86]. The majority of data arise from minor resections but the proportion

of major resections is increasing^[64]. A recent analysis performed in a general medical population, including all liver resections in France along the year 2013, resulted that 15% of liver resections were performed through minimally invasive surgery^[87]. Another surgical population profile indicates that less than 10% of all liver resections done for benign conditions are carried out with laparoscopy in North American centers^[88]. In fact, there are few centers with extensive experience with LLR, Table 2 presents per operative results in high-volume centers with more than 150 cases.

Indications for LLR do not differ from those for open surgery^[3,89,90]. Indications are based on tumour characteristics, liver function and patient's general health status. In patients who cannot tolerate pneumoperitoneum due to their cardiopulmonary status LLR is contraindicated.

MILS may be used for benign and malignant (primary and metastatic) tumors and living donor liver harvesting. A high percentage of benign tumors was presented in early series of MILS, whereas the proportion of malignant has significantly increased in recent years^[15,79,91,92]. Between June 2007 and December 2014, 214 LLR were performed at the Liver Surgery Unit, University of Sao Paulo Medical School. In our experience, 65.9% of LLR patients were by malignant diseases and their proportion has significantly increased in recent years (Table 2).

Classic indications for LLR are tumours confined to the so-called "laparoscopic segments": The left lateral section (segments 2 and 3) and the anterior segments (segments 4b, 5, 6). It is also preferable to operate on tumours smaller than 5 cm, located away from major blood vessels and hilar structures. Those are the most frequently adopted indications, but are not restrictive, once indications can be shifted and extent of resection can be expanded according to the expertise of a particular center^[85,93]. For instance, peripheral tumours are amenable to laparoscopic approach, even when greater than 5 cm. On the other hand, LLR is not advised for large intrahepatic lesions, because of difficult tumor mobilization and risk of rupture^[3]. Laparoscopic LLS is considered the gold standard treatment for lesions located on segments 2 and 3 and should be routinely applied^[33,71,94]. This successful policy has led some experts to expand the indication of routine laparoscopic approach to left hepatectomy^[95].

Major liver resections (*i.e.*, right hepatectomy) showed to be feasible but remain technically demanding procedures reserved to experienced surgeons. Patients with bilateral or central tumors, close to the liver hilum, major hepatic veins or inferior vena cava (IVC) are not standard candidates for a laparoscopic approach. However, in some expert centers, even these cases are addressed laparoscopically in selected patients^[96,97].

Posterior and superior segments of the liver have been traditionally considered as "non-laparoscopic segments" because laparoscopy offers a caudal vision of the liver and there is a great amount of parenchyma interposed between the surgeon's view and those

Table 2 Single center series of laparoscopic liver resection including more than 150 cases

Ref.	Cases (n)	Malignancy (%)	Minimally invasive approach (%)	HALS	Hybrid	Major resections (%)	Conversion (%)	Operative time (median/mean, min)	Blood loss (median/mean, mL)	Transfusion (%)	LOS (median/mean, d)	Complication (%)	Mortality (%)
Koffron <i>et al.</i> ^[63]	300	34	80.3	10.6	9	39	7.3	99	102	0.6	1.9	9.3	0
Buell <i>et al.</i> ^[66]	306	42	NR	NR	NR	45	2.4	162	229	7	2.9	16	1.6
Bryant <i>et al.</i> ^[68]	166	60	95.2	4.8	0	18.6	9.6	180	329	5.4	6	15.1	0
Long <i>et al.</i> ^[64]	173	100 (HCC)	100	0	0	8.3	2.3	112	194	NR	6.5	2.4	0
Cai <i>et al.</i> ^[81]	365	27.1	100	0	0	22.2	17.2	150	370	NR	9.2	12.2	0
Gobardhan <i>et al.</i> ^[68]	476	79	NR	NR	NR	33.8	4.2	NA	NA	4.6	NR	21	0.8
Troisi <i>et al.</i> ^[99]	265	64.1	99.3	0	0.7	17.4	6.4	254	171	NR	5.5	14	0
University of Sao Paulo series 2015	214	65.9	75.2	5.6	19.2	14.5	6.5	205	240	7.4	4.5	15	0.5

PLL: Pure laparoscopic liver resection; HALS: Hand-assisted liver surgery; HCC: Hepatocellular carcinoma; LOS: Length of stay; OLR: Open liver resection; NR: Not reported; NA: Not available.

segments^[64,98]. The combination of oddly located lesions and extensive liver mobilization implies in worst operative outcomes, such as prolonged operative time, higher blood loss and narrower margins^[61,99,100]. Moreover, lesions located on the posterior and superior segments have been identified as an independent risk factor for bleeding and conversion^[99].

Fortunately, there are strategies to overcome limitations of laparoscopy, as some authors have pointed out, HALS and hybrid procedures are safe methods of performing "difficult" and major resections^[68,69]. Other alternative accesses include the superior and lateral approaches with or without use of intercostal or transthoracic trocars. These techniques offer direct access to superior segments, but they have been performed only in few expert centres with small case series reported^[101-104].

Disease specific indications

Benign diseases: There is general consensus that indications for benign lesions should not be expanded in face of lesser invasive technology^[14]. Symptomatic benign diseases (complex cystic diseases, haemangioma, focal nodular hyperplasia) or risk bearing tumours (hepatocellular adenomas) might be suitable for LLR. Cases of segmental hepatolithiasis associated with parenchymal atrophy are also good candidates for LLR^[105]. Some series have demonstrated the feasibility and safety of LLR for benign diseases with low morbidity (< 20%) and no mortality (Table 3)^[12,17,25,28-33]. There are few comparative studies between LLR and OLR for benign tumours^[30,33], showing significantly reduced blood loss, time to oral intake, hospital stay and total cost of hospitalization in patients that underwent LLR. Recently, Ding *et al.*^[25] published a randomized trial comparing patients with hepatolithiasis undergoing laparoscopic and OLR, showing benefits for the LLR group. In the authors' experience with 73 LLR for benign liver diseases, the main indication was hepatocellular adenoma (HA) (n = 50; 68.5%). There were 11 (15.1%) major resections: 9 right and 2 left hepatectomies. Blood transfusion was required in 4.1% of patients and there was no need for conversion. Postoperative complications occurred in 6.9% of the patients and operative mortality was nil (Table 3).

Despite rare benign tumours, HA are clinically relevant due to the risk of malignant degeneration and bleeding. HA have specific indications for surgery such as male sex and lesion larger than 5 cm or symptomatic in females^[17,106]. When operation is required, LLR has proved to be safe and feasible, even when major resections were required^[17,31]. In a recent series by our group, we found excellent results using PLLR, with low rate of operative complications, without mortality or long-term recurrence^[17].

This group of patients seems to be specially benefited by laparoscopic surgery, once this disease occurs in patients along their productive life where a less invasive approach offers faster recovery, shorter hospital stay, lower morbidity and better cosmetic result. LLR should be considered standard of care for patients with adenomas, when performed by experienced laparoscopic liver surgeons^[17].

HCC

HCC usually occurs in the setting of chronic liver disease and liver transplantation (LT) would offer adequate treatment for HCC as well as for the underlying disease. In

Table 3 Studies of laparoscopic liver resection for benign liver diseases (studies with over 10 cases)

Ref.	Cases (n)	Type of study	Major hepatectomies (%)	Conversion (%)	Transfusion (%)	Complication (%)	Mortality (%)
Katkhouda <i>et al.</i> ^[26]	12 ¹	Retrospective	0	8.3	0	0	0
Descottes <i>et al.</i> ^[23]	87	Retrospective multicenter	3.4	10	6	5	0
Ardito <i>et al.</i> ^[29]	50	Retrospective	16	8	2	10	0
Troisi <i>et al.</i> ^[30]	20	Comparative (LLR × OLR)	2.5	10	10	20	0
Abu Hilal <i>et al.</i> ^[23]	50	Retrospective	28	2	2	7	0
Abu Hilal <i>et al.</i> ^[31]	13 HA only	Retrospective	62	0	7.7	7.7	0
Herman <i>et al.</i> ^[17]	31 HA only	Retrospective	16.7	0	0	6.5	0
de'Angelis <i>et al.</i> ^[19]	36 HA only	Comparative (LLR × OLR)	25	8.3	0	8.3	0
Dokmak <i>et al.</i> ^[33]	31 LLS only	Comparative LLS (LLR × OLR)	0	6.5	NR	9.7	0
Ding <i>et al.</i> ^[25]	49 hepatolithiasis only underwent LLS	Prospective randomized trial (LLR × OLR)	0	4.1	NR	6.1	0
University of Sao Paulo series 2015	73		15.1	0	4.1	6.9	0

¹Included LLR (n = 12) and cyst fenestration/pericystectomy (n = 31); Results of patients submitted to LLR: HA: Hepatocellular adenomas; LLR: Laparoscopic liver resection; LLS: Left lateral sectionectomy; OLR: Open liver resection; NR: Not reported.

patients with preserved liver function or limited signs of portal hypertension, resection is the mainstay treatment and provides the same results in an intention-to-treat fashion that LT offers^[66,107].

In the early experience with LLR the chronically diseased liver was believed to increase the feared hazard of intraoperative bleeding^[108,109]. However, some initial series demonstrated the safety and feasibility of LLR in selected patients^[34-46,48,49,110]. Pioneer specialized centers performed minimally invasive resections on patients with preserved liver function (Child-Pugh class A), limited signs portal hypertension (platelet count over 80000-100000; oesophageal varices grade 1 or less; absence of ascites) and good general health (ASA III or less)^[65,66].

In addition to liver function, tumour characteristics also restrict the use of laparoscopy in the treatment of HCC. In Tranchart series, case selection resulted in 27% of HCC patients treated with minimally invasive approach^[35]. Usually, centrally located lesions are managed via ablative techniques and larger resections (> 2 segments) are rarely carried out. Laparoscopy is preferred for anterolateral segments, smaller tumours (less than 5 cm) and lesions far from vascular structures^[111]. Anatomical resection is preferred whenever possible for the treatment of HCC in order to achieve adequate margins and prevent local recurrence. However, in small peripheral and well-differentiated HCC there are studies showing similar results for anatomic and non-anatomic resections^[112-114].

Judicious patient selection improved surgical outcomes and the accumulated experience once again ruled out the initial fears of LLR for HCC^[34-46,48,49,110]. Since 2000, over 600 cases of LLR of HCC were reported^[23] and, interestingly, LLR results in less blood loss and less requirement for blood transfusion^[86,115]. The reduced blood loss must be considered an outstanding outcome, once operative blood loss has a strong association with prognosis in HCC patients^[116].

Laparoscopy also reduces operative morbidity, considering general and liver specific complications. Patients suffer fewer pulmonary complications and, importantly, there is an impressive reduction in postoperative ascites and liver insufficiency^[23,109,117,118]. Laparoscopy avoids abdominal wall disruption; consequently avoiding discontinuation of the compensatory collateral circulation secondary to portal hypertension. Laparoscopic surgery also implies in limited liver manipulation, restricted fluid management, decreased blood loss and consequently reduced third space accumulation and hyper aldosteronism^[111]. Table 4 summarizes operative results of MILS in comparatives series with more than 30 patients in each studied group (OLR × LLR).

Another beneficial implication of LLR in cirrhotic patients is better results of LT after laparoscopic resection when compared with OLRs^[119]. After laparoscopic procedures there are fewer adhesions, which ultimately translates as a shorter dissection time, with less bleeding from hypervascularized adhesions associated to portal hypertension. Therefore LLR resulted in shorter operative time, less blood loss and quicker hepatectomy phase during LT^[119,120]. Other studies also pointed out that reoperations for recurrent HCCs are feasible and facilitated by a previous LLR^[121-123]. This is a clear advantage in the setting of chronic liver disease, where patients are prone to develop new

Table 4 Comparative studies of laparoscopic and open liver resection for hepatocellular carcinoma including more than 30 patients in each arm

Ref.	No. of patients		Blood loss (mean/median, mL)		Blood transfusion (%)		Conversion (%)		Complication (%)		Perioperative mortality (%)		5-yr overall survival (%)		5-yr recurrence free survival (%)					
	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR				
Belli <i>et al</i> ^[64]	54	125	297	580	< 0.001	11	25.6	0.03	7	19	36	0.02	2	4	NS	67 ¹	NS	52 ¹	NS	
Tranchart <i>et al</i> ^[65]	42	42	364	723	< 0.0001	9.5	16.7	NS	4.7	21.4	40.5	NS	2.4	2.4	NS	59.5 ¹	47.4 ¹	NS	60.9 ¹	NS
Truant <i>et al</i> ^[66]	36	61	452	447	NS	2.8	3.8	NS	19.4	25	35.8	NS	0	7.5	NS	70	46	NS	35.5	NS
Lee <i>et al</i> ^[67]	33	50	150	240	NS	6.1	10	NS	18.2	6.1	24	0.033	0	0	NS	76	76.1	NS	45.3	NS
Hu <i>et al</i> ^[100]	30	30	520 g	480 g	NS	NA	NA	-	0	13.3	10	NS	0	0	NS	50	50.3	NS	NR	NR
Ker <i>et al</i> ^[98]	116	208	139	1147	< 0.0001	6.9	50.9	< 0.0001	5.2	6	30.2	< 0.0001	0	2.9	NS	62.2	71.8	NS	NR	NR
Cheung <i>et al</i> ^[99]	32	64	150	300	0.0001	0	4.7	NS	NR	6.3	18.8	NS	0	1.6	NS	76.6	57	NS	54.5	44.3
Ai <i>et al</i> ^[60]	97	178	460	454	NS	4.6	2.8	NS	9.28	9	30	0.001	0	0	NS	86 ¹	88 ¹	NS	66 ¹	NS
Memeo <i>et al</i> ^[61]	45	45	200	200	NS	0	0	NS	NR	20	45	0.01	2	13	0.04	59	44	NS	19	23
Kim <i>et al</i> ^[62]	70	70	NA	NA	-	24.3	40.8	0.001	8.57	7.1	14.5	NS	NR	NR	-	65.3	65.7	NS	58.3	62.6
Kim <i>et al</i> ^[98]	43	162	484	261	NS	3.4	0	NS	23.3	13.8	37.9	NS	0	0	NS	92.2	87.7	NS	54	40.1
Ahn <i>et al</i> ^[45]	51	51	350	355.2	NS	5.9	9.8	NS	Excluded	5.8	9.8	NR	0	0	NS	80.1	85.7	NS	67.8	54.8
Yamashita <i>et al</i> ^[41]	63	99	455	436	NS	6	2	NS	NA	10	26	0.046	0	0	NS	69	77	NS	33	41
Yoon <i>et al</i> ^[49]	58	174	NA	NA	-	3.4	7.5	0.04	0	6.9	22.4	0.02	NR	NR	-	88 ²	68 ²	NS	56 ²	62 ²
Martin <i>et al</i> ^[66]	100	254	336	755	< 0.0001	1.2	2.4	0.043	NR	44	57	NS	6	8	NS	60.7 ¹	41.8 ¹	NS	20 ¹	26 ¹
Lee <i>et al</i> ^[67]	43	86	300	700	0.004	NR	NR	-	14	23.3	39.5	NS	NR	NR	-	89.7	87.3	NS	53.5	58.6
Han <i>et al</i> ^[68]	88	88	500	525	NS	20	26.1	NS	9.1	12.5	20.4	0.042	1.1	1.1	NS	76.4	73.2	NS	44.2	41.2
Xiao <i>et al</i> ^[69]	41	86	272.2	170.8	0.001	7.3	13.9	NS	7.32	17.1	37.3	0.021	0	0	NS	78 ¹	76.7 ¹	NS	70.7 ¹	68.6 ¹

¹Data computed for 3-yr survival; ²Data computed for 4-yr survival. LLR: Laparoscopic liver resection; OLR: Open liver resection; NR: Not reported; NS: Non significant.

tumours or hepatic insufficiency, requiring further resection or LT.

CRLM

Resection is considered the gold standard treatment for CRLM and offers the best chance of long-term survival^[124,125]. Many of the oncological fears were shared with HCC and included surgical margins, adequate intraoperative staging, peritoneal dissemination and port site seeding.

Laparoscopic treatment of CRLM was one of the most recent achievements of MILS. Until 2008, only 35% of LLR for malignancy were performed for CRLM^[14]. The first multi-institutional cohort with 109 patients was published only in 2009^[126], with a stringent selection criteria: tumours smaller than 5 cm, lesions located on the peripheral segments and multiple lesions were treated only if tumor clearance could be achieved with a single anatomic resection. The transfusion rate was 10%, the resection margin was negative in 94.4% of the patients and the conversion rate was 3.7%^[126].

Case series and comparative studies indicated that well selected patients presented reduced morbidity and blood loss^[50-58] (Table 5). Recent meta-analysis confirmed the benefits of laparoscopy approach when compared to OLR (Table 6)^[127-130].

A recent paper made an interesting matched pair analysis of open and laparoscopic approaches for CRLM^[56] and showed increased rate of third liver resections on the laparoscopy group. This confirms, once again, that laparoscopy eases further interventions, as mentioned for HCC.

Good outcomes have encouraged some specialized centres to widen the indications of MILS, for instance, in elderly patients^[131]. Another progress appears related to synchronous resections of the colorectal primary tumour and CRLM. The association of these two operations appears to be feasible and safe in specialized centers^[127,132,133].

Other malignant diseases

Other liver malignancies such as peripheral cholangiocarcinoma, hilar cholangiocarcinoma, as well as non-CRLM have had only anecdotal reports^[16,134,135]. Although

Table 5 Comparative studies of laparoscopic and open liver resection for colorectal liver metastases including more than 30 patients in each arm

Ref.	No. of patients		Blood loss (mean/median, mL)		Blood transfusion (%)		Conversion (%)		Complication (%)		Perioperative mortality (%)		5-yr overall survival (%)		5-yr recurrence free survival (%)		
	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	
Castaing <i>et al</i> ^[50]	60	60	NR	NR	15	36	0.007	10	27	28	NS	1.7	1.7	64	56	30	20
Abu Hilal <i>et al</i> ^[51]	55	119	363	500	NR	NR	NR	12	15	20.2	NR	0	2	NR	NR	NR	NR
Cannon <i>et al</i> ^[52]	35	140	202	392	<0.001	17	25	NS	23	50	0.004	0	1.4	NS	42	NS	22
Qiu <i>et al</i> ^[53]	30	140	215	390	<0.001	10	25	<0.05	6.6	26.2	55	0	0	NS	NR	NR	NR
Guerron <i>et al</i> ^[54]	40	40	376	753	0.041	5	20	0.04	5	15	20	NS	0	NS	NR	NR	NR
Kubota <i>et al</i> ^[55]	43	62	287.3	579.3	<0.001	2.4	21	0.004	NR	2.4	9.7	NS	0	NS	88.4 ¹	74.2 ¹	NS ¹
Montalti <i>et al</i> ^[56]	57	57	454.2	691.5	0.003	NR	NR	-	15.8	15.8	31.6	0.03	0	NS	65	NS	38
de'Angelis <i>et al</i> ^[57]	52	52	200	300	0.001	5.8	21.2	NS	5.8	17.3	22	NS	0	NS	73.1	62.5	NS
Hasegawa <i>et al</i> ^[58]	102	69	127	620	0.000	NR	NR	NR	1	8.8	24.6	0.005	0.98	NS	56.8	48.8	NS

¹Data computed for 3-yr survival. LLR: Laparoscopic liver resection; OLR: Open liver resection; NR: Not reported; NS: Non significant.

considered a contraindication for LLR by most specialized centers, successful minimally invasive approach to gallbladder cancer has been performed in few cases with no reports of port site metastasis^[1,36]. Despite being an interesting topic, to date the available data is very limited and no major conclusion can be disclosed.

Laparoscopic living donor graft harvesting

Laparoscopic graft harvesting has raised the same questions on technical issues and operative hazards as other LLR. One specific limitation associated with laparoscopic organ harvesting is the risk of prolonged warm ischemia time^[19], although this has not shown to be harmful and had no negative effect on graft function^[65]. Thenappan *et al*^[137] compared laparoscopic and open donor hepatectomies and found no significant differences except a minor increase in international normalised ratio on day 7 in the laparoscopic group. Perioperative allograft biliary and vascular complication rates were also comparable between groups. One-year graft and patient survival for laparoscopic group was 100% compared with 93% for the open group^[137].

Cherqui *et al*^[138] reported the first pure laparoscopic LLS for donor hepatectomy in 2002. Subsequently, studies have identified benefits for the donor as decreased blood loss, decreased postoperative complication rates and shorter postoperative recovery and hospital stay^[20,65,139]. Experienced centers point out that laparoscopic LLS should be shortly accepted as standard of care^[19,20].

Laparoscopic major hepatectomies are usually performed in the setting of adult-to-adult LDLT. Left liver harvesting offers a lower risk strategy for the donor while gives to the recipient a relative large amount of functioning liver parenchyma^[140]. Smaller grafts tend to shift the risks from the donor to the recipient, as they increase the risk of a small for size syndrome. Technical improvements have led to better results and small series have shown that this strategy can be undertaken with low morbidity^[141,142].

Right hemilivers offer great amount of functional liver parenchyma, but implies in a larger resection associated with higher risks to donors^[143]. Some centers advocated that laparoscopic harvesting could decrease postoperative complication rates; however there are concerns about the safety of the procedure. Some authors advocate HALS and hybrid procedures in order to reduce donor morbidity^[70,144-146]. Cauchy *et al*^[19] reported 167 right livers harvested through laparoscopy being 98.2% operated with HALS or hybrid techniques. Results showed no mortality, and low rate of severe complications (0% to 17%).

In a recent meta-analysis by Berardi *et al*^[147] 11 studies were included (608 adult patients) comparing minimally invasive and open living donor hepatectomy. Blood loss and operative time were comparable between groups, while hospital stay, analgesia use, donor morbidity rate and wound-related complications were significantly reduced in laparoscopic group^[147].

At present, laparoscopic major hepatectomy for LDLT graft harvesting is a debatable procedure, restricted to few centers and needs further scientific confirmation. According to the 2nd ICC laparoscopic donor harvesting requires both ongoing institutional ethical approval and a reporting registry of all cases to determine the short and long-term outcomes in donors and recipients. Considering the high level of surgical skills required, it is advised to perform this procedure only at centers with experience in MILS and LT^[59].

Table 6 Meta-analysis published comparing open vs laparoscopic liver resection

Ref.	No. of studies/ period	Type of studies	End point	No. of OLR x LLR	Conversion rate	Favors ORL	Favors LLR	Equal OLR x LLR
Simillis <i>et al</i> ^[151]	8 1998-2005	Observational Nonrandomized Comparative Benign and malignant disease	Short-term outcomes	244 (59.7%) x 165 (40.3%)	3.7%	Need and duration of portal clamping	Operative blood loss Return to oral intake LOS	Blood transfusion rate Operative time Incidence of portal triad clamping Adverse events Oncologic clearance Blood transfusion rate Operative time Incidence of portal triad clamping Oncologic clearance Recurrence risk Portal triad clamping time Margin size DFS for HCC
Croome <i>et al</i> ^[150]	26 1998-2009	Observational Nonrandomized Comparative Benign and malignant disease	Short and long-term outcomes	1019 (53.9%) x 871 (46.1%)	3.5%	Lower risk of margins smaller than 1 cm	Operative blood loss Return to oral intake Need for intravenous narcotics Overall complication rate All cause mortality in 2-5 yr Operative blood loss Return to oral intake Overall and specific complications Incidence of portal triad clamping Lower risk of margins smaller than 1 cm Lower rate of positive margins Increased overall survival for HCC Operative blood loss Blood transfusion rate Overall and liver specific complications LOS	Blood transfusion rate Operative time Incidence of portal triad clamping Oncologic clearance Recurrence risk Portal triad clamping time Margin size DFS for HCC
Mirnezami <i>et al</i> ^[149]	26 1998-2009	Observational Nonrandomized Comparative Benign and malignant disease	Short and long-term outcomes	961 (57%) x 717 (43%)	7%	Operative time	Operative blood loss Return to oral intake Overall and liver specific complications LOS	Operative time Postoperative mortality Size of resection margins DFS Overall survival Operative time
Zhou <i>et al</i> ^[118]	10 2001-2010	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	281 (56.9%) x 213 (43.1%)	6.1%	-	Operative blood loss Blood transfusion rate Overall and liver specific complications LOS	Operative time Postoperative mortality Size of resection margins DFS Overall survival Operative time
Mizuguchi <i>et al</i> ^[152]	11 2001-2008	Observational Nonrandomized Comparative Benign and malignant disease	Short-term outcomes	253 (52.2%) x 232 (47.8%)	NR	-	Operative blood loss Postoperative complications LOS	Operative time Postoperative mortality Size of resection margins DFS Overall survival Operative time
Fancellu <i>et al</i> ^[111]	9 2001-2010	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	363 (61.5%) x 227 (38.5%)	4%	-	Rate of positive margins Operative blood loss Blood transfusion rate LOS Overall and liver specific complications	Liver haemorrhage Bile leakage OS DFS Operative blood loss Blood transfusion rate Rate of positive margins
Rao <i>et al</i> ^[64]	7 2005-2009	Observational Nonrandomized Comparative only patients undergoing laparoscopic x open LLS	Short-term outcomes	111 (45.3%) x 134 (54.7%)	2.7%	-	Operative blood loss Postoperative complications LOS Operative time LOS	Operative blood loss Blood transfusion rate Rate of positive margins
Li <i>et al</i> ^[173]	10 2001-2011	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	383 (61%) x 244 (39%)	6.6%	-	Operative blood loss Blood transfusion rate Postoperative complications LOS	Operative time Surgical margin size Rate of positive margins Tumor recurrence Overall and liver specific complications Operative mortality Margin width DFS OS Recurrence rate
Rao <i>et al</i> ^[148]	32 1998-2009	Observational Nonrandomized Comparative Benign and malignant disease	Short and long-term outcomes	1305 (52.9%) x 1161 (47.1%)	2.3%	Operative time	Operative blood loss Blood transfusion rate LOS Return to oral intake Rate of positive margins Overall complication rate	Operative time Surgical margin size Rate of positive margins Tumor recurrence Overall and liver specific complications Operative mortality Margin width DFS OS Recurrence rate

Xiong <i>et al</i> ^[171]	15	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	316 (57.5%) × 234 (42.5%)	0% to 19.4%	-	Operative blood loss Blood transfusion rate LOS Incidence of liver failure and ascites	Operative time Pulmonary complications Bleeding Bile leakage Operative mortality Rate of positive margins Tumor recurrence Operative time Ascites Postoperative liver failure DFS OS
Rao <i>et al</i> ^[172]	10	Observational Nonrandomized Comparative Malignant tumors	Short-term outcomes	404 (57.7%) × 296 (42.3%)	NR	-	Operative blood loss Blood transfusion rate Negative margins rate Overall complication rate LOS	Recurrence rate Surgical margins Operative time Negative margins rate Recurrence rate OS RFS
Yin <i>et al</i> ^[174]	15	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	753 (60.8%) × 485 (39.2%)	2.6%	-	Operative blood loss Blood transfusion rate Postoperative morbidity LOS	Operative time
Zhou <i>et al</i> ^[129]	8	Observational Nonrandomized Comparative CRLM only	Short and long-term outcomes	427 (61.4%) × 268 (38.6%)	8.2%	-	Operative blood loss Blood transfusion rate Postoperative morbidity LOS Negative margin OS DFS	Operative time
Twaij <i>et al</i> ^[168]	4	Observational Nonrandomized Comparative HCC only with cirrhosis	Short and long-term outcomes	270 (64.3%) × 150 (35.7%)	7% to 19.4%	-	Surgical margin size Operative blood loss Blood transfusion rate Postoperative morbidity LOS	Operative time OS DFS
Parks <i>et al</i> ^[167]	15	Observational Nonrandomized Comparative Malignant tumors	Short and long-term outcomes	556 (55.5%) × 446 (44.5%)	4.2%	-	Operative blood loss LOS	Operative time 30-d mortality OS
Luo <i>et al</i> ^[128]	7	Observational Nonrandomized Comparative CRLM only	Short and long-term outcomes	383 (61.4%) × 241 (38.6%)	NR	Margin size	Operative blood loss Blood transfusion rate Postoperative complications Rate of R1 margins Operative blood loss Blood transfusion rate LOS Postoperative complications	Operative time LOS OS DFS Operative time Perioperative mortality OS DFS
Wei <i>et al</i> ^[127]	14	Observational Nonrandomized Comparative CRLM only	Short and long-term outcomes	599 (61.4%) × 376 (38.6%)	NR	-	Postoperative complications LOS	Operative time Perioperative mortality OS DFS
	2002-2013						¹³ Simultaneous resection LOS	¹³ Simultaneous resection Morbidity, operative time, operative blood loss

¹³ studies comparing simultaneous laparoscopic × open resections

Schiffman <i>et al.</i> ^[130]	8	Observational Nonrandomized Comparative CRLM only	Short and long-term outcomes	368 (60.3%) × 242 (39.7%)	NR	-	Operative blood loss Blood transfusion rate Overall complication rate LOS	Operative time Number of major resections Mean number of resected tumors Tumor size Positive margins Margin width OS DFS
Jackson <i>et al.</i> ^[153]	46	Observational Nonrandomized Comparative	Short-term outcomes	1741 (47.8%) × 1901 (52.2%)	5.68%	Cost	Operative blood loss Negative margin LOS	Operative time 30-d mortality
Morise <i>et al.</i> ^[169]	21	Benign and malignant disease Observational Nonrandomized	Ascites	602 (63.1%) × 352 (36.9%)	NR	-	Postoperative complications Less ascites Less postoperative liver failure	-
	2001-2014	Comparative HCC only	Postoperative liver failure	220 (54.6%) × 183 (45.7%)				

[†]Results of a subset of studies (3) comparing simultaneous resection of the primary tumor and liver metastases. CRLM: Colorectal cancer liver metastases; DFS: Disease free survival; HCC: Hepatocellular carcinoma; LLR: Laparoscopic liver resection; LOS: Left lateral sectionectomy; LOS: Length of stay; OLR: Open liver resection; OS: Overall survival; NR: Not reported.

INTRAOPERATIVE CONSIDERATIONS

Operative time

Operative time varies significantly between studies, influenced by the type of resection and surgeon's experience. Viganò *et al.*^[72] studied three consecutive periods, each with 58 patients undergoing LLR, and observed a significant decrease in mean operative time. Other authors have confirmed the trend of significant reduction in operative time related to increasing experience, both in minor and major resections^[77,82].

When compared to open approach, results are conflicting. Some studies have shown longer operative time in LLR group, including 2 meta-analysis^[148,149]. Other authors, however, showed comparable operative times (Table 6)^[150-152]. In a recent meta-analysis, Jackson *et al.*^[153] analyzed 46 publications and found similar results (OLR 203.9 min vs LLR 203.6 min), although there was great heterogeneity among the studies.

Gas embolism

A serious concern in the early days of LLR was the use of pneumoperitoneum with positive pressure. There was a theoretical increased risk of CO₂ embolism due to the elevated gradient between the insufflation pressure and the central venous pressure (CVP).

Animal model studies using transesophageal echocardiography demonstrated that gas embolism occurs in more than 2/3 of the animals undergoing LLR. Despite radiologic demonstration of CO₂ embolism, this was not associated with any clinical deterioration^[21,22,154]. Indeed, the occurrence of gas embolism in clinical practice is anecdotal^[91]. CO₂ is a highly diffusible gas, which minimizes the risk of embolism as compared to air, and low pneumoperitoneum pressure further reduces its incidence^[22,155].

In 2002, Biertho *et al.*^[156] reviewed published series of LLR and reported only two cases (1.1%) of possible gas embolism in approximately 200 LLR. In a meta-analysis of comparative studies, Mirnezami *et al.*^[149] reported 0.1% incidence of gas embolism.

During major LLR the risk of gas embolism was believed to be higher than for minor hepatectomy due to the wide transection plane with dissection of major hepatic

veins and long operative time. However, the occurrence of gas embolism in this scenario is also extremely low. Dagher *et al*^[67] in a multicenter study with 210 cases of major LLR; reported 3 (1.43%) patients that developed gas embolism. However, there was no influence of gas embolism on postoperative morbidity and mortality^[67]. Otsuka *et al*^[157] reviewed 477 major hepatectomies from high-volume centers and observed only 3 (0.2%) cases of gas embolism. In recent series, as well as in our experience, no cases of air embolism were observed.

The occurrence of gas embolism has been also related to argon beam coagulation, which increases intra-abdominal pressure leading to an increased risk of gas embolism^[158-160]. As argon is not diffusible as CO₂, the use of argon beam coagulator during liver transection is not recommended by many experts^[59].

Intraoperative bleeding

The main technical challenge of LLR remains intraoperative hemorrhage during parenchymal transection. Even though intraoperative bleeding rarely occurs, it is difficult to manage in the absence of manual compression.

Some cases of hemorrhagic complications have been reported, mainly related to hepatic veins injuries^[161,162], and were managed either laparoscopically or by conversion to laparotomy. Intraoperative bleeding is the main cause of conversion to laparotomy in most series^[13,14,81,93,99,163-165].

Major blood loss during liver resection has a direct effect on postoperative course^[166] and negatively affects oncological outcomes^[116]. Perioperative blood transfusions are associated with a higher rate of recurrence and lower survival after surgical treatment of malignant diseases, especially HCC^[10].

Blood loss reported during laparoscopic surgery varies between series, and is directly related to the type and difficulty of LLR^[13,14,81,93,99,163-165]. In several meta-analysis of comparative studies intraoperative bleeding tends to be lower at laparoscopic approach than at open resection resulting in decreased requirement for blood transfusion (Table 6)^[149,151,153].

Studying patients with malignant diseases (HCC and CRLM), Parks *et al*^[167] showed significantly lower blood loss in the group undergoing LLR than in the group undergoing OLR. Analyzing only patients with HCC, other meta-analyses yielded similar results, with systematic advantage for the group undergoing LLR, with less intraoperative bleeding and lower rates of blood transfusion^[117,118,168,169].

The factors responsible for reduced blood loss during LLR are magnified view of the operating field, the positive pressure of the CO₂ pneumoperitoneum that avoids retrograde bleeding from hepatic veins, the emergence of new transection devices and adequate inflow and outflow control^[170]. In order to address essential steps in bleeding control during LLR, a recent experts' literature review made some recommendations: Maintenance of pneumoperitoneum between 10-14

mmHg; low CVP (< 5 mmHg); laparoscopy control of inflow and outflow; and surgeons should be experienced with the use of all surgical devices for liver transection and should master laparoscopic suture before starting LLR^[170].

Conversion

The reported conversion rate is in the range of 0%-20%^[171], varying mostly according to the indication for LLR. Series on benign disease show conversion rates from nil to 10%^[12,17,25,28-33]. Observational comparative studies focused on malignant diseases (Tables 4 and 5) showed conversion rates ranging from 0% to 23.3%^[34-58]. However, with surgical expertise the conversion rate can be reduced to < 5% in high-volume expert centers^[32,58]. In our experience the overall conversion rate was 6.5%; however, in the last 100 cases, the conversion rate was 3.0%.

The conversion rate is also related to the complexity of the surgical procedure and accumulated experience. In a multicentric review of 210 major hepatectomies conversion rate was 12.4%. To evaluate the effects of learning curve on outcomes, a comparison was made between the first 15 major LLR performed at each center and the subsequent 120 major hepatectomies. Conversion rate (18.8% vs 7.5%, $P = 0.0018$) was significantly lower in the late group^[67]. In patients with cirrhosis reported conversion rates are higher, ranging from 7% to 19.4%^[168].

EFFICACY OF LLR

Postoperative outcomes: Comparison with OLR

The literature data cited above indicate that LLR is feasible and safe when compared to OLR for both benign and malignant liver lesions. At present, there are 20 meta-analysis summarized on Table 6 comparing the results of LLR and OLR^[94,111,117,118,127-130,148-153,167-169,172-174]. Most studies have consistently demonstrated a significantly lower length of stay (LOS) as compared to the open approach. The overall shorter LOS in laparoscopic resection is not only associated with quicker hospital discharge, but an earlier return of bowel activity and lesser requirement of analgesics^[148-151]. Rao *et al*^[148] pooled analysis of 32 comparative studies showed significant reduction in LOS (2.96 d, 95%CI: -3.70 to -2.22) and in the time to oral intake (1.33 d, 95%CI: -1.86 to -0.80) in the laparoscopic group.

Morbidity and mortality

Nguyen *et al*^[15] found that the overall mortality rate was 0.3% (range 0% to 10%) in 2804 patients operated by LLR until 2008. There were no reported intraoperative deaths. Most common cause of postoperative death was liver failure^[15]. Modern series from large volume centers report mortality for LLR in the range of 0% to 2.4%^[17,25,32,33,35-49,52-58,81,93,99,164,165]. Jackson *et al*^[153] pooled results of 40 studies comparing mortality rates between LLR and OLR and there were no significant differences

between the groups for both in-hospital mortality and postoperative mortality within 30 d of discharge^[153].

The comprehensive review of LLR published series by Nguyen *et al*^[15] found an overall morbidity rate was 10.5% (range 0% to 50%). The most common liver-related complication was bile leakage (1.5%) followed by transient hepatic insufficiency (1.0%). The most common general and surgical-related complications were pleural effusions, incisional bleeding and wound infections each with less than 1%^[15].

In large series including benign and malignant disease, the overall morbidity rate ranges from 3.2%^[175] to 45%. In our series of 214 LLR, morbidity rate was 15% and mortality was 0.5% (one cirrhotic patient died of sepsis). The most common postoperative complications were: Ascitis (15.6%) followed by incisional hernias (9.4%), ileus (9.4%) and pneumonia (9.4%).

Comparative studies showed significant decrease in the complication rate in patients undergoing LLR^[149,150,152,153,172]. A meta-analysis published by Mirnezami *et al*^[149] showed a significant decrease in the incidence of liver-specific complications with LLR compared with OLR. Similarly, Jackson *et al*^[153] analyzed 47 studies and demonstrated that patients who underwent LLR had lower postoperative complications rates when compared with OLR. Specifically, minimally invasive approaches had lower rates of wound infections, incisional hernias, and cirrhotic decompensation events.

Regarding malignancies, patients with CRLM who underwent laparoscopic resections also have lower rates of postoperative complications than the open group^[127,128,130].

Recently, our group published a series including 30 patients with HCC that underwent LLR. Postoperative complications were observed in 40% of patients (75% grade I by Dindo-Clavien classification) and the mortality rate was 3.3%^[176]. A consistent finding among the meta-analysis of LLR for HCC includes reduced complication rates^[117,169,173,174]. Xiong *et al*^[117] examined ascites and postoperative liver failure and reported reduced incidences of both. Recently, Morise *et al*^[169] analyzing the subset of patients with known cirrhosis also noted a significant reduced incidence of postoperative ascites and liver failure.

Cost analysis

There are concerns that LLR may be associated with increased cost due to laparoscopic equipment^[13,74]. Koffron *et al*^[13] showed that the operating room costs for MILS were significantly higher than those of OLR; however, overall costs were reduced due to shorter LOS. Similarly, Polignano *et al*^[177] reported increased disposable instrument costs with LLR. However, these expenses were offset by reduced high dependency unit and ward stay costs, resulting in significantly lower total costs with LLR^[177].

In a recent meta-analysis published by Limongelli *et al*^[178], 9 studies were analyzed comparing the costs of patients undergoing LLR ($n = 344$) vs conventional

approach ($n = 338$). LLR was associated with lower ward stay cost than OLR (2972 USD vs 5291 USD) but costs related to operation (equipment and theatre) were higher in the group of patients undergoing LLR. The total cost was lower in patients managed by LLR (19269 USD) compared to OLR (23419 USD). The same trend of overall cost reduction was observed when the subset of patients undergoing minor LLR was analyzed (total cost: LLR 12720 USD vs OLR 17429 USD).

Regarding major hepatectomies results are contradictory. There is no proven economic benefit related to the laparoscopic procedure when compared to conventional counterparty^[13,179-181].

ONCOLOGICAL RESULTS

Initial limitations of laparoscopic liver surgery included the fear of unfavorable oncological outcomes^[3]. As a new technique, LLR should prove to be non-inferior when compared to the established methods. Pursued oncological results were two-fold: Intraoperative tumor clearance (complete resection with adequate margins) and long-term survival.

Surgical margins

As observed for any laparoscopic operation, LLR is performed without tactile feedback along with a limited bi-dimensional field of view. Moreover, as mentioned earlier, the insertion of the laparoscope through or near the umbilicus implicates in a caudal view of the liver^[84,98]. Complete resection is the goal for the treatment of hepatic malignancies and the limitations in tactile feedback associated with the modified field of view made surgeons concern about adequate intraoperative oncological results.

The encouraging results of LLR set surgeons to search alternatives to overcome those limitations. LLR performed either with laparoscopic or hand assistance offers the possibility of placing the surgeon's hand into to the operative field, ruling out the lack of tactile feedback^[14]. Moreover, during LLR intraoperative ultrasound should be extensively used, not only to identify occult previously unknown lesions, but most importantly to aid surgical planning in order to obtain clear surgical margins^[182].

The best evidence available to date indicates that surgical margins in LLR are as good as in conventional procedures. Comparative studies and meta-analysis have indicated that patients operated with LLR have no increased risk of positive surgical margins^[111,117,118,128-130,149,150,168,172-174]. LLR is carried out under a magnified field of view, which implies in augmented perception of operative blood loss and induces surgeons to be more meticulous, especially when employing a new technique^[86,115]. Another reason for adequate margins relies on patient selection and surgical planning for laparoscopic cases. Surgery should be extensively planned to include peripheral tumors located away from vascular structures and far from the transection plane^[3,14,63,85,93].

Long-term outcomes - CRLM

Inadequate intraoperative staging, insufficient surgical margins, port-site seeding and peritoneal dissemination were feared outcomes that limited the application of LLR to the treatment of CRLM. Those fears were not confirmed and LLR slowly gained acceptance for operations on CRLM.

The cautious progress demonstrated that results on selected patients proved to be equally good for LLR when compared to conventional operations (Tables 5 and 6)^[128,130]. Moreover, LLR increases the chance for future resections once laparoscopy reduces operative adhesions and eases future interventions^[56]. Other technical benefits include the expansion of liver resections to elderly patients and the possibility of synchronous colorectal resections made feasible by a less morbid approach^[131,132,183].

Long-term outcomes - HCC

HCC is the most common primary liver malignancy and figures as a leading cause of cancer related death^[184]. It has a frequent association with chronic liver disease, which implies that management of such tumors comes along with the management of cirrhosis and its complications.

Initial results of laparoscopic operations on cirrhotic patients have shown excellent short-term perioperative outcomes^[23,35,66]. One of the intraoperative benefits of LLR is reduced blood loss; perioperative blood transfusions have a negative impact in survival for HCC^[116], indicating that laparoscopic resection is a useful tool to improve long-term outcomes.

Comparative and meta-analytical studies took a look into survival rates of LLR and long-term outcomes were superimposed to conventional results (Tables 4 and 6)^[111,117,168,173,174]. Thus, LLR is an acceptable option for treating patients with HCC.

TECHNICAL CONSIDERATIONS

PLLR is the most frequent method of LLR and is mostly applied to less complex operations, such as wedge resections, non-anatomic and anatomic resections on the anterolateral segments^[14]. Some expert teams also perform PLLR for major resections and complex procedures such as living donor graft harvesting^[19]. HALS offers the advantage of regaining tactile feedback lost with PLLR. It is also helpful in instances where extensive liver mobilization is required, such as posterior sectionectomies and major resections^[68]. Hybrid resection associates laparoscopy for liver mobilization with an auxiliary incision for parenchymal transection and specimen removal^[14]. Hybrid resections have been reported as a useful tool to increase the frequency of major resections^[69]. Figure 1 demonstrates the rationale from the Liver Surgery Unit at University of Sao Paulo Medical School for selecting the best MILS approach for each scenario.

Minor resections

Minor resections were responsible for the successful start of LLR during the 1990's and still represent one of the major indications of LLR. Especially when located in easily accessible, minor resections should be routinely performed through laparoscopy^[14].

Another LLR minor resection that should be routinely performed is LLS^[14,33,95]. This resection was the first published successful anatomic LLR and has been extensively studied^[8]. Comparative studies have shown that LLS is technically feasible, with superior short-term outcomes and equal long-term oncological results^[71,185-187]. Moreover, it is a standardized procedure, allowing reproducibility and training for surgeons initiating their experience with LLR^[76,77].

Major resections

Laparoscopic major resections have been compared to conventional resections and operative results favor LLR on reduced blood loss, shorter length of stay and fewer complications^[188,189]. Major resections are feasible procedures but are clearly experts' job. Published series derive from multi-institutional studies that gather the experience of high-volume centers, where operations are carried out by experienced liver surgery teams^[62-64,67].

Difficult resections

Access to "non-laparoscopic" segments is difficult once they are located posterior and superior to the liver. Moreover, the postero-superior location demands extensive mobilization in order to bring these segments to the operative field^[190]. Mobilization can be toilsome once the right liver should be detached from its ligaments, the diaphragm, retroperitoneum and, sometimes, the IVC.

The perceived technical difficulty to operate on the non-laparoscopic segments has been confirmed in papers that indicate posterior sectionectomies as "major operations" (despite including only two segments), associated with higher conversion rates, higher blood loss, prolonged operative times and narrower surgical margins^[61,85,99,100].

Resections on these difficult segments can be performed, but usually demand special techniques to overcome above-mentioned limitations. HALS, laparoscopy-assisted and trans-thoracic port placement are useful strategies applied to difficult resections^[103,104,190,191].

NEW TECHNOLOGIES

MILS has evolved during the past two decades and still moves forward. Robot assisted resections are feasible as reported in case series. Robotic surgery might improve results of LLR once it offers a three-dimensional view and has a greater range of movements, which can be useful for complex resections^[24,192,193].

Another perspective for LLR is the association of three-dimensional (3D) image guidance to help surgeons

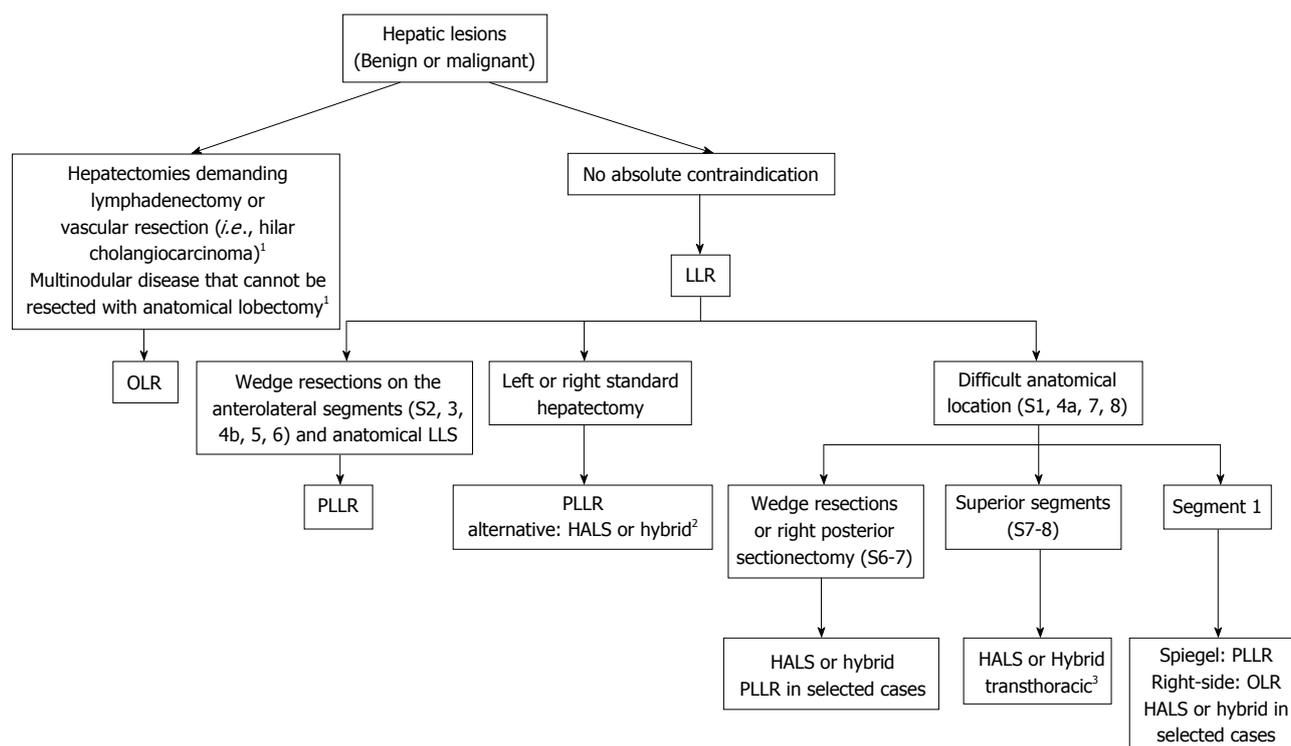


Figure 1 Flowchart demonstrating a suggested approach to the liver nodules using the minimally invasive approach (Liver Surgery Unit, University of São Paulo Medical School). ¹HALS or hybrid in selected cases; ²When technical difficulties are anticipated/intraoperative difficulties; ³When abdominal approach is not possible. HALS: Hand-assisted liver surgery; LLR: Laparoscopic liver resection; OLR: Open liver resection; LLS: Left lateral sectionectomy; PLLR: Pure laparoscopic liver resection.

to navigate along the liver anatomy while planning and executing de resection. 3D image simulation appears to be useful for surgical planning and has a high accuracy for predicting surgical margins and liver volumes. Further dynamic applicability of the 3D planning to navigation during operation is expected to improve operative results^[194].

Single port operations have been recently incorporated to LLR and anecdotally described. Recent reviews of the scarce available data identified around 30 reported cases. Most cases were highly selected and included small resections, even though major hepatectomy has also been performed. At this point no conclusion or recommendation can be made for single port LLR, further studies are needed to indicate it's role in LLR^[195,196].

CONCLUSION

LLR has been progressively developed along the past two decades. Despite initial skepticism, improved operative results made LLR incorporated to surgical practice and operations increased in frequency and complexity. However, the expansion of MILS becomes essential when we consider that countries with long-standing tradition in surgery apply laparoscopy to liver surgery in less than 15% of cases. High quality studies allied with high-level surgical training are required to base surgical practice and to disseminate the benefits of MILS to many centers as possible. LLR should be

standard practice for anterolateral resections and LLS, major resections are feasible procedures but restricted to experienced centers. Future applicability of new technologies such as robot assistance and image-guided surgery is still under investigation.

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Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery

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Abstract

According to the United States census bureau 20%

of Americans will be older than 65 years in 2030 and half of them will need an operation - equating to about 36 million older surgical patients. Older adults are prone to complications during gastrointestinal cancer treatment and therefore may need to undergo special pretreatment assessments that incorporate frailty and sarcopenia assessments. A focused, structured literature review on PubMed and Google Scholar was performed to identify primary research articles, review articles, as well as practice guidelines on frailty and sarcopenia among patients undergoing gastrointestinal surgery. The initial search identified 450 articles; after eliminating duplicates, reports that did not include surgical patients, case series, as well as case reports, 42 publications on the impact of frailty and/or sarcopenia on outcome of patients undergoing gastrointestinal surgery were included. Frailty is defined as a clinically recognizable state of increased vulnerability to physiologic stressors resulting from aging. Frailty is associated with a decline in physiologic reserve and function across multiple physiologic systems. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. Unlike cachexia, which is typically associated with weight loss due to chemotherapy or a general malignancy-related cachexia syndrome, sarcopenia relates to muscle mass rather than simply weight. As such, while weight reflects nutritional status, sarcopenia - the loss of muscle mass - is a more accurate and quantitative global marker of frailty. While chronologic age is an important element in assessing a patient's peri-operative risk, physiologic age is a more important determinant of outcomes. Geriatric assessment tools are important components of the pre-operative work-up and can help identify patients who suffer from frailty. Such data are important, as frailty and sarcopenia have repeatedly been demonstrated among the strongest predictors of both short- and long-term outcome following complicated surgical procedures such as esophageal, gastric, colorectal, and hepato-pancreatico-biliary resections.

Key words: Sarcopenia; Outcomes; Frailty; Morbidity;

Mortality

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Core tip: It is estimated that by the year 2030, 36 million Americans > 65 years will require surgery. Frailty as defined by a clinically recognizable state of increased vulnerability due to physiologic stressors resulting from aging has been associated with a decreased physiologic reserve and function across multiple physiological systems. Recently, a loss of muscle mass or sarcopenia has been proposed as an accurate and quantitative global marker of frailty. The current review demonstrates that frailty as defined by sarcopenia can be accurately used as a preoperative predictor of poor short- and long-term postoperative outcomes following complex gastrointestinal surgery.

Wagner D, DeMarco M, Amini N, Buttner S, Segev D, Gani F, Pawlik TM. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. *World J Gastrointest Surg* 2016; 8(1): 27-40 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i1/27.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i1.27>

INTRODUCTION

The life expectancy of the average person doubled over the course of the last century. In addition, between 1982 and 2003 the American population aged over 65 years doubled and the population older than 85 years quadrupled^[1]. According to the United States census bureau 20% of Americans will be older than 65 years in 2030 and half of them will need an operation - equating to about 36 million older surgical patients^[2]. The process of aging is associated with an increasing prevalence of frailty, comorbidities, a decline of functional reserve and a progressive restriction in personal and social resources. All of these factors can contribute to less favorable postoperative outcomes among older patients^[3]. Older patients are at increased risk for complications which include delirium, urinary incontinence, pressure ulcers, depression, infection, functional decline and adverse drug affects^[4-8]. Despite the fact that surgery is the most effective cancer therapy, complication rates, mortality, length of hospital stay and intensive care unit admissions increase with patient age, which can offset oncologic advantages^[9-13].

Many cancer treatment guidelines have been formulated based on clinical data that may have under-represented older and more frail patients; therefore, more attention is needed to guide the management of this vulnerable population^[14,15]. Several studies have noted potential differences in gastrointestinal surgical care between older and younger patients^[16,17]. For example, commonly used predictor scores for postoperative complications like the American Society of Anesthesiology

score have substantial limitations in older patients, as most are based on a single organ system, are subjective and none measures the patients' physiologic reserve^[18]. In fact, a recent review by McCleary *et al*^[16] stressed that older adults are prone to complications during gastrointestinal cancer treatment and therefore need to undergo special pretreatment assessments incorporating frailty and sarcopenia assessments.

More recently, sarcopenia and frailty have increasingly been recognized as important factors that can be markers of decreased physiologic reserve. Several studies have highlighted the importance of frailty and sarcopenia to predict perioperative outcomes among patients undergoing surgery for gastrointestinal cancer^[19-22]. Recent guidelines from the American College of Surgeons have highlighted the importance of assessing both frailty and sarcopenia prior to oncologic surgery in the elderly^[23]. As such, there is increasing interest in screening patients for frailty and sarcopenia to better predict patients at highest risk of complications after surgery^[24]. Given this, we sought to review the available literature on the association of frailty and sarcopenia with patient outcome, as well as the risk of perioperative morbidity and mortality after gastrointestinal surgeries.

SYSTEMATIC LITERATURE REVIEW

A focused, structured literature review was performed using PubMed and Google Scholar to identify primary research articles, review articles, as well as practice guidelines on frailty and sarcopenia among patients undergoing gastrointestinal surgery. Articles published between January 2000 to March 2015 were identified using the search terms "sarcopenia and gastrointestinal surgery", "frailty and gastrointestinal surgery", "sarcopenia and outcome and surgery", as well as "frailty and outcome and surgery". In addition, references of relevant articles were also reviewed to identify potentially eligible studies. As per the methodology specified under the PRISMA guidelines, only studies published in English were included, while conference abstracts that did not proceed to publication in peer-reviewed journals were excluded^[25]. The initial search identified 343 articles; 53 duplicates were eliminated and 290 abstracts were reviewed for further assessment. Among these 25 editorials, 97 studies that did not include gastrointestinal patients, 99 articles that did not use standard frailty or sarcopenia assessments, 19 case series, as well as 5 case reports and 3 consensus statements were eliminated (Figure 1). In total 42 publications assessing the impact of frailty and/or sarcopenia on postoperative outcomes among patients undergoing gastrointestinal surgery were identified that met inclusion criteria. Among all studies that were included, 10 studies were performed prospectively (2 gastroesophageal surgery, 6 colorectal surgery, and 2 hepato-pancreaticobiliary surgery, Tables 1-3)^[26-33]. Sixteen studies were conducted retrospectively on an unmatched cohort (2 gastroesophageal, 4 colorectal, and 10 hepato-

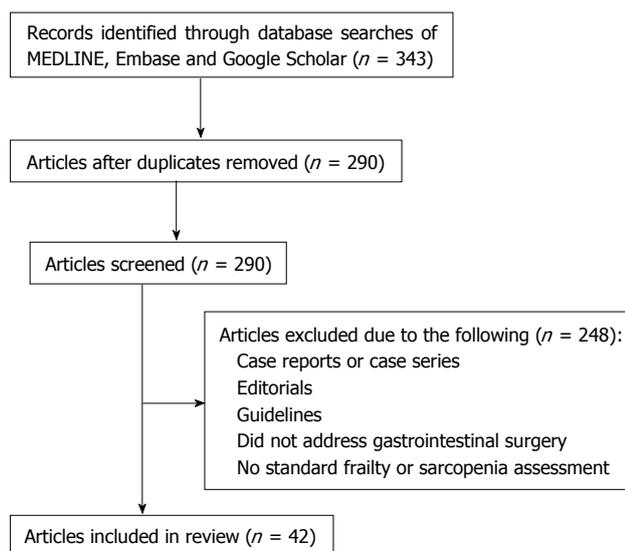


Figure 1 Flow chart depicting the review process for the inclusion of publications.

pancreatico-biliary), 2 studies retrospectively analyzed prospectively collected data while two articles analyzed data from multiple centers in the United States^[34-50]. Additionally, 15 narrative reviews were included in the study. The quality of each study was assessed using the Newcastle-Ottawa Scale based on case selection, comparability, and outcome reporting (Tables 1-3); the median quality score of the studies was 6.5 (range 4-9).

Data pertaining to patient demographics (age and sex), assessment used, type of surgery and the number of patients were collected for each article and are displayed in Table 4. Additionally, data relating to short-term clinical outcomes such as 30-d morbidity and mortality, as well as long-term outcomes including median, 5-year overall and 1-year overall survival were recorded from each study. Sarcopenia and frailty, as well as other end points used for analyses were not homogeneously defined throughout the studies. The different approaches to define sarcopenia and frailty along with relevant clinical and outcome parameters used along with the quality scale of the included studies (Tables 1-3). While a direct comparison between the studies was therefore not possible due to their heterogeneity, data were amassed from these studies to inform a comprehensive review.

FRAILTY AND SARCOPENIA IN OLDER ADULTS UNDERGOING SURGERY: GENERAL CONSIDERATIONS

Frailty is associated with a decline in physiologic reserve and function across multiple physiologic systems^[51]. In the absence of a gold standard, frailty has been operationally defined by Fried *et al.*^[20] as meeting 3 out of 5 phenotypic criteria indicating compromised energetics: Low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss.

While frailty has not been widely evaluated in surgical patients, Makary *et al.*^[22] did report on the surgical outcomes of a large cohort of older patients in which frailty was assessed using a frailty scale based on the Fried frailty phenotype (Table 4). The authors reported that preoperative frailty was associated with an increased risk of postoperative complications. Specifically, patients with moderate or severe frailty had roughly twice (moderate: OR = 2.06, 95%CI: 1.18-3.6; severe: OR = 2.54, 95%CI: 1.12-5.77) the odds of complications compared with non-frail patients. The authors also reported that frailty independently predicted length of stay with moderate or severe frailty having a 44%-53% and 65%-89%, respectively, longer hospital stays than non-frail patients. Of note, the power of frailty to predict worse outcomes was much higher than traditional peri-operative assessments alone (Figure 2). These data emphasize how frailty adds valuable information to standard preoperative risk assessments, yet highlight how defining frailty in the peri-operative period can be challenging.

A full combined geriatric assessment (CGA) can take several hours and includes assessments such as activities of daily living, geriatric depression scores, and timed "up and go" tests^[52]. Specifically, the risk of mortality among patients with frailty ranged from 1.1%-11.7%, with frail patients up to 12 times more likely to die compared with non-frail patients in a recent review on the use of CGA in gastrointestinal surgery^[52]. Due to its time consuming nature, the National Cancer Institute and the National Institute of Aging recommends this scoring system only for patients with special needs who are deemed at high risk^[7]. In addition to CGA, other parameters have been used to assess frailty and sarcopenia in older patients undergoing gastrointestinal surgery. For example, in a large cohort study of 76106 patients from the NSQIP database, Amrock *et al.*^[53] reported that preoperative impaired cognition, low albumin level, previous falls, low hematocrit levels and a high prevalence of comorbidities were associated with an increased 6 mo mortality and post discharge institutionalization among older patients undergoing major abdominal operations. While the authors concluded that preoperative data could help define frailty and predict the geriatric-specific surgical risk, the study failed to provide a clear definition for frailty in gastrointestinal surgical patients. Other studies have suggested that the Charlson index, timed "up and go" tests, Katz score or the Mini cog score, as well as serum albumin levels below 3.4 g/dL and the Braden score all may be associated with postoperative outcomes^[28,54,55]. Each of these parameters have not been shown, however, to improve the risk prediction compared with the Fried Frailty Phenotype when used alone.

Sarcopenia has been proposed as another means to assess frailty. In fact, when Fried *et al.*^[20] first described the frailty phenotype and its association with mortality and morbidity, the potential link between frailty and sarcopenia was noted. Specifically, patients deemed

Table 1 Compiles all studies evaluated in patients undergoing esophageal or gastric resection

Ref.	Country	Quality score ¹	Study design	Sample size	Age (yr)	Male sex (%)	Surgery type	Parameter used to define frailty	Postoperative complication rate	Follow-up (mo)	30-d morbidity (%)	30-d mortality (%)	1-yr OS (%)	5-yr OS (%)	Outcome parameter	Frailty/OS (OR)
Hodari <i>et al</i> ^[54]	United States	5	R	2095	NR	NR	Esophagectomy	Modified Canadian age index	17.8	NR	NR	NR	96	NR	Postoperative complications	OR = 31.84, P = 0.015
Sheetz <i>et al</i> ^[55]	United States	7	R	230	62	88	Transhiatal esophagectomy	Lean psoas area (L4 level)	57.8	12.8	NR	NR	11	0	Overall survival	OR = 0.456; 95%CI: 0.197-1.054; P = 0.067
Yip <i>et al</i> ^[26]	United Kingdom	5	P	36	63	86	Neoadjuvant chemotherapy and esophagectomy	Body composition	26	30	26	0	NR	NR	No multivariate outcome analysis	NR - significant increase in complications and decrease in survival
Awad <i>et al</i> ^[27]	United Kingdom	7	P	47	63		Esophagectomy gastrectomy	Body composition	NR	24	NR	2.2	23.9	19	No multivariate outcome analysis	NR - significant increase in complications with frailty
Tegels <i>et al</i> ^[60]	The Netherlands	5	R/P	70	59		Gastrectomy	Groningen frailty index	28	6	NR	9.1	NR	NR	30-d mortality	3.96 (95%CI: 1.12-14.09, P = 0.03)

¹ According to the Newcastle-Ottawa Scale ranging from 1 to 9 stars. Age and OS are presented as median values unless indicated otherwise. NR: Not reported; OS: Overall survival; OR: Odds ratio; P: Prospective trial; P/R: Retrospective analysis on prospectively collected data; R: Retrospective trial.

to be frail who had a concomitant decrease in muscle mass were more likely to suffer from disabilities and a worsening in their mobility vs non-frail patients. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. Unlike cachexia, which is typically associated with weight loss due to chemotherapy or a general malignancy-related cachexia syndrome, sarcopenia relates to muscle mass rather than simply weight. As such, while weight reflects nutritional status, sarcopenia - the loss of muscle mass - is a more accurate and quantitative global marker of frailty^[56]. Usually characterized as low muscle mass and low muscle function (strength/performance), sarcopenia is typically defined using an axial cross-sectional image of the psoas muscle at the level of L3^[57,58]. Using this technique, sarcopenia is defined as the total psoas area (TPA), with sarcopenic patients having a smaller TPA^[58]. More recent studies have suggested that assessment of the entire volume of the psoas muscle (TPV) may be a better means to define sarcopenia rather than a single axial image (Figure 3)^[47,59]. In addition, other investigators have suggested the use of dual X-ray absorptiometry as an alternative means to screen for sarcopenia. This tool has not been widely adopted, however, as routine computed tomography is more commonly utilized in patients prior to surgery.

Both the European and the American Society of Ageing have recommended that sarcopenia be recognized as a geriatric syndrome^[57]. In addition, several studies have noted an association between sarcopenia and increased risk of adverse outcomes following surgery^[15,59]. For example, Brant *et al*^[58] reported that patients with sarcopenia were particularly vulnerable in the setting of significant physiologic stressors like major surgery. The importance of sarcopenia in the prediction of outcome after gastrointestinal surgery has been particularly highlighted in several studies^[43,47,59]. The hope is that identification of patients with frailty or sarcopenia who are at high risk of perioperative morbidity can guide patient-physician discussions prior to surgery, as well as identify appropriate patients for "pre-habilitation"^[60].

GASTRO-ESOPHAGEAL MALIGNANCIES

Gastric and esophageal cancer represent a worldwide major health problem. While the incidence in Western countries is relatively low with 18170 and 22220 new esophageal

Table 2 Compiles the characteristics of all studies evaluated in patients undergoing colorectal resections

Ref.	Country	Quality score ¹	Study design	Sample size	Age (yr)	Male sex (%)	Surgery type	Parameter used to define frailty	Postoperative complication rate	Follow-up (mo)	30-d morbidity (%)	30-d mortality (%)	1-yr OS (%)	5-yr OS (%)	Outcome parameter	Frailty/outcome (OR)
Rønning <i>et al</i> ^[67]	New Zealand	6	P	84	82	41	Colorectal surgery	Combined geriatric assessment	NR	22	NR	NR	NR	NR	No outcome analysis	NR - significant postoperative decrease of ADL
Obeid <i>et al</i> ^[36]	United States	5	R	58448	NR	48	Colectomy (33% malignant causes)	Canadian frailty index	26	NR	15.9	4.6	NR	NR	30 d mortality and morbidity	OR = 14.4; 95%CI: 18.76-31.2
Neuman <i>et al</i> ^[67]	United States	6	R	12979	84	39	Colectomy for colorectal cancer	Johns Hopkins adjusted case mix system	NR	16	NR	NR	85.7	NR	1 yr survival	OR = 8.4; 95%CI: 6.4-11.1, P = 0.001
Robinson <i>et al</i> ^[68]	United States	4	P	60	75	97	Colectomy for colorectal cancer	Individual frailty score	10	6	10	2	NR	NR	Hospital and health care costs	NR - significant association to costs and length of stay
Tran Ba Loc <i>et al</i> ^[20]	France	7	P	1186	76	NR	Major colorectal surgery	Elderly POSSUM score	41	3	NR	2	NR	NR	30 d mortality	AUC 0.86 (0.81-0.92)
Tan <i>et al</i> ^[31]	China	6	P	83	82	NR	Colorectal resections	Fried frailty criteria	22	NR	29	0	NR	NR	30 d morbidity	OR = 4.08; 95%CI: 1.43-11.64, P = 0.006
Sabel <i>et al</i> ^[38]	United States	5	R	302	68	52	Colorectal resection	Psoas area;	58	34	NR	NR	NR	NR	No outcome analysis	NR
Lieffers <i>et al</i> ^[39]	Canada	5	R	234	63	135	Colorectal resection	Skeletal muscle index	6	NR	NR	NR	NR	NR	Postoperative complications	OR = 4.6; 95%CI: 1.513-9, P = 0.007
Reisinger <i>et al</i> ^[50]	The Netherlands	5	P/R	340	69	50	Colorectal resection	L3 muscle index	21	24	NR	4.5	NR	NR	Postoperative complications	OR = 43.3; 95%CI: 2.74-685.2, P = 0.007
Huang <i>et al</i> ^[30]	China	6	P	142	62	62	Colorectal resection	L3 muscle index and gait speed and grip strength	28	NR	NR	NR	NR	NR	Postoperative complications	OR = 4.524, 95%CI: 1.584-12.921, P = 0.007

¹According to the Newcastle-Ottawa Scale ranging from 1 to 9 stars. Age and OS are presented as median values unless indicated otherwise. NR: Not reported; OS: Overall survival; OR: Odds ratio; P: Prospective trial; P/R: Retrospective analysis on prospectively collected data; R: Retrospective trial.

United States in 2014, gastro-esophageal cancer is a leading indication for cancer resection in the Eastern hemisphere^[61,62].

Frailty and gastro-esophageal malignancies

Because the incidence of esophageal and gastric cancer increases with age, there has been a particular interest in the management of these diseases in older patients. In

Table 3 Compiles the characteristics of all trials which evaluated frailty in patients undergoing hepato-pancreaticobiliary resections

Ref.	Country	Quality score ¹	Study design	Sample size	Age (yr)	Male sex (%)	Surgery type	Parameter used to define frailty	Postoperative complication rate	Follow-up (mo)	30-d morbidity (%)	30-d mortality (%)	1-yr OS (%)	5-yr OS (%)	Outcome parameter	Frailty/outcome (OR)
Harimoto <i>et al</i> ^[40]	Japanese	6	R	186	67	40	Partial hepatectomy HCC	L3 muscle area	NR	60	NR	NR	NR	71	5 yr survival	OR = 0.9; 95%CI: 0.84-0.93, P = 0.002
van Vledder <i>et al</i> ^[41]	The Netherlands	5	R	196	65	61	Liver resection for CRLM	Skeletal muscle mass	NR	29	NR	NR	94	43	Overall survival	OR = 14.4; 95%CI: 18.76-31.2
Valero <i>et al</i> ^[42]	United States	7	R	96	62	61	Liver resection liver transplantation	Total psoas area and total psoas volume	29	26	NR	NR	82	47	Complication rate	OR = 3.06; 95%CI: 1.07-8.52, P = 0.003
Englesbe <i>et al</i> ^[43]	United States	5	R	163	53	NR	Liver transplantation	Total psoas area and psoas density	NR	36	NR	NR	NR	NR	Overall survival rate	OR = 0.27; 95%CI: 0.11-0.33, P = 0.001
Waits <i>et al</i> ^[44]	United States	8	R	348	51	62	Liver transplantation	Total psoas area and psoas density and age - summarized in new parameter "monomorphometric age"	NR	60	NR	NR	85	59	1 and 5 yr survival	OR = 1.04; 95%CI: 1.03-1.06, P = 0.001
Masuda <i>et al</i> ^[45]	Japanese	5	R	2014	48	50	Living donor liver transplantation	Total psoas area	18	60	NR	NR	75	89	1 and 5 yr survival	OR = 2.06; 95%CI: 1.1-4.2, P = 0.05
Kaido <i>et al</i> ^[46]	Japanese	6	P	124	54	NR	Living donor liver transplantation	Skeletal muscle mass and bioimpedance analysis	NR	60	NR	NR	80	73	1 and 5 yr survival	OR = 4.85; 95%CI: 2.092-11.79, P = 0.001
Peng <i>et al</i> ^[46]	United States	6	R	259	68	60	Liver resection for CRLM	Total psoas area	10	60	NR	NR	65	26	Postoperative complications	OR = 3.1; 95%CI: 1.14-8.29, P = 0.02
Amini <i>et al</i> ^[47]	United States	7	R	763	67	57	Pancreatic resection	Total psoas area and total psoas volume	48	24	0.5	48	76	24	Postoperative complications	OR = 1.79; 95%CI: 1.15-2.56, P = 0.002
Dale <i>et al</i> ^[48]	United States	9	P	76	67	55	Pancreaticoduodenectomy	Fried's criteria, Short Battery, Vulnerable Elderly Survey	80	1	4	21	NR	NR	Postoperative complications	OR = 4.06, P = 0.01
Joglekar <i>et al</i> ^[49]	United States	6	R	118	65	75	Pancreatic resection	Total psoas index and psoas density	78	3	NR	23	NR	NR	Postoperative complications	OR = 2.78; 95%CI: 2.28-22, P = 0.02
Peng <i>et al</i> ^[45]	United States	6	R	557	66	53	Pancreatic resection	Total psoas area	47	36	NR	NR	62	3 a OS: 36	3 yr OS	OR = 1.68; 95%CI: 1.32-2.11; P = 0.001

¹According to the Newcastle-Ottawa Scale ranging from 1 to 9 stars. Age and OS are presented as median values unless indicated otherwise. NR: Not reported; OS: Overall survival; OR: Odds ratio; P: Prospective trial; P/R: Retrospective analysis on prospectively collected data; R: Retrospective trial.

fact, in 2014 Balducci *et al*^[63] published guidelines on the treatment of older patients with gastro-esophageal malignancies. The authors noted that for individuals whose life expectancy without cancer exceed that with cancer, the estimated risk of chemotherapy complications may reveal those patients in need of additional care and those patients in whom the risk of treatment may exceed the potential benefits. Importantly, the authors noted that the individual's general life expectancy should be defined using the CGA and an assessment of patient frailty.

Table 4 Makary *et al*^[22] did report on the surgical outcomes of a large cohort of older patients in which frailty was assessed using a frailty scale based on the fried frailty phenotype

Characteristic	
Weakness	Weakness should be assessed by grip strength and measured directly with a hand held JAMAR dynamometer (Sammons, Preston Rolyan). Three serial tests of maximum grip strength with the dominant hand will be performed and a mean of the three values will be calculated and adjusted by body mass index and gender. Actual weakness will be defined in the lowest 20 th percentile of a community dwelling adults of 65 yr and older
Shrinking	Shrinking should be defined through a self-report as unintentional weight loss above 10 pounds during the last year
Exhaustion	Exhaustion should be measured by responses following 2 statements from the modified 10 items Center for Epidemiological Studies - Depression scale: "I felt that everything I did was an effort and I could not get going" and "How often in the last week did you feel way?" and will be given the opportunity to reply with 0 = rarely or none of the time (< 1 d); 1 = some or a little time (1-2 d); 2 = a moderate amount of time (3-4 d); and 3 = most of the time. Patients answering either with 2 or 3 will be classified as exhausted
Low activity	Physical activities should be assessed using the Minnesota Leisure Time Activities Questionnaire which includes frequency and duration. The focus should be placed on activities in the past 2 wk prior to operation. Weekly tasks will be converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure in the lowest 20 th percentile for their gender will be classified as having low activity
Slow walking speed	Walking speed should be measured combining 3 trials of walking 15 feet at a normal pace for the patient. Patients with a walking speed in the lowest 20 th percentile, adjusted for gender and height, will be scored as having a slow walking speed

Sarcopenia and gastro-esophageal malignancies

Specific publications on the impact of frailty and sarcopenia on postoperative outcomes following gastro-esophageal surgery are rather scarce (Table 1)^[34,35,63]. In a small study, Pultrum *et al*^[64] reported that esophagectomy was justified in older patients as advanced age alone had only a minor impact on a patients' postoperative course. The authors noted, however, that frailty was much more strongly associated with both short- and long-term outcomes among patients undergoing esophageal surgery. In a separate study, Hodari *et al*^[34] examined a much larger cohort of 2095 patients undergoing esophagectomy and reported that higher frailty scores were associated with increased postoperative morbidity and mortality. In this study, the frailty score was divided into 5 different categories and the incidence of peri-operative mortality incrementally increased with the frailty score, with mortality only 1.8% among patients with a frailty score 0 vs 23.1% among those patients with a frailty score 5 ($P = 0.001$). While the authors assessed several other parameters associated with postoperative outcomes, only age and

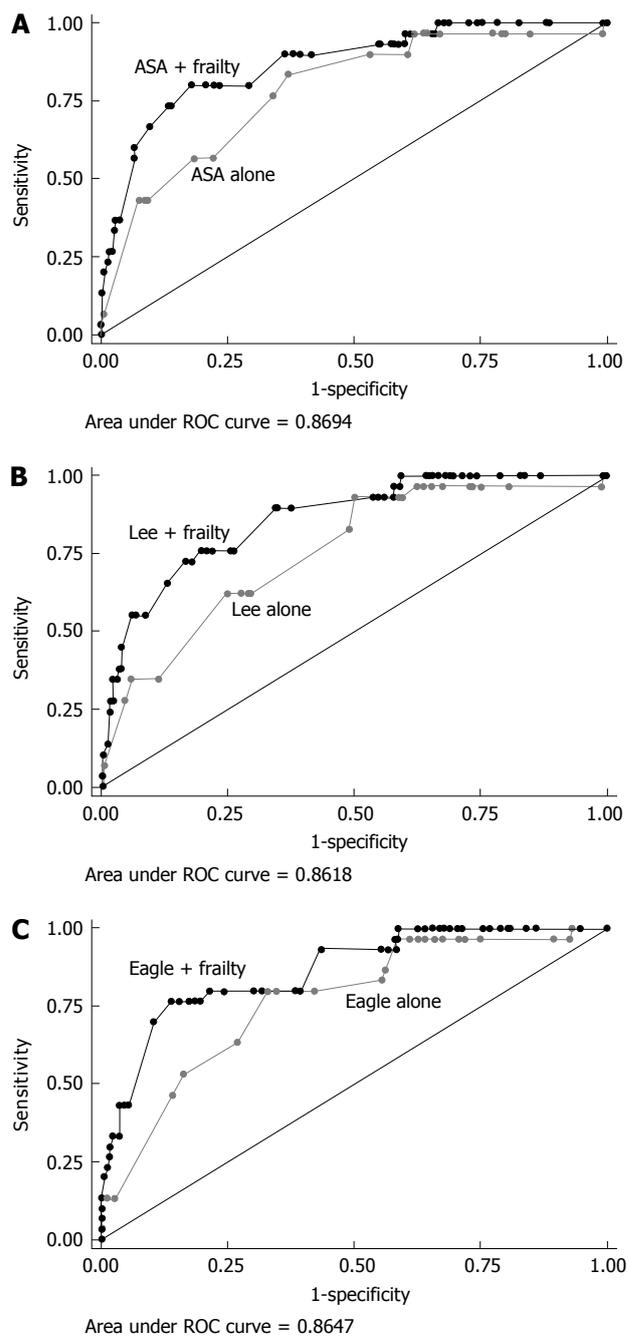


Figure 2 Power of frailty to predict worse outcomes was much higher than traditional peri-operative assessments. A: American Society of Anesthesiologists (ASA); B: Lee; C: Eagle risk indices. Each panel shows the area under the receiver operator characteristics (ROC) curve to demonstrate the ability of the specific risk index to predict surgical complications and discharge to an assisted or skilled nursing facility. Frailty was added to the risk index scoring to demonstrate the combined ability of these indices to predict discharge disposition. Used with permission Makary *et al*^[22], 2010.

frailty were significantly associated with risk of peri-operative morbidity and mortality. Examining a separate cohort of patients undergoing esophageal cancer, Sheetz *et al*^[35] confirmed a strong association between frailty, sarcopenia and peri-operative risk of morbidity among patients undergoing esophagectomy. Using preoperative computed tomography scans in 230 subjects who had undergone transhiatal esophagectomy for malignancy,

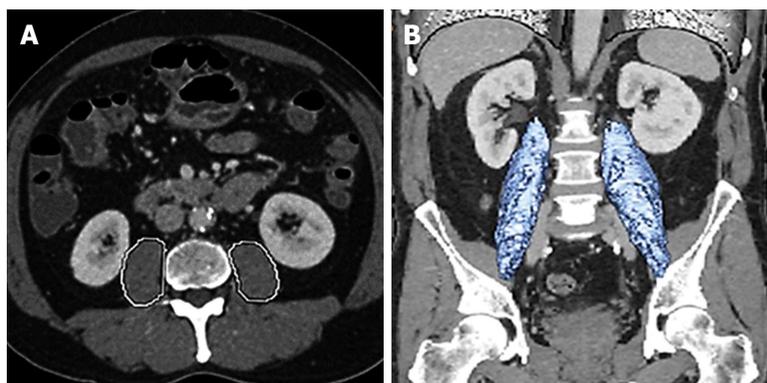


Figure 3 Define sarcopenia rather than a single axial image. A: Total psoas area is measured by circling both psoas muscles at the level of the patients computed tomography where both iliac crests are visible; B: Total psoas volume is measured at the full length of the psoas muscles and normalized for the patients body surface area. Used with permission Amini *et al*^[47], 2015.

the authors assessed lean psoas area (LPA) and correlated it with overall and disease-free survival^[35]. Analyses demonstrated that increasing LPA correlated with both overall and disease-free survival and the authors concluded that core muscle size appeared to be an independent predictor of outcome^[35].

To date, the role of sarcopenia to predict perioperative outcomes among patients undergoing esophagectomy has been evaluated in only a handful of studies^[26,27]. Yip *et al*^[26] studied 35 patients who received neoadjuvant chemotherapy followed by surgical resection for esophageal cancer. The authors noted that changes in computed tomography body composition were associated with outcomes. Specifically, fat mass, subcutaneous fat to muscle ratio and visceral to subcutaneous adipose tissue ratio were each associated with circumferential resection margin. While sarcopenia was more prevalent after neoadjuvant chemotherapy, changes in body composition were not associated with perioperative complication or survival. In a separate study, Awad *et al*^[27] similarly noted marked changes in body composition following neoadjuvant chemotherapy for esophageal cancer. In this study, the authors reported on 47 patients treated with neoadjuvant chemotherapy for esophageal cancer. The proportion of patients with sarcopenia increased from 57% pre-therapy to 79% post-neoadjuvant therapy. Similar to the study by Yip *et al*^[26], no association was demonstrated between sarcopenia and hospital stay, morbidity or mortality. Given the very small number of patients included in the studies by Yip *et al*^[26] ($n = 35$) and Awad *et al*^[27] ($n = 47$), the lack of association between sarcopenia and peri-operative outcomes may have been due to low sample size and a type II statistical error. Future larger studies are necessary to better delineate the impact of sarcopenia on peri-operative and long-term outcomes among patients with esophageal cancer undergoing surgical resection.

Similar to esophageal cancer, gastric cancer patients are at high risk for malnutrition and therefore older patients with gastric cancer may be at a particularly high risk of frailty. In fact, the prevalence of frailty and

sarcopenia among patients with gastric cancer has been reported to be as high as 30% and 38%, respectively^[49,65]. Despite the high incidence, data on the association of frailty, sarcopenia and outcomes of patients after gastric resection are limited. In a review on the topic of gastric cancer surgery, Tegels *et al*^[49] described a strong association between frailty, sarcopenia and increased postoperative mortality after gastric resections. Specifically, the authors highlighted the need for better preoperative risk assessment using comorbidity index, assessment of nutritional status, and frailty assessment. In particular, Tegels *et al*^[65] noted that assessment tools such as the Groningen Frailty Indicator (GFI), Edmonton frail scale, or the Hopkins frailty scale should be used to help identify patients for preoperative optimization using pre-habilitation. In a separate prospective study of 180 patients with gastric cancer, the same authors examined the association of frailty with morbidity and mortality after gastric cancer surgery. In this study, patients scheduled for gastric cancer surgery were preoperatively assessed with the GFI and the Short Nutritional Assessment Questionnaire (SNAQ). Of note, patients with a GFI ≥ 3 had a mortality of 23.3% vs 5.2% in the lower GFI group. Similarly, those patients who scored poorly on the SNAQ had a higher mortality (13.3%) vs those deemed to have better nutritional status (3.2%). The authors concluded that frailty and nutritional status were important factors in preoperative decision making among elderly patients being considered for gastric resection. While the impact of frailty and malnutrition on perioperative outcomes has been examined, no study on the role sarcopenia to predict morbidity and mortality of patients undergoing gastric surgery has been reported to date.

COLORECTAL CANCER

In 2014, 132700 patients were diagnosed with colorectal cancer in the United States. More than half of patients with colorectal cancer are older than 65 years and approximately 70% are diagnosed at early stages, when surgical resection is feasible^[66].

Frailty and colorectal cancer

Among older patients undergoing surgery for colorectal cancer, frailty and sarcopenia have been investigated as predictors of outcome in a small number (Table 2). In particular, pre-operative frailty has been associated with a decline in the patients' activities of daily living and the instrumental activities of daily living after colon resection^[67]. Other studies have noted that frailty can significantly impact peri-operative outcomes. For example, Obeid *et al*^[36] reported on a large group of patients ($n = 58448$) with colorectal cancer derived from the NSQIP database. The authors noted that the proportion of patients who experienced a severe Clavien class IV-V complication following colorectal surgery increased from 5.8% to 56.3% when comparing non-frail vs frail patients ($P = 0.0001$). Frailty was also independently associated with a longer intensive care unit stay and increased peri-operative mortality. In a different study, Neuman *et al*^[37] reported on 12979 patients from the SEER-Medicare database above the age of 80 who underwent a colorectal resection. Older age, male gender, frailty, and dementia were all associated with decreased survival at 1 year. Although only 4.4% of patients were considered frail, this factor had the strongest association with mortality with an odds ratio of 8.4. While the authors concluded that frailty was an important predictor of outcome, the study was limited due to the nature of the administrative data used in the analyses. In a different study that utilized institutional data, Robinson *et al*^[68] reported on 201 subjects, many of whom underwent an elective colorectal surgery. Pre-operative frailty was associated with increased post-operative complications after colorectal surgery (frail 58% vs non-frail 21%); frail patients also had longer hospital stays and higher 30-d readmission rates. Furthermore, frailty has noted to be a good predictor of complications (AUC 0.702). Other authors have noted that an elderly modified Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (E-POSSUM) is also a good tool for predicting mortality after major colorectal surgery in the elderly (AUC 0.86)^[29,31].

Sarcopenia and colorectal cancer

Similar to frailty, the effect of sarcopenia on post-surgical outcomes of patients with colorectal cancer has only been evaluated in a limited fashion. Robinson *et al*^[68] prospectively examined 302 patients who underwent resection of colorectal cancer and noted that psoas density was a better predictor of postoperative complications compared with age, body mass index or preoperative patient comorbidities. The authors reviewed patient computed tomography scans to measure psoas area, density, subcutaneous fat, visceral fat and total body fat. Among the parameters studied, psoas density was found to be the best predictor of surgical complications among patients undergoing colectomy for colon cancer. In a separate prospective study by Lieffers *et al*^[39] that included 234 older patients who underwent

colon resection, sarcopenia was strongly associated with delayed recovery, postoperative infections (23.7% sarcopenic patients vs 12.5% non sarcopenic patients, $P = 0.025$), as well as an increased risk of discharge to a nursing facility (14.3% sarcopenic patients vs 5.6% non sarcopenic patients, $P = 0.024$)^[39]. Similarly, Reisinger *et al*^[50] reported a series of 331 older patients who underwent colorectal cancer surgery and demonstrated that a combination of age related parameters such as frailty, sarcopenia and malnutrition were strongly associated with adverse outcomes. Sarcopenia alone was predictive of 30 d in hospital mortality (8.8% sarcopenic vs 0.7% nonsarcopenic patients, $P = 0.001$). Most recently, Huang *et al*^[30] defined sarcopenia through a combination of monomorphometric measurements and physical performance and used it to define low postoperative outcomes. By this, the authors showed, that including the muscles' functional aspect (handgrip strength and 6-m usual gait speed) to the definition of sarcopenia results in a better prediction for postoperative complications as compared to measurement alone.

HEPATO-PANCREATO-BILIARY MALIGNANCIES

Surgery is commonly used to treat patients with a wide variety of hepato-pancreato-biliary (HPB) diseases. Many of these disease including liver, biliary, and pancreatic malignancies are more common in an aged population. In addition, HPB procedures tend to be complex operations that can be associated with substantial possible morbidity. As such, accurate preoperative assessment of aged patients being considered for HPB surgery is of particular importance.

In 1997, in one of the earlier studies to examine the impact of age on HPB surgery, Fong *et al*^[69] reported on the outcome of 133 patients over the age of 65 years who underwent a hepatic resection. In this study, Fong *et al*^[69] noted that age was an independent risk factor for increased risk of morbidity. Perhaps more importantly, however, the authors noted that major hepatic resection could be performed safely and with good functional outcomes among well-selected aged patients. Over the last several decades, multiple other investigators have similarly reported good outcomes in well-selected older patients undergoing hepatic resection^[70,71]. For example, Reddy *et al*^[71] reported on 856 patients who underwent a major hepatectomy (resection of 3 or more segments) and noted that increasing age was independently associated with postoperative mortality. In fact, each 1-year and 10-year increase in age resulted in an odds ratio of mortality after major hepatic resection of 1.036 and 1.426, respectively. In a separate study of 7764 patients who had colorectal liver metastasis, Adam *et al*^[72] noted that age was associated with outcome, but major resection could be performed in elderly patients with acceptable morbidity. The authors found higher

mortality and morbidity rates in older than in younger patients [3.8% and 32.3% in older, 1.6% and 28.7% in younger patients (both $P < 0.001$)] but did not further investigate frailty or sarcopenia in this cohort. Sixty-day postoperative mortality and morbidity were 3.8% and 32.3%, respectively, compared with 1.6% and 28.7% in younger patients. Of note, 5-year survival was relatively comparable even among very aged patients (70–75 years: 57.8% vs 75–80 years: 55.3% vs > 80 years: 54.1%), suggesting that surgery may have potential benefit even in very well selected aged patients.

Frailty and hepato pancreatico biliary malignancies

While age has been the topic of several investigations, the specific impact of frailty itself has been less well studied. Giovannini *et al.*^[73] suggested that a decrease in serum albumin may be a marker of frailty due to an altered albumin synthesis and the patient's inability to compensate for albumin loss. Unlike frailty, while still limited, several papers have investigated the impact of sarcopenia on outcomes after liver surgery^[40,43,74,75]. Several studies have noted an association between sarcopenia and both short- and long-term outcomes among patients undergoing hepatic surgery^[40,41,43,74,75]. For example, Durand *et al.*^[74] studied whether muscle atrophy was of prognostic value among patients with cirrhosis undergoing surgery. The authors demonstrated that transversal psoas muscle thickness was significantly associated with mortality, independent of Model for End Stage Liver Disease (MELD) score. In a different study, Valero *et al.*^[42] examined whether sarcopenia impacted the risk of post-operative complications following resection or transplantation in patients with primary liver tumors. Among 96 patients, the presence of sarcopenia was an independent predictive factor of post-operative complications, but was not associated with long-term survival. In a study that examined only liver transplant recipients, Englesbe *et al.*^[43] noted that psoas area correlated poorly with MELD score and serum albumin. Central sarcopenia strongly correlated with mortality after liver transplantation, as 1-year survival was 49.7% among transplant recipients with the smallest psoas area vs 87.0% among transplant recipients with the largest psoas area. Kaido *et al.*^[32] reported a similar effect on a cohort of 124 living donor liver transplant patients in 2013. In this study the overall survival rate in patients with low skeletal muscle mass was significantly lower than in patients with normal/high skeletal muscle mass ($P < 0.001$). Other studies have similarly noted that morphometric age correlated with morbidity and mortality after liver transplantation with better discrimination than chronological age^[44,76]. Sarcopenia has similarly been demonstrated to be an important prognostic factor for patients undergoing liver resection for colorectal liver metastasis. Peng *et al.*^[46] reported that sarcopenia was strongly associated with an increased risk of major complications, extended intensive care unit stay, and a longer overall hospital.

Sarcopenia and hepato pancreatico biliary malignancies

Similar to liver resection, frailty and sarcopenia have not been widely assessed in patients after pancreatic operations. Several studies have reported that age is a risk factor for increased morbidity and mortality^[77-79]. For example, in one large study that investigated over three-thousand patients who underwent pancreatic resection in the state of Texas, Riall *et al.*^[77] reported that increased age was an independent risk factor for mortality after pancreatic resection. In fact, in-hospital mortality increased with each increasing age group from 2.4% among patients < 60 years to 11.4% among patients > 80 years. Likewise, postoperative length of stay increased with each increasing age group, going from 11 to 15 d. Of particular interest was the authors' finding that the increase in mortality among older patients was most pronounced among those patients treated at a low vs high volume hospital. While these data and others suggest therefore that age may be associated with outcomes, multiple other studies have noted that pancreatic surgery can be performed safely in well selected older patients^[78-80]. Dale *et al.*^[33] prospectively evaluated the additional value of geriatric assessment in a cohort of older patients undergoing a pancreaticoduodenectomy for pancreatic tumors. Among 76 older patients, significant unrecognized vulnerability was identified using the geriatric assessment. In turn, Fried's exhaustion, a vulnerable elders survey score > 3, as well as a short physical performance battery score < 10 all correlated with an increased risk of severe complication after pancreaticoduodenectomy. As such, the authors concluded that geriatric assessment may help identify older patients at high risk for complication from pancreatic surgery.

Several series have similarly suggested that sarcopenia may be an important predictor of post-operative morbidity and mortality following pancreatic surgery^[45-48]. For example, Joglekar *et al.*^[48] reported a relation between sarcopenia defined by the psoas muscle density and worse outcome after pancreatic resection. In a separate study, Peng *et al.*^[45] examined 557 patients undergoing resection of pancreatic adenocarcinoma and reported on the impact of sarcopenia on outcomes following surgery. Sarcopenia was associated with an increased three year mortality (HR = 1.63, $P < 0.001$) (Figure 4A). Of note, even after controlling for tumor-specific factors such as poor tumor differentiation, margin status, and lymph node metastasis, sarcopenia defined by TPA remained independently associated with risk of long-term death. More recently, rather than assessing sarcopenia using only two-dimensional imaging, the same group reported on the effect of three-dimensional psoas volume (TPV) on outcomes following pancreatic resection^[47]. In this study, Amini *et al.*^[47] noted that more patients were identified as sarcopenic by TPA than TPV. Perhaps more importantly, while TPA-sarcopenia was not associated with a higher risk of postoperative complications (OR = 1.06), TPV-sarcopenia was as strong predictor of post-operative morbidity (OR = 1.79). On multivariate analysis, TPV

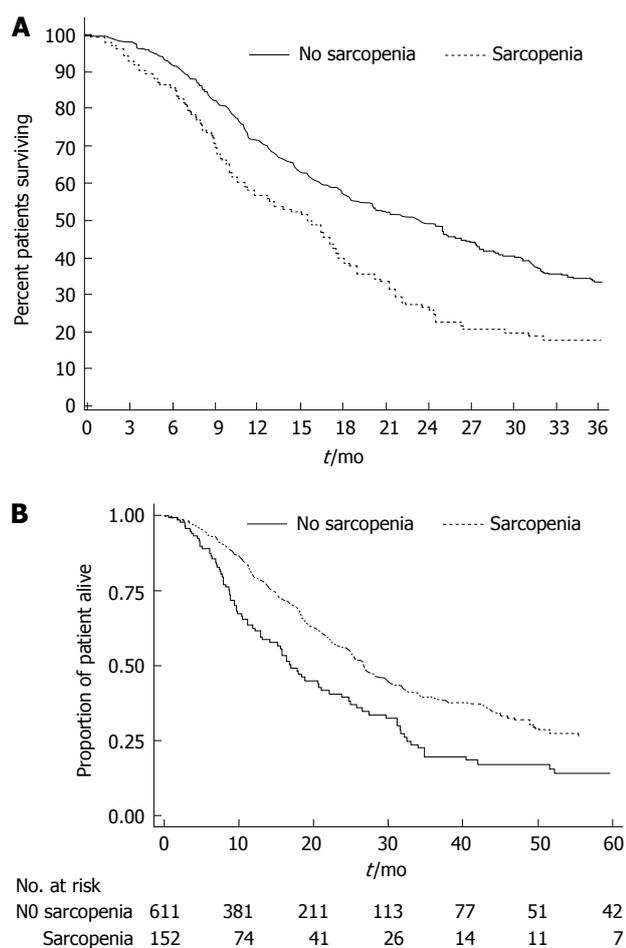


Figure 4 Sarcopenia was associated with an increased three year mortality. A: The presence of sarcopenia was also associated with the risk of death (no sarcopenia, 18.0 mo; 40.0% vs sarcopenia, 13.7 mo; 23.0% vs median, 3-yr survival, respectively; $P = 0.01$) in patients undergoing pancreatic surgery. Used with permission Peng *et al*^[45], 2012; B: The overall survival according to total psoas volume stratified by sarcopenia patients vs no sarcopenia patients quartiles in patients undergoing pancreatic surgeries. Used with permission Amini *et al*^[47], 2015.

- sarcopenia remained an independent risk factor of postoperative complications (OR = 1.69), as well as long-term survival (OR = 1.46) (both $P < 0.05$) (Figure 4B).

CONCLUSION

As the population ages, an increasing number of older patients will require complex gastrointestinal surgical procedures. While chronologic age is an important element in assessing a patient's peri-operative risk, physiologic age is a more important determinant of outcomes. Geriatric assessment tools are important components of the pre-operative work-up and can help identify patients who suffer from frailty. Such data are important, as frailty has repeatedly been demonstrated to be one of the strongest predictors of both short- and long-term outcome following complicated surgical procedures such as esophageal, gastric, colorectal, and HPB resections. Frailty can sometimes, however, be difficult to assess in an accurate and timely manner.

As such, there has been an increasing interest in determining a patient's "morphometric age". Sarcopenia, or wasting of lean muscle mass, has been noted to be an emerging important metric of frailty that is associated with peri-operative outcomes. As demonstrated by the data herein reviewed, screening of patients being considered for gastrointestinal surgery should include an assessment of frailty and sarcopenia to target high risk patients for pre-habilitation. Future studies will need to continue to define the optimal combination of factors (e.g., clinical, performance, and morphometric) to predict optimally a patient's peri-operative risk.

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Anal cancer and intraepithelial neoplasia screening: A review

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Abstract

This review focuses on the early diagnosis of anal cancer

and its precursor lesions through routine screening. A number of risk-stratification strategies as well as screening techniques have been suggested, and currently little consensus exists among national societies. Much of the current clinical rationale for the prevention of anal cancer derives from the similar tumor biology of cervical cancer and the successful use of routine screening to identify cervical cancer and its precursors early in the disease process. It is thought that such a strategy of identifying early anal intraepithelial neoplasia will reduce the incidence of invasive anal cancer. The low prevalence of anal cancer in the general population prevents the use of routine screening. However, routine screening of selected populations has been shown to be a more promising strategy. Potential screening modalities include digital anorectal exam, anal Papanicolaou testing, human papilloma virus co-testing, and high-resolution anoscopy. Additional research associating high-grade dysplasia treatment with anal cancer prevention as well as direct comparisons of screening regimens is necessary to develop further anal cancer screening recommendations.

Key words: Anal cancer; Secondary prevention; Anal Papanicolaou test; High-resolution anoscopy; Screening

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Core tip: Anal cancer is a low prevalence, highly morbid disease. With the success of secondary prevention practices for other human papilloma virus-associated malignancies, screening strategies may similarly decrease rates of anal cancer. No national guidelines formally support screening. This review summarizes possible screening modalities and what further evidence is needed to support routine screening for anal cancer.

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INTRODUCTION

Anal cancer is a rare disease whose outcomes continue to underperform those of other malignancies. There are approximately 7000 cases of anal cancer in the United States annually^[1], and the 5-year survival rate is 65.7%^[2]. Unlike other common gastrointestinal malignancies, the incidence of anal cancer is increasing at an average rate of 2.2% per year for the last decade. This increasing rate is above a historical baseline in the 1970s and 1980s where anal cancer incidence remained unchanged^[2,3]. Much of this increase is due to the rise of new high-risk immunocompromised populations in the last three decades, including chronic human immunodeficiency virus (HIV) infected patients and organ transplant recipients. This review will focus on squamous cell carcinoma of the anus, which is responsible for 80% of all anal cancers^[4].

Anal cancer has long been a delayed diagnosis. Historical studies reported a delay of more than two years in diagnosis in more than half of patients^[5], and 44% of patients present with disseminated disease at diagnosis^[2]. This epidemiologic trend is even more troubling when one considers that early stage anal cancer has been shown to respond exceptionally well to low-morbidity chemoradiation therapy while later stage disease often requires highly morbid and quality of life-changing surgical interventions such as abdominoperineal resection with a permanent colostomy for residual primary tumor and groin dissection for inguinal nodal metastases.

Historically, anal cancer was sufficiently rare that population screenings for the disease were not warranted. After 1997, the American Cancer Society dropped its recommendation for annual digital rectal examinations in favor of colonoscopies and sigmoidoscopies for colorectal cancer screening. This further contributed to a lack of screening for anal cancer, in an era where high-risk anal cancer populations were coming into existence.

It has been recognized that certain groups are at substantially higher risks of anal cancer than the general population. The association of sexually transmitted infections and sexual practices with anal cancer has been recognized since the 1980s^[6]. One of the most closely associated sexually transmitted infections has been human papilloma virus (HPV), which was found in 88% of anal cancer patients in a case-controlled cohort^[7] as well as in tissue samples containing anal intraepithelial neoplasia, an anal cancer precursor^[8]. Other risk factors of anal cancer identified include smoking^[9] and organ transplantation^[10].

A number of similarities exist between squamous cell anal cancer and cervical cancer. Both occur at squamocolumnar junction epithelium. The transformation zones of the anal canal and the cervix are both characterized by high turnover epithelium that is thought to be particularly vulnerable to malignancy-inducing genetic alterations^[11]. Both are HPV-associated which is thought to promulgate changes to cells' DNA^[12]. Immu-

nosuppression is also an increasingly important risk factor for both cancers likely due to the increased activity of HPV seen in immunocompromised tissue substrates^[13-15]. Finally, both types of cancer also have widely divergent outcomes for early vs late presenting disease^[16].

Unlike anal cancer, diagnoses of cervical cancer have been markedly reduced in the last 40 years. Between 1975 and 2010, the incidence of cervical cancer has decreased by more than 50%^[16]. This public health success story is largely attributed to the widespread and routine use of cervical cancer screening, primarily employing the cytology-based cervical Papanicolaou (Pap) test^[17]. It is thought that a similar screening effort applied to anal cancer could potentially reverse the disturbing recent trends in disease incidence.

This review focuses on the early diagnosis of anal cancer and its precursor lesions through routine screening. A number of risk-stratification strategies as well as screening techniques have been suggested (Table 1), and currently little consensus exists among national societies (Table 2). No national screening guidelines for anal cancer exist, and the AIDS advocacy groups that note the increased risk of anal cancer in the HIV-positive population differ in their recommended approaches^[18-21]. We provide here a balanced examination of the current clinical science to guide both practitioners and policy-makers in this rapidly developing field.

ANAL CANCER AND AIN PATHOPHYSIOLOGY

Although this review will not cover the cancer cell biology of anal cancer in detail, a general understanding is helpful because it influences the rationale for routine screening. Much of the current consensus on how anal dysplasia evolves is derived directly from cervical cancer literature. In cervical cancer, it is well recognized that the human papilloma virus infection is a necessary step in the development of cervical dysplasia and ultimately invasive neoplasia^[22]. Anal cancer is a more heterogeneous set of malignancies with anal canal tumors that have pathology more similar to squamous cell cervical cancer in addition to perianal squamous cell carcinoma that behaves more like penile or vulvar cancer. Anal canal tumors' similarity to cervical cancer is also shared by the high rate of HPV co-infection - particularly HPV 16 subtypes - in the latter with studies reporting rates over 90% while perianal tumors' HPV co-infection rate vary from 30%-80%^[23-25]. This ongoing close association between HPV and anal cancer has led to parallel frameworks of oncogenesis for both anal and cervical cancer.

Like cervical cancer, anal cancer is thought to most frequently develop at the transformation zone between squamous and columnar epithelium of the anal canal. HPV infects squamous epithelial cells, and the interaction between virion gene expression and cellular growth regulators leads to loss of differentiation and clonal

Table 1 Summary characteristics of anal cancer screening modalities

	DARE	Anal Pap test	HPV testing	High resolution anoscopy
Sensitivity ^[56,57,61,62,101]	Not studied	69%-93%	Alone: 100% Co-testing with Pap ^[49] : 72%-96%	Current diagnostic standard
Specificity ^[56,57,61,62,101]	Not studied	32%-59%	Alone: 16%	Current diagnostic standard
Resource availability	N/A	Ubiquitous	Ubiquitous	Highly selective centers
Provider availability	Universal	Specialty clinics	Specialty clinics	Highly selective centers
Learning curve	Part of usual clinical training	Part of usual clinical training	Part of usual clinical training	> 200 cases
Current consensus ^[52]	Annually, all HIV-positive patients	Annually in highest-risk groups	Alone: No recommendation Co-testing: No recommendation	Second-line screen following positive Pap test

DARE: Digital anorectal exam; HPV: Human papilloma virus; N/A: Not applicable; HIV: Human immunodeficiency virus; Pap: Papanicolaou.

Table 2 Professional society recommendations for anal cancer screening

	Routine screening of general population	Routine screening of high-risk individuals	Assesses modalities for diagnosis	Specific modalities assessed
American Society of Colon and Rectal Surgeons ^[54]	No recommendation	No recommendation	Screening and surveillance	Anal Pap test, high-resolution anoscopy
European Society of Medical Oncology	No recommendation	No recommendation	Surveillance only	Digital anorectal exam, standard anoscopy, computed tomography, magnetic resonance imaging
European Society of Surgical Oncology and Oncology ^[102]				
National Comprehensive Cancer Network ^[103]	No recommendation	No recommendation	Surveillance only	Digital anorectal exam, standard anoscopy
Centers for Disease Control and Prevention ^[104]	No recommendation	No recommendation	Screening and surveillance	Digital anorectal exam, HPV testing
New York State Department of Health ^[52]	No recommendation	All HIV infected adults	Screening only	Digital anorectal exam, anal Pap test, high resolution anoscopy
HIV Medicine Association of the Infectious Diseases Society of America ^[20]	No recommendation	Men who have sex with men, women with a history of abnormal cervical Pap tests, and all HIV-positive persons with genital warts	Screening only	Digital anorectal exam, HPV co-testing, anal Pap test, high resolution anoscopy
British HIV Association ^[21]	No recommendation	No recommendation	Screening and surveillance	Digital anorectal exam, anal Pap test, high resolution anoscopy

HIV: Human immunodeficiency virus; HPV: Human papilloma virus; Pap: Papanicolaou.

proliferation^[12]. These cells have a predictable pattern of stepwise cellular transformation that leads from normal squamous epithelium to low-grade dysplasia to high-grade dysplasia to invasive cancer^[12,26-28].

HPV-associated cellular transformation is characterized by cyclical cellular proliferation and regression. An area of cellular atypia may progress to low-grade dysplasia before then regressing to normal tissue. The occurrence of cancer is when a particular transformed cell line breaks out of this characteristic cycling and linearly progresses to invasive disease^[11].

The natural history of disease progression is largely unknown. Historical reports of the incidence of the progression from premalignant to invasive disease range from 2%-9%^[29-32]. However, more recent series have reported rates as high as 13%-50% in immunocompromised patients managed expectantly^[27,33].

Several case reports point toward anal squamous cell cancer arising in a background of high-grade dysplasia, supporting the dysplasia-to-cancer sequence. Per Scholefield *et al.*^[34] the estimated risk of progression

from anal intraepithelial neoplasia (AIN) to invasive anal cancer is 10% in 5 years. However, this rate needs to be interpreted with caution as progression rates may vary according to such factors as eradication of disease by surgical therapy and the aforementioned risk factors that increase the risk of progression to invasive disease. Furthermore, Simard *et al.*^[35] showed that the incidence of high-grade dysplasia in men in San Francisco has been on the rise - increasing by 11.48% per year between 2000 and 2009.

The basic principle behind screening for anal dysplasia is the early identification of these proliferating cell lines that have established irreversible high-grade dysplasia or local invasive disease. Early stage anal cancer 5-year survival rates exceed 80% while disseminated disease 5-year survival rates are 30%^[2]. Clinical studies demonstrating a morbidity or mortality benefit from routine screening for anal dysplasia are currently ongoing (see "Future Directions"), and the success of such efforts for cervical cancer suggests that further consideration is warranted.

AT-RISK POPULATIONS

Compared to other cancers, anal cancer is rare and no support for general population screening exists. Anal cancer is the 26th most common cancer type in the United States with approximately 7000 cases a year^[1]. Although evidence suggests that the majority of anal cancers are initially asymptomatic^[36], such a low pre-test probability does not make screening tests feasible for the general population.

However, there are populations with disproportionate prevalence of anal cancer that are more conducive to group-wide screening. Immunosuppressed patients are increasingly recognized as one of the groups at highest risk for anal cancer^[13,37]. Much of this recognition has developed over the rise of the HIV/AIDS epidemic in the last three decades. Infection with HIV is associated with a 30-fold increased lifetime risk in anal cancer and a 4-fold increase in 5-year mortality^[37,38]. Although sexual practices - particularly anoreceptive intercourse - have been previously associated with anal cancer, recent studies have shown that the risk of anal cancer in HIV-positive individuals exists independently of sexual practices^[39,40]. The risk of anal dysplasia progression appears to correlate directly with degree of immunosuppression as measured by T cell CD4⁺ count with a cell count less than 200 cells/mm³ most closely associated with increased prevalence^[41-43]. Surprisingly though increased access to highly active antiretroviral therapies has not eliminated the increased risk of anal cancer in the HIV-infected population. It is thought that immune system restoration does not entirely eliminate the increased risk of dysplastic changes and then antiretroviral treated patients are living longer thereby increasing the lifetime interval risk of disease incidence^[44].

Similarly, other immunosuppressed populations share an increased incidence of anal cancer. Increased rates of anal cancer have been identified through controlled studies in kidney^[45,46] and liver transplant recipients^[47]; anogenital malignancy rates after renal transplant are estimated to be 30- to 100-fold higher than the general population^[48].

Currently, no national or international society formally supports routine screening of at-risk populations for anal dysplasia. This lack of recommendation stems from the absence of high-quality studies that demonstrate improved morbidity and mortality for those participating in routine screening. Nevertheless, practice patterns by infectious disease specialists suggest that anal dysplasia screening of high risk individuals is becoming common^[49-51], and influential regional societies like the New York State Department of Health AIDS Institute have begun recommending routine annual examination of the anus in all HIV-infected adults and cytologic testing in ultra high-risk HIV-positive patients such as men who have sex with men (MSM), those with a history of condylomata, and women with cervical or vulvar dysplasia^[52]. Recent population health studies have

even suggested that such selective screening remains inadequate and that anal dysplasia occurs frequently enough in the general HIV-positive population that all should undergo some form of extended screening^[53].

SCREENING MODALITIES FOR ANAL CANCER PREVENTION

Digital anorectal exam

The digital anorectal exam (DARE) is widely considered to be an essential but not sufficient component of any anal cancer screening evaluation. Although the American Society of Colon and Rectal Surgeons does not formally recommend routine screening for anal cancer, a visual perianal skin exam, DARE, and anoscopy are the suggested initial workup for any patient with history or symptoms concerning for anal cancer^[54]. Any abnormal finding necessitates biopsy. There is no evidence that has demonstrated a screening benefit from physical examination and historic surveillance studies with digital examination suggest low sensitivity for recurrent disease^[55]. But the risks to the patient are minimal. The leading guidelines for HIV-infected adults recommend an annual DARE with further screening only if meeting certain high-risk criteria such as MSM, prior history of anogenital condylomas, and women with abnormal cervical or vulvar histology^[52]. As the availability of enhanced low cost screening practices such as the anal Pap test and high-resolution anoscopy become more widely available the accepted adequacy of the DARE as a primary screening test will likely diminish.

Anal Pap test

The cervical Pap test was introduced in the 1960s to help identify premalignant cervical dysplasia that could be intervened upon. Although never demonstrated in a randomized clinical trial, the introduction of the Pap test coincided with a substantially decreased incidence of invasive cervical cancer^[17]. The basis of the test is to collect a swabbed cellular sample that is then collected and prepared on a microscope slide for examination by a pathologist. A number of pathology classification systems have been developed with the modified Bethesda System classification in most contemporary use^[12].

Anal Pap testing was more recently introduced in the 1990s with a similar methodology and grading scheme as a primary screening tool for a premalignant anal dysplasia^[56]. The technique has been well described and is analogous to the cervical Pap test^[52]. Sensitivity and specificity have been shown to be similar to cervical cytology^[57]. Using large cohort databases for retrospective analysis, Markov modeling of the anal Pap test has demonstrated that its role in anal cancer prevention is likely both cost-effective and efficacious^[58].

The test is not without its limitations. Like the cervical Pap test, neither cytologic test has ever been studied in a randomized clinical trial between cytologic screening and

expectant management. The anal Pap test also suffers from a similar inter-rater unreliability of cervical cytologic testing which is then further complicated by varied and evolving classification systems^[59,60]. Sensitivity and specificity estimates range widely from 69% to 93%, and 32% to 59%, respectively^[56,57,61,62]. The anal Pap tests specificity for diagnosing the correct degree of dysplasia is even less accurate with Pap testing routinely reporting low-grade atypia for lesions that ultimately are found to be high-grade dysplasia^[63]. Moreover, sensitivity decreases in the highest risk groups. False-negative cytology results in MSM can be as high as 23% for HIV-negative patients, and 45% for HIV-positive patients^[64]. Such high rates of missed pathology in high-risk populations most needing effective anal cancer screening have led some to suggest that anal Pap tests are inadequate on their own and should be paired with a direct visual modality such as high-resolution anoscopy in order for them to be considered an appropriate screening test^[64]. Even with these limitations, the anal Pap test's low cost, technical ease and familiarity to many primary care physicians, and acceptable sensitivity have supported its role as the most practical screening option currently available^[52,54].

HPV testing

HPV testing is typically performed as part of a Pap test. With modern, liquid-based Pap testing, the same swab sample can be used for both cytology as well as HPV DNA testing^[65].

The necessity of HPV for cervical cancer is well established^[66] and its relationship as a prerequisite for cervical dysplasia has been used as the rationale for routine HPV testing with abnormal Pap test results. The use of HPV testing as a risk stratification tool for cervical dysplasia has become standard practice^[11,67]. Some have even argued that HPV testing as a first-line screening tool for cervical cancer prevention may be sufficient without the need for cytology. Multiple large trials have demonstrated that a single negative HPV test virtually eliminated the risk of death from cervical cancer^[68,69]. The United States Food and Drug Administration approved an HPV primary screening test in 2014^[65].

The role of HPV in anal cancer is thought to be nearly as important, and many studies have routinely assessed HPV status when screening for anal dysplasia^[70-72]. In select high-risk populations, HPV testing has been shown to be an important and clinically useful screening tool in conjunction with anal Pap testing^[73]. Descriptive studies also associate more rapid progression of anal dysplasia with high-risk subtypes of HPV^[42,74,75]. However, early studies have not shown any benefit to anal cancer prevention with or without HPV testing^[76]. More broadly, no guidelines formally recommend HPV testing alone or in combination with Pap testing. Availability of this diagnostic modality is also limited by the lack of coverage by most insurance plans and thereby is a limited offering at most healthcare institutions^[77]. The increasing benefit of HPV testing as part of cervical cancer prevention

practices suggests that the nature and scope of the use of HPV testing for anal cancer prevention will need reconsideration in the future.

High resolution anoscopy

High resolution anoscopy has been proposed as a screening modality that addresses the sensitivity issues of the other methods described above. Modeled off of colposcopy for cervical cancer, high resolution anoscopy uses a high-magnification colposcope with a transparent anoscope to examine the entire anal canal and perianal skin under close visual inspection. Five percent acetic acid is used to identify areas of rapid cell growth; Lugol's solution is employed to improve biopsy yield and accuracy since higher grade dysplastic lesions initially found with acetic acid will not uptake Lugol's unlike low-grade dysplasia^[78]. Originally reported in Europe in 1989^[79], the procedure has been practiced and comprehensively described by its American introducers at the University of California San Francisco since the early 1990s^[78].

The benefits of high resolution anoscopy (HRA) remain unchallenged. Decision models have also demonstrated the superiority of HRA-only screening to combined modalities^[80]. The leading recommendations from the New York State Department of Health AIDS Institute state that HRA be considered standard of care for any patient with prior abnormal anal Pap test^[52]. Its most important contribution being that it effectively addresses some of the limitations of anal cytology-based screening practices^[81]. A longitudinal study of 368 asymptomatic MSM undergoing serial HRAs for a mean of 4.2 years found that 11% of high-grade dysplasia identified with HRA coincided with normal results from an anal Pap test^[82]. In particular, high-risk groups such as HIV-positive MSM have lower sensitivity results from anal Pap testing^[83]. Anal Pap testing may be useful as a way of alerting HRA clinicians to more closely examine suspicious lesions for low- vs high-grade heterogeneity thereby increasing biopsy yields. Some have suggested that HRA and anal Pap test co-testing be performed as a useful quality control measure for HRA^[82,83].

Unfortunately, HRA's usefulness as a screening test is impaired by the logistical needs of its use. Colposcopes are an additional piece of equipment needed for the clinic setting and training for HRA is important^[52]. Surprisingly, HRA has been shown to be cost-effective though with the real obstacle being availability^[80]. Anecdotally, the original group of researchers who brought HRA to the United States note a high degree of dexterity and technical prowess required to effectively visualize the entire anal canal and obtain reliable biopsy specimens^[78]. A new provider logged the first 2 years of cases performed and found that it took approximately 200 cases before results demonstrated no missed high grade lesions found on follow-up^[84]. This substantial learning curve and the lack of practitioners trained formally in residency or fellowship have led to a lack of providers able to provide HRA as a screening option. Hence, HRA is typically utilized as a second-line screening tool for abnormal Pap test or HPV

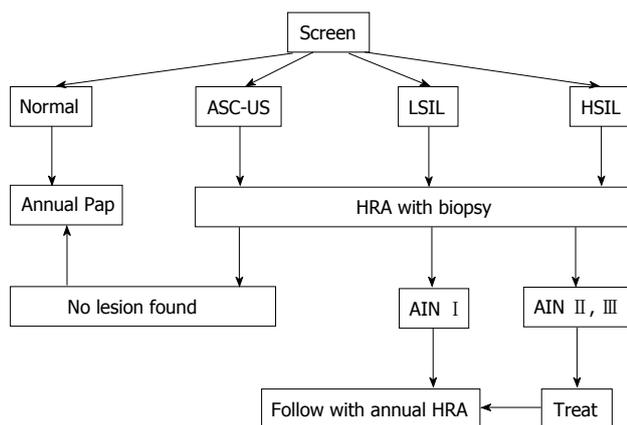


Figure 1 San Francisco algorithm for anal cancer screening of high-risk patients. ASC-US: Atypical squamous cells of undetermined significance; LSIL: Low-grade squamous intraepithelial lesions; HSIL: High-grade squamous intraepithelial lesions; Pap: Papanicolaou; HRA: High-resolution anoscopy; AIN: Anal intraepithelial neoplasia (adopted from Chin Hong, Palefsky. *Clin Inf Dis* 2002).

results^[53,85].

AREAS OF UNCERTAINTY

As described above, the anal cancer prevention literature is rife with screening techniques resulting from rational considerations of cancer biology but with minimal clinical evidence demonstrating their efficacy. This situation is further worsened by the lack of clear-cut guidelines from any national or international society of how best to address this rare but devastatingly morbid malignancy. Some of the most important ongoing clinical questions to be answered are noted here.

First, one of the most critical areas of further research is optimizing both the screening process and post-screen recommendations for a positive result. Until the data provides further guidance on HPV testing or sufficient HRA-trained providers are available to staff screening clinics, the anal Pap smear will remain the standard of care for anal cancer prevention's primary screening modality. What to do with a positive screening test is a matter of ongoing debate. Without formal recommendations, individual expert opinion has driven institutions' screening processes. The most widely disseminated screening algorithm was popularized by researchers at the University of California San Francisco and is reproduced in Figure 1^[29]. The authors' institution uses a modified algorithm that provides HRA screening for all referred patients (Figure 2). The basis of both of these algorithms is that all high-risk patients (*e.g.*, HIV with high-risk sexual history or practices, MSM) get screened annually with an anal Pap test; all atypical cytology results are referred for HRA; and AIN I is followed yearly with HRA while AIN II or III is surgically removed. The diverse modalities for removal of high-grade dysplasia and carcinoma *in situ* are beyond the scope of this review but little guiding evidence exists and most practice is based off of cervical cancer excisional

biopsy techniques.

There is also increasing evidence that the stringent risk stratification currently being employed may be too restrictive. The commonly followed New York State Department of Health's AIDS Institute guidelines for anal cancer screening stratify HIV-positive patients into intermediate risk vs high risk groups. The latter risk stratified group recommends enhanced screening with annual anal Pap tests for any HIV-positive patient who also endorses MSM behaviors, history of anogenital condylomata, or women with history of abnormal cervical or vulvar pathology^[52]. Increasing evidence suggests that HIV-positivity alone affords one a prevalence of approximately 20% for at least some form of anal intraepithelial neoplasia^[39,40,64,86,87]. Such high rates of atypia may be unacceptably high for a population that under current recommendations would only receive a symptoms questionnaire, perianal visual inspection, and digital rectal examination. The previously mentioned high rate of cellular turnover and immunosuppression also suggests that less traditionally screened groups such as all anoreceptive sex practitioners and transplants would both warrant from annual screening as well.

Finally, one other line of inquiry that continues to be considered is the perception of patients who have to undergo these anorectal inspections annually awake and often with tissue samples taken. All of the evidence argues against this concern being a real obstacle to routine screening. Self-performed anal visual inspection^[88], provider-performed digital rectal exam^[89], and anal Pap testing^[90,91] have all been explored with high-risk groups with favorable results. A Toronto study repeatedly screened patients for psychological distress at multiple points throughout the patient's screening algorithm and found less than one-third ever felt negatively distressed throughout the process^[92]. Rather than emotional distress, the greatest patient-oriented obstacles to care appear to be lack of knowledge of increase anal cancer risk and economic barriers to screening^[90,91,93].

FUTURE DIRECTIONS

While controversies remain that will continue to shape the management of anal cancer screening today, there are also a number of expected future developments that may drastically change how we approach anal cancer prevention.

An ongoing Australian study may help address the role of HPV testing in anal cancer screening as well as provide more light on an evidence-based screening plan that incorporates one or more of the modalities described in this review. The Study of the Prevention of Anal Cancer (SPANC) is a 3-year prospective cohort that began recruitment in 2010 with follow-up planned through 2018 that will examine the overlapping roles of digital anorectal exam, HPV testing, anal Pap tests, and HRA^[94]. Each participant will undergo all of these potential screening studies over multiple time points throughout the study, and it is expected that comparisons of sensitivity and

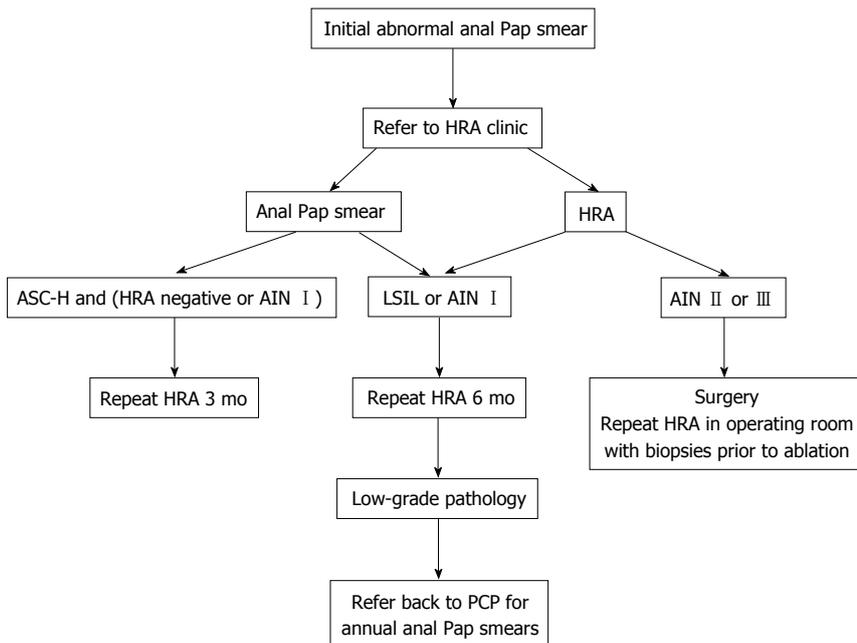


Figure 2 Johns Hopkins Hospital algorithm for anal cancer screening of high-risk patients. Pap: Papanicolaou; HRA: High-resolution anoscopy; ASC-H: Atypical squamous cells of undetermined significance, cannot rule-out high-grade dysplasia; AIN I : Anal intraepithelial neoplasia I ; PCP: Primary care physician; LSIL: Low-grade squamous intraepithelial lesion; AIN II : Anal intraepithelial neoplasia II ; AIN III : Anal intraepithelial neoplasia III.

specificity as well as the practical matters of performing each screen will be better understood. The study selected HIV-positive men over 35 years old living in the Sydney area with a total recruitment of over 350 participants. It is likely that the results of this study will provide a major contribution to the ongoing debate surrounding how best to utilize to the various anal cancer screening modalities at clinicians' disposal.

The ANCHOR Study [anal cancer high-grade squamous intraepithelial neoplasia (HSIL) Outcomes Research] is an ongoing 5-year prospective randomized trial that has the goal of enrolling 5085 patients in the United States. This study aims to follow HIV-positive men over age 35 years with the diagnosis of HSIL over a 5-year period by anal Pap testing and HRA. The two arms of the study include a monitoring arm and a treatment arm for HSIL by ablation through infrared coagulation, with the ultimate goal of determining whether active surveillance with ablative treatment of HSIL will ultimately decrease the incidence of anal cancer^[95].

There are also promising early signs to suggest that anal cancer may be an even more rare disease in the future. The HPV vaccine was developed out of the longstanding consensus that HPV infection is a necessary precursor to cervical cancer. Since its 2006 introduction the HPV vaccine has already been shown to reduce the prevalence of HPV infection among vaccinated populations. Estimating the reduction in cervical cancer cases from the already observed reduced in HPV infection suggests that disseminated vaccination will eliminate more than half of cervical cancers each year^[96]. The similar tumor biology of cervical cancer and anal cancer suggests that HPV vaccination *via* herd immunity and more recent recommendations to vaccinate men

as well will lead to a similar reduction in HPV-associated anal cancer^[97]. There have also been clinical trials to demonstrate the efficacy of the HPV vaccine at reducing anal HPV infection^[98,99]. This supportive evidence helped support a change in the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practice's recommendation to begin routine HPV vaccination of all young males in addition to existing recommendations for female-only vaccination^[100]. If general population uptake of these vaccine-based prevention practices is as successful as the early years suggest, it is likely that there will be dramatic reductions in HPV-associated cancer rates. Changes in prevalence will likely influence what kind of secondary prevention measures are appropriate for anal cancer screening later in life.

CONCLUSION

The low but rising incidence of anal cancer - particularly in vulnerable populations - makes it a concerning and difficult disease to manage with existing evidence-based care. Studies on its diagnosis and management are limited, and nearly all anal cancer guidelines avoid any direct recommendation regarding routine screening. The state of the literature suggests that further descriptive studies will be inadequate to advance consensus. Instead, large randomized clinical trials are necessary to demonstrate the increasing consensus among practitioners that anal cancer screening offers a cost-effective and prevalence lowering intervention in high-risk groups. The SPANC and ANCHOR studies will be helpful in determining whether routine screening through to a cancer diagnosis will ultimately be necessary to build the evidence for a population-wide recommendation.

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Esophageal surgery in minimally invasive era

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Abstract

The widespread popularity of new surgical technologies such as laparoscopy, thoracoscopy and robotics has led many surgeons to treat esophageal diseases with these methods. The expected benefits of minimally invasive

surgery (MIS) mainly include reductions of postoperative complications, length of hospital stay, and pain and better cosmetic results. All of these benefits could potentially be of great interest when dealing with the esophagus due to the potentially severe complications that can occur after conventional surgery. Moreover, robotic platforms are expected to reduce many of the difficulties encountered during advanced laparoscopic and thoracoscopic procedures such as anastomotic reconstructions, accurate lymphadenectomies, and vascular sutures. Almost all esophageal diseases are approachable in a minimally invasive way, including diverticula, gastro-esophageal reflux disease, achalasia, perforations and cancer. Nevertheless, while the limits of MIS for benign esophageal diseases are mainly technical issues and costs, oncologic outcomes remain the cornerstone of any procedure to cure malignancies, for which the long-term results are critical. Furthermore, many of the minimally invasive esophageal operations should be compared to pharmacologic interventions and advanced pure endoscopic procedures; such a comparison requires a difficult literature analysis and leads to some confounding results of clinical trials. This review aims to examine the evidence for the use of MIS in both malignancies and more common benign disease of the esophagus, with a particular emphasis on future developments and ongoing areas of research.

Key words: Esophageal disease; Esophageal cancer; Laparoscopic; Robotic; da Vinci; Heller; Reflux disease; Esophageal diverticula

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Core tip: Minimally invasive surgery for esophageal diseases is very attractive for reducing potentially serious complications that can occur after conventional surgery. However, if the oncologic long-term results remain the cornerstone of any procedure to treat malignancies, determining the outcomes of surgery for benign diseases requires a deep analysis of published evidence

and a comparison with alternative pharmaceutical or endoscopic treatments.

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INTRODUCTION

For many years, esophageal surgery has been recognized as very challenging for surgeons and risky for patients^[1-3]. However, subspecialized training of surgeons and a case-load centralization have been shown to reduce both perioperative mortality and the so-called "failure to rescue" rates after a life-threatening complication occurs^[2,4].

This type of surgery is complicated by the deep location of the esophagus in the neck, the posterior mediastinum and the upper abdomen. Moreover, the esophagus crosses all of these sectors very close to major vascular structures, including the carotids, the jugular vein and the aorta, while the trachea and the pericardium have important connections. Furthermore, the absence of a formal serous layer leads to unsafe anastomosis with a great risk of leakage.

All of these issues, together with the older age and comorbidities of many patients affected by esophageal cancer, could explain the disappointing outcomes of patients who are candidates for surgery. In this scenario, the adoption of the concept of a minimally invasive (endoscopic, thoraco-laparoscopic and robotic) approach could represent an attractive and valuable option.

The introduction of the da Vinci[®] Robot system to surgical practice added other benefits in terms of feasibility of the most complex esophageal procedures, which were previously precluded by pure laparoscopy and thoracoscopy procedures.

The proven and unquestionable advantages of minimally invasive surgery (MIS) are mainly represented by a reduction in pulmonary complications, wound infections, postoperative pain, and length of postoperative stay compared to open surgery. A superior cosmetic result is an additional benefit, especially when dealing with benign diseases in younger patients. Another recent field of research has demonstrated the important role of MIS in decreasing the pro-inflammatory and immunologic responses to surgery, which is, hypothetically, related to improved immediate or even long-term oncologic results^[5,6].

However, many of the minimally invasive surgical esophageal procedures failed to reach a consistent level of evidence-based efficacy to enable their routine application^[5]. The evidence-based literature is limited for many reasons. First, there is an intrinsic and well-known difficulty in conducting clinical surgical research.

Second, a relatively low incidence of esophageal diseases (*i.e.*, cancer) compared to stomach and colorectal cancers limits the gain of sufficient experience in Western countries. Finally, the large spectrum of new technologies, including laparoscopy, thoracoscopy, robotics, hybrid procedures and endoscopy, contributes to unclear and confusing results in clinical trials^[7].

We focused this review on minimally invasive surgical procedures, including laparoscopy, thoracoscopy and robotics, for the treatment of the more frequent esophageal diseases, with an emphasis on clinical outcomes rather than on the technical details of each approach. Pure endoscopy, although recognized as the standard of care in some esophageal impairments and as important in many others, does not represent the core focus of article and was treated marginally.

A search of the PubMed, EMBASE and Cochrane databases through March 2015 was conducted, including important cross-matched manual references. Randomized controlled clinical trials (RCTs) and meta-analyses were considered a priority. Data arising from English-written, multicenter, international studies and those with long-term follow-up and oncologic results were also of major interest. A few small studies on the feasibility of the newest procedure were also included.

REFLUX DISEASE AND HIATUS HERNIA

The largest number of medical consultations for esophageal diseases involve symptoms related to hiatus hernia and gastroesophageal reflux disease (GERD). Fortunately, most of the affected patients are managed properly by a medical regiment of proton pump inhibitors (PPIs) and drugs targeted to dyskinesia. However, a subgroup of patients requires further invasive approaches, including endoscopy and surgery, while a few with long-standing disease are at risk of developing cancer.

It is commonly accepted that laparoscopic fundoplication (LF) greatly improves GERD symptoms, and it is considered as the standard operation, although in some patients symptoms can recur, necessitating a return to PPI use^[8]. Interestingly, the best surgical results are achieved in those patients with optimal responses to medical therapy, which reflects an ongoing health-policy and cost-efficacy problem^[9-11]. Morbidly obese patients require peculiar integrated multidisciplinary surgical approaches and will not be considered further in this study.

A debate that has lasted for years still exists on the extent of the stomach wrap (total or partial). The most common approaches are the classical 360° posterior fundoplication [laparoscopic Nissen fundoplication (LNF)], the 270-degree posterior fundoplication [laparoscopic Toupet fundoplication (LTF)], the 180-degree laparoscopic anterior fundoplication (180-degree LAF) and the 90-degree anterior laparoscopic anterior fundoplication (90-degree LAF or Dor fundoplication). All of these partial fundoplications have been adopted to avoid the post-operative negative symptoms associated

with LNF (mainly gas bloating syndrome and dysphagia).

Neither of the two approaches (partial vs total plication) has been demonstrated to be sufficiently superior to justify abandoning the other completely. A recent, updated selective review^[12] concluded that LTF is the therapy of choice for normal-weight GERD patients who qualify for surgery because no better pharmaceutical, endoluminal or surgical alternatives exist to date.

The technical option of performing a laparoscopic 180-degree LAF should be validated compared to the Toupet fundoplication, while the division of the short gastric vessels is not recommended, nor is the use of a boogie or a mesh in the vast majority of patients undergoing surgery^[11]. Interestingly, anti-reflux surgery is considered to be a field for expert surgeons, although no consensus exists on the adequate learning curve^[12].

Most of the benefits of LF for patients suffering from GERD still persist after long-term follow-up. A multicenter Scottish trial^[13] included more than 350 patients randomized to medical management and surgery (or who expressed a preference for one arm over the other) who were followed for five years using structured questionnaires. The authors reported that 44% of those who underwent surgery and 82% of those who had initial medical management were still taking anti-reflux medications. Differences in the REFLUX scores significantly favored the surgery group (mean difference 8.5, 95%CI: 3.9-13.1, $P < 0.001$, at five years). Postoperative complications that required surgical intervention occurred in 3% of patients, while 4% had further reflux-related operations, most often revision of the wrap.

Few rigorous articles have been published on the robotic approach to GERD and most of those compared it to open or laparoscopic techniques. Globally, the updated surgical approach to GERD has led to a hard scientific comparison among medical therapies, the endoscopic approach and surgery using an open, laparoscopic or robotic route. Unfortunately, these types of studies are very difficult (if not utopian) to design and conduct^[7].

One of the largest analyses was that published by Owen^[14], which included more than 12000 patients from an American national database. The group was retrospectively divided into those who received open fundoplication (OF), LF, and robot-assisted fundoplication (RLF). Interestingly, RLF matched favorably with OF in terms of morbidity (5.6% vs 11%; $P < 0.05$), length of stay (LOS) (6.1 ± 7.2 d vs 3.0 ± 3.5 d; $P < 0.05$), intensive care unit (ICU) admissions (11.5% vs 23.1%; $P < 0.05$), and cost (United States \$10644 \pm 6041 vs United States \$12766 \pm 13982; $P < 0.05$), although LF remained superior to RLF when considering the 30-d re-admission rate (1.8% vs 3.6%; $P < 0.05$) and the cost (United States \$7968 \pm 6969 vs United States \$10644 \pm 6041; $P < 0.05$).

A meta-analysis^[15] of 221 patients from six selected RCTs comparing LF and RLF found similar results, with

RLF having a longer duration of surgery, higher costs and similar patient outcomes.

According to the current literature, it is very hard to consider robotic procedures as cost-effective (as compared to standard laparoscopy) when dealing with simple routine operations, such as esophago-gastric junction and functional surgery^[16,17].

Hiatus hernia has several epidemiologic, anatomic and pathophysiological correlations with GERD and its correction is often by LF. Moreover, some patients suffering from hiatus hernias experience gastric volvulus with life threatening complications or become highly symptomatic, which justifies a surgical repair. However, the early minimally invasive approaches could lead to an increased incidence of recurrence compared to traditional open surgery^[18,19]. Currently, laparoscopic mesh crural reinforcement and Collis gastroplasty in selected cases have achieved excellent functional results, with a recurrence rate of less than 20%^[20,21].

From a comprehensive point of view, laparoscopic surgery for GERD and hiatal hernia is considered as a standard of care in most hospitals worldwide. The high grade of effectiveness, together with the proven lower mortality and morbidity, are reasons for abandoning open surgery on a routine basis^[22,23].

ESOPHAGEAL DIVERTICULA

Esophageal diverticula are rare pathologies. The exact incidence is unknown because patients are often asymptomatic, and diagnosis is mostly incidental. Confirmation is based on a barium esophagogram and a thorough endoscopy to exclude the presence of concomitant malignancies^[24,25]. Many cases are acquired pulsion diverticula, caused by an impaired motility that results in higher intraluminal pressure and mucosa herniation through the muscular wall^[25,26].

Zenker's diverticulum (ZD) is the most common type in the esophagus (70%). It usually begins in the upper third, with an estimated prevalence of 0.01%-0.11%^[26] and some age, geographic and gender-related differences^[27].

The choice of treatment for ZD for many years has been an open surgical diverticulectomy with cricopharyngeal myotomy, while an endoscopic myotomy with a rigid or flexible endoscope is a recent emerging option that can be achieved with multiple techniques^[28-32]. Current literature is mostly based on retrospective studies with heterogeneous results, and the gold standard of treatment is not yet established^[33]. However, the endoscopic staple-assisted esophago-diverticulostomy is often considered the first choice of treatment^[34].

Endoscopic repair of ZD is safe and effective, allowing a shorter operative time, a reduction of hospital stay, and a quicker resumption of oral intake^[35-37]. In the available literature, the endoscopic repair has a morbidity rate of up to 4% and a mortality rate lower than 1%. The mean recurrence rate is approximately 6% (0%-22%)^[38].

The traditional surgical techniques consist of a stapled or manual diverticulectomy for larger diverticula associated with a myotomy; a myotomy alone for small diverticula (less than 1 cm); and a myotomy with suspension or inversion for moderate-sized diverticula (1-4 cm)^[39,40]. Despite proven efficacy, open surgery is associated with a high rate of complications (ranging from 3% to 19% depending on the technique), such as pharyngo-cutaneous fistula, mediastinitis, larynx muscles paralysis, recurrence and death (1.6%)^[27,41-43].

The prevalence of epiphrenic diverticula (ED) is approximately 0.015%, and patients are usually elderly men. ED are usually localized in the terminal esophagus and tend to project into the right thoracic cavity, accounting for less than 20% of esophageal diverticula^[44-46]. The remaining 10% of diverticula of the esophagus are located in the mediastinal space.

Because of the high morbidity and mortality rates, treatment of ED is recommended only for selected patients with severe symptoms and a high risk of aspiration pneumonia, rather than being based on the dimension of the diverticular sac itself^[44,46,47].

Surgical treatments of ED include diverticulectomy, myotomy and fundoplication (often partial) due to the higher recurrence rates of diverticulectomy alone^[48]. The procedures could be achieved by a traditional thoracotomy, a thoracoscopy, or a laparoscopic and robotic-assisted transhiatal technique. The minimally invasive approach is generally preferred for its lower morbidity and mortality rates and a similar success rate (83%-100%)^[49].

Fumagalli Romario *et al.*^[50] reported on 30 patients treated with a laparoscopic transhiatal diverticulectomy with only a suture leak (3%) and no recurrence after a median follow-up of 52 mo, while Zaninotto *et al.*^[45] reported on 17 laparoscopic diverticulectomies (associated with myotomy and anti-reflux procedures) and 7 that used a combined laparoscopic-thoracotomy approach. The latter study found 4 leakages (16.6%) and good functional outcomes in all patients.

Unfortunately, most of the studies published are single, monocentric case studies without robust statistical calculations.

ACHALASIA

Achalasia is the most common primary motility disorder of the esophagus and, after GERD, is the second most common functional disorder of the esophagus requiring operative treatment. Most people are diagnosed between the ages of 25 and 60. It initially presents with a difficulty in swallowing that progressively becomes chronic and is not resolved by conventional interventions^[51].

A number of medical and endoscopic treatments, including dilatation and myotomy^[52-55], are available for achalasia with promising results, but a surgical Heller myotomy (HM) with fundoplication has been recognized as having excellent long-term outcomes and is considered as the standard to which others options

should be compared^[56-58].

The goal of myotomy is to improve esophageal emptying by dividing the esophageal and gastric muscle fibers that contribute to the lower esophageal sphincter mechanism. The original operation was developed by Heller^[59] in 1913 and consisted of anterior and posterior esophageal myotomies. Because this approach resulted in excessive gastroesophageal reflux, it later was modified to involve a single myotomy, which still is the mainstay of surgical treatment.

In the early 1990s, Shimi *et al.*^[60] and Pellegrini *et al.*^[61] were the first to describe the use of minimally invasive techniques for the treatment of achalasia. Laparoscopic HM (LHM) has been shown not only to be feasible but also to decrease hospital stay and costs^[57]. The use of LHM spread rapidly, motivating a change in the treatment algorithm for esophageal achalasia^[56]. The standard technique includes both myotomy and fundoplication, while the Dor partial anterior plasty has been shown to be superior to the Nissen total plication^[62]. Most of the patients affected had consistent symptom relief within a few weeks of the operation, with clinical improvements maintained after several years^[63].

Similar to many esophageal procedures, the surgical treatment of achalasia with robotic assistance has been studied^[64]. The first study on a robotic HM (RHM) with a Toupet fundoplication was published by Melvin *et al.*^[65] in 2001. Since then, several larger studies on the use of a RHM have been published^[66-68].

Interestingly, esophageal perforations represent a life-threatening complication but have rarely been studied^[69,70]; the studies that do exist have included immediate repairs with good outcomes. In a meta-analysis of the efficacy of robotic abdominal surgery that included 3 studies relevant to RHM, the authors reported the risk of perforation to be lower with robotic assistance^[71]. It should be noted, however, that the lower perforation rate of RHM may be subject to bias, as most authors compare their results with laparoscopic myotomy cases performed earlier in their learning curve.

Another retrospective multicenter trial suggested decreased esophageal mucosal perforations with the use of a robot (0% vs 16% with conventional laparoscopy; $P < 0.05$) with similar patient outcomes and equal operative times, after an appropriate learning curve^[67]. Huffmann *et al.*^[72] reported a lower rate of esophageal perforations and better quality of life with RHM compared to LHM as well.

From a robust comparative perspective, Shaligram *et al.*^[73] analyzed 2683 patients suffering from achalasia who were treated by open Heller myotomy (OM), LHM, or RHM. No differences in mortality, morbidity, ICU admission, LOS, or 30-d re-admission were observed in the three groups. However, the overall hospital costs decreased in the LHM group (United States \$7441 ± 7897 vs United States \$9415 ± 5515; $P = 0.0028$). Interestingly, when comparing OM and RHM, the authors

found significantly lower morbidity (9.08% vs 4.02%; $P = 0.02$), ICU admission rate (14.01% vs 3.36%, $P = 0.0002$), and LOS (4.42 ± 5.25 d vs 2.42 ± 2.69 d; $P = 0.0001$) in the RHM group. The authors concluded that the RHM group had also a slight improvement in perioperative outcomes compared to the LHM, at the price of increased costs.

Another large review^[74] of LHM vs RHM, which including only 6 RCTs (of low quality), also reported comparable outcomes and increased costs for the robotic technique.

The Society of American Gastrointestinal and Endoscopic Surgeons' guidelines^[75] state that compared with laparoscopy, robotic assistance for the treatment of esophageal achalasia decreases the rate of intraoperative mucosal perforations, but no clear differences in post-operative morbidity, symptom relief, or long-term outcomes have been confirmed to date. Further studies are needed to better establish the role of RHM.

ESOPHAGEAL PERFORATION

Esophageal perforation (EP) is an uncommon situation, although its incidence has increased over the last 20 years. The most common cause is iatrogenic (60% of cases are caused by an endoscopic procedure)^[76,77]. Otherwise, EP can occur spontaneously after vomiting or in cases Boerhaave syndrome or a diseased esophagus (*i.e.*, diverticula, Barrett's esophagus, infective esophagitis, cancer)^[78]. Other rare causes are blunt or penetrating trauma to the epigastrium and ingestion of foreign bodies or caustics. The mortality rate is as high as 60%^[79-81] and is mainly secondary to the onset of a septic shock and the presence of comorbidities^[82].

The ideal management of EP is not yet standardized, and no technique has shown a real superiority over the others. Nevertheless, the number of patients treated aggressively with surgery has been lower over the last several years^[83], while many patients (approximately 25% of EP cases) are being managed non-operatively. Early total parenteral nutrition and antibiotic therapy, in those patients without signs of sepsis, can lead to a medical management success rate of more than 80%^[78].

Endoscopic stenting, associated with or without a percutaneous or surgical thoracic drainage, has a success rate up to 90% in patients with EP due to benign perforations of less than 5 cm or an anastomotic leak with a minimal contamination if treated within 24 h of the perforation^[84-86]. Endoscopic closure of the leak with clips or suture is also effective^[87].

Nevertheless, the surgical approach to EP is still appropriate in case of severe acute sepsis, extended leaks or failure of endoscopic/percutaneous treatments. A feeding jejunostomy is often recommended^[88]. Surgical drainage of the contaminated space, debridement with primary repair, esophageal diversion with delayed repair and esophagectomy with immediate or delayed repair have all been used for several years, with high

morbidity and mortality rates^[78,81,88,89].

Open surgery is widely considered the standard, even though some case studies have reported on the feasibility and safety of laparoscopic^[90-93]/thoracoscopic^[94] primary repair of EP associated with or without stent placement^[95] in hemodynamically stable patients. Again, most of the published studies are monocentric case studies and anecdotal reports with short-term follow-up.

Pleural percutaneous drainage alone may achieve acceptable mortality rates in appropriately selected patients with cervical EP^[96,97], although it is usually associated with thoracoscopy or laparoscopy for complete surgical debridement^[98].

BENIGN AND MALIGNANT TUMORS

Both benign and malignant tumors arising in the esophageal tract are candidates for a minimally invasive approach, although the widespread adoption of minimally invasive techniques has been limited by many challenging technical issues. In addition, the oncologic outcomes remain the foundation of any procedure to cure malignancies, rather than the feasibility itself. Obviously, any laparoscopic or robotic procedure should follow the standards of oncologic surgery, including sufficient margins of resection and extended proper lymphadenectomy^[99].

The need for a surgeon with advanced skills, the availability of instruments and the high case volume together have limited the use of MIS for esophageal neoplasms to few subspecialized centers.

Benign lesions are rare, representing only 20% of all esophageal neoplasms at autopsy, with more than 70% being leiomyoma^[100]. Nevertheless, the anatomic location in the esophageal tract, together with the well-known challenges of esophageal reconstructions, lead to potential life-threatening complications after surgery. A minimally invasive surgical approach would be of crucial interest to limit the risks of perioperative deaths and the length of hospital stay.

Most studies have included a limited number of anecdotal experiences^[101-103] with excellent results from a thoracoscopic or laparoscopic transhiatal enucleation for esophageal leiomyomas. However, the optimal approach should be tailored for each patient according to the location and size of the tumor^[104]. For example, Palanivelu *et al.*^[105], in one of the largest single-center studies (18 cases), reported that leiomyomas are frequently located in the middle and lower third of the esophagus. The author suggested that the proximal ones should be best approached by a right thoracoscopy and the distal ones through an abdominal route. Nevertheless, a laparoscopic transhiatal operation is also feasible to manage benign lesions of the thoracic esophagus^[106,107].

Many of the published studies include very few patients, and those comparing laparoscopic/thoracoscopic procedures with open traditional approaches have poor statistical relevance. However, most studies

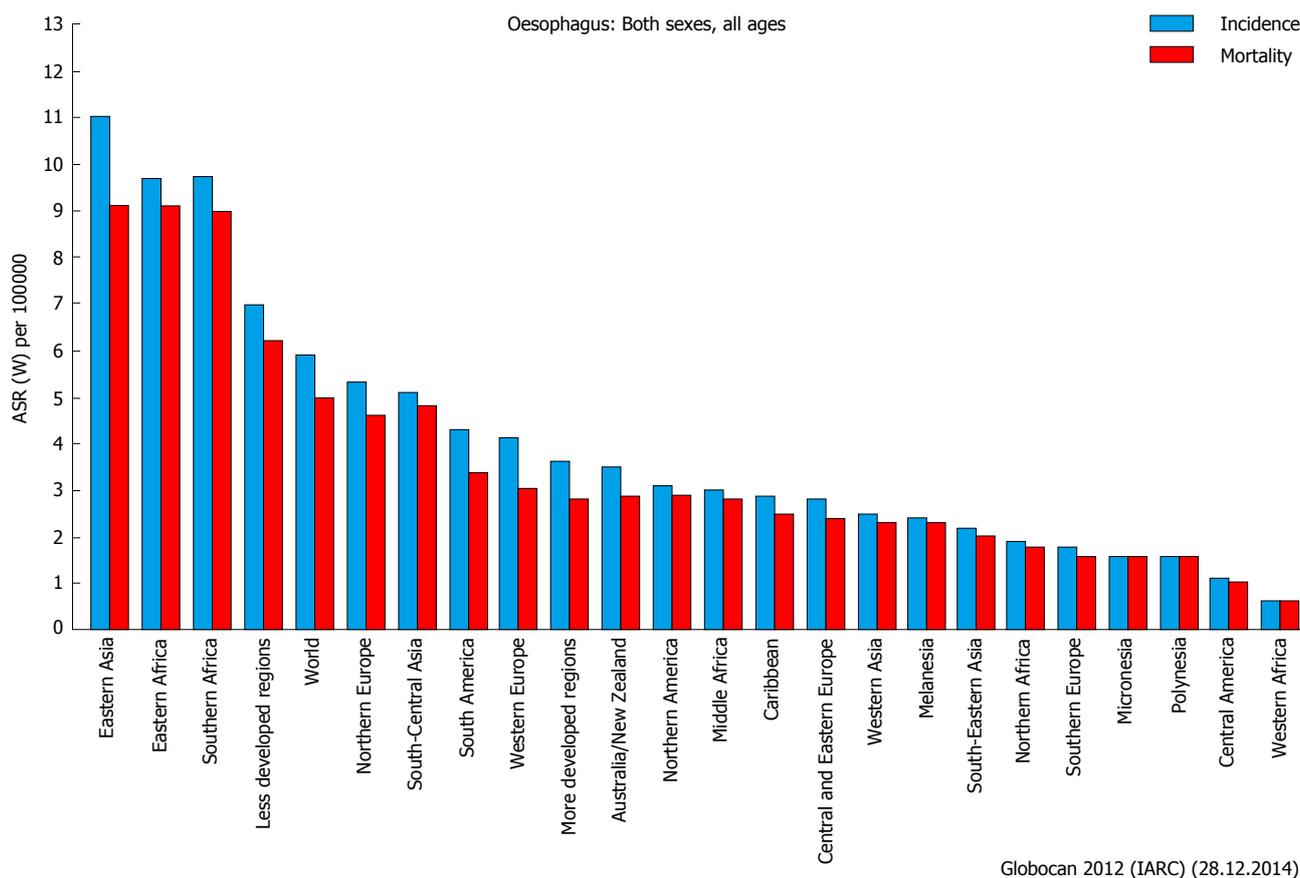


Figure 1 Incidence and mortality rates of esophageal cancer worldwide^[114].

have reported superior results of MIS in terms of reductions of perioperative complications and length of hospital stay^[108,109].

The robotic approach was also described as a procedure very suitable for managing benign esophageal masses that require careful dissection in deep, narrow spaces. Obviously, all these experiences were reported as case studies performed by skillful subspecialized surgeons^[64,110-113].

The different interventions for esophageal benign diseases range from a simple enucleation achieved through a thoracic or an abdominal route to a formal Ivor-Lewis partial esophagectomy. Interestingly, Khalailah *et al.*^[113] reported favorable results of robotic approaches compared to the corresponding open or traditional laparoscopic/thoracoscopic operations (overall complications of 0%, 10% and 13%, respectively). Unfortunately, that retrospective review included fewer than 100 patients in each group, with scarce homogeneity of characteristics and very different approaches.

Cancer of the esophagus is relatively rare in Europe, North America and other developed countries, although it represents a major concern in Eastern Asia, Eastern and Southern Africa, and, generally speaking, in less developed regions (Figure 1). In Eastern Asia, the incidence is almost double than in rest of the world (more than 10 per 100,000 per year)^[114], with some differences in the histopathological features (adenocarcinoma

and squamous). The oncologic outcomes are still disappointing, with a 5-years survival rate of less than 40%^[115]. New adjuvant regimens have been proven to significantly increase the survival after curative surgery, with few or no detrimental perioperative complications^[115,116].

From a comprehensive point of view, the fundamental esophageal cancer cure is always resective surgery with regional lymphadenectomy and (neo) adjuvant chemo or radiochemotherapy. Conversely, many technical debates still exist regarding the opportunity of performing a partial or a total esophagectomy, with or without a transthoracic approach^[117].

In brief, the three-field esophagectomy (McKeown procedure) has been the treatment of choice for esophageal cancer for many years and includes abdominal, thoracic and cervical incisions. The two-field partial esophagectomy with an esophagogastric intrathoracic anastomosis (Ivor-Lewis procedure) has gained popularity in recent years due to comparable oncologic results with the McKeown operation and minor complications. The transhiatal esophagectomy, which avoids the thoracotomy (Orringer procedure), probably offers inferior oncologic outcomes^[118].

In the recent literature, many groups of esophageal surgeons have reported trends in reducing the use of the three-field McKeown total esophagectomy in favor of the two-field Ivor-Lewis partial esophagectomy (except

for cases of cancer arising in the upper third of the esophagus). The significant reduction of perioperative complications, including leaks, recurrent laryngeal nerve injuries, alteration of swallowing and pharyngeal transit, is the major benefit of the limited approach^[119,120].

Despite the different surgical techniques proposed, patients are expected to have a high incidence of complication of up to 60%. Most are pulmonary complications, with an increase in the postoperative stay, costs and mortality^[1,3].

To improve such those disappointing figures, many minimally invasive approaches had been developed, replacing conventional operations with laparoscopy, thoracoscopy or hybrid routes (with open surgery combined), with excellent results^[119,121,122].

The minimally invasive esophagectomy (MIE) is expected to reduce pulmonary impairment, intraoperative bleeding, wound infections and, consequently, length of hospital stay and mortality. Increases in the operative time and of the base costs are the principal concerns^[123].

One recent multicenter (selected hospitals with specific credentials) prospective phase II trial^[124] evaluated the feasibility of MIE in patients with high-grade dysplasia or esophageal cancer with a rigorous protocol. According to the authors' results, surgery was completed in 95 of the 104 patients (91.3%), with a 30-d mortality rate of 2.1%. The major complications were anastomotic leak (8.6%), acute respiratory distress syndrome (5.7%), pneumonitis (3.8%), and atrial fibrillation (2.9%). The 3-year overall survival rate was 58.4% and a locoregional recurrence occurred in only 7 patients (6.7%).

However, the rapid worldwide use of MIS for esophageal cancer has not been followed by a rigorous scientific analysis of results, and the issue of cost-effectiveness is still unresolved^[5,125]. Therefore, large-scale multicenter trials are still lacking, and few studies have had sufficient follow-up to judge the long-term oncologic results.

Aside from the intrinsic difficulty in conducting surgical clinical trials, the challenging learning curve and the numerous technical variables (including the patient's position - prone vs supine or the transoral anvil introduction vs the transthoracic route during an Ivor-Lewis esophagectomy) have jeopardized the results^[126].

One large retrospective cohort study also confirmed the superiority of MIE in terms of postoperative pulmonary complications (13% in the thoraco-laparoscopic MIE group, 38% in the thoracoscopic MIE group, and 39% in the open group)^[122].

Nevertheless, to date, only one prospective, multicenter RCT that including 56 patients and compared open transthoracic oesophagectomy with the minimally invasive approach has been published^[127]. The authors reported that 29% of patients in the open group had pulmonary infections in the first 2 wk compared to five (9%) in the minimally invasive group ($P = 0.005$), while 19 (34%) and 7 (12%) patients in the two groups

had in-hospital pulmonary infections, respectively ($P = 0.005$)^[127]. Another trial to evaluate the benefits of laparoscopic gastric mobilization during Ivor-Lewis intervention is still ongoing^[128].

Conversely, Hanna *et al.*^[129], who selected thirty of the best published papers concerning MIE and open approaches for cancer (including only 1 RCT), found that in most studies a suboptimal lymphadenectomy was described (with the average number of nodes retrieved below 23 considered as the standard) and included a superficial description of the complications that occurred. However, the disease-free survival and the overall survival rates were similar to those achieved by open surgery^[129].

In recent years, robotic-assisted MIE (RAMIE) has been introduced for the treatment of esophagogastric malignancies. The robotic platform would reduce the complexity of the laparoscopic-thoracoscopic maneuvers using endo-wrist arm technology (articulation of the instruments with 7 degrees of freedom). The deeper high-definition 3D vision, the motion scaling and the tremor filtration are other potential advantages of a robotic approach during esophageal dissection, allowing the execution of an extended lymphadenectomy and hand-sewn visceral anastomoses^[130]. Another intriguing advantage of robotic surgery is the reduction of the learning curve (20 procedures in one study^[131]), as compared to standard MIE, which increases the number of surgeons who can gain adequate and specific proficiency.

In the published literature, studies on all three types of esophageal resections (total esophagectomy, partial transthoracic and partial transhiatal resection) using a full robotic or a hybrid approach are available (Figure 2).

For example, Boone *et al.*^[132] reported on 47 robotic three-field total esophagectomies with a pulmonary morbidity of 44% and a postoperative mortality of 6%, which were highly comparable with the results of historical open outcomes in terms of safety and short-term results.

As in standard MIE, the robot-assisted Ivor-Lewis transthoracic esophageal resection has replaced the three-field approach in most cases^[133-135]. The perioperative outcomes and the oncologic parameters reported were highly sufficient to judge the technique to be as safe as traditional MIE and the conventional open approach^[133,136]. From a purely technical point of view, the transthoracic surgical step could be achieved throughout a standard supine or semi-lateral position, while recently some authors^[137] have reported excellent results using the prone position (only a 6% rate of pulmonary complications).

Another peculiar issue of RAMIE is represented by the possibility of performing a hand-sewn intrathoracic esophagogastric anastomosis, which is virtually impossible or very time-consuming for even very skilled laparoscopists due to tremor and anti-ergonomic positions. However, only two papers^[138,139] have specifically addressed the use of RAMIE with a hand-sewn intratho-

Table 1 Recommended approaches to esophageal procedures

Type of procedure	Open surgery	Laparoscopic surgery	Robotic	Level of evidence ¹
Total esophagectomy (McKeown)	Standard	Accepted	Developing	LE 3
Partial esophagectomy (Ivor-Lewis)	Standard	Accepted	Developing	LE 2
Transhiatal esophagectomy (Orringer)	Standard	Accepted	Developing	LE 3
Anti-reflux surgery	Abandoned	Standard	Developing	LE 1
Heller myotomy	Abandoned	Standard	Developing	LE 1
Local excision	Standard	Accepted	Developing	LE 4
Others	Standard	Accepted	Developing	LE 4

¹Oxford Centre for Evidence-Based Medicine. Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". <http://www.cebm.net/index.aspx?o=5653>

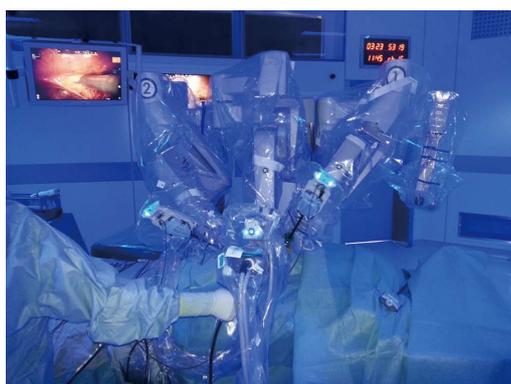


Figure 2 da Vinci® docking during the thoracic step of a completely robotic esophagectomy at the Division of Oncologic Surgery and Robotics, Careggi Hospital.

racic anastomosis. The authors reported few leakages or cases of stenosis and no significant prolonging of the operative time.

Finally, even a transhiatal esophagectomy is feasible robotically, at the price of a higher complications rate reported in one of the very few anecdotal reports (35% of patients with temporary laryngeal nerve paresis and 25% of patients with self-limiting cervical leaks)^[140].

In conclusion, although the first cases of RAMIE were described in the early 2000s^[69,141], rigorous, well-designed, large comparative studies are still lacking, and none of the existing studies have demonstrated the tangible benefits of robotics over thoraco-laparoscopy or open surgery^[133,142]. Interestingly, a monocentric trial specifically targeted to RAMIE was recently launched^[143].

CONCLUSION

Most of the surgical operations for the treatment of benign and malignant esophageal diseases are suitable for a minimally invasive approach, with the goal of reducing the wide spectrum of perioperative complications.

Thoracoscopy, laparoscopy, hybrid procedures and robotic assistance have been shown to favorably impact pulmonary morbidity and length of hospital stay in many recent papers. However, most of these minimally invasive esophageal procedures were achieved in a limited number of subspecialized centers worldwide and were performed by surgeons with significant experience

in esophageal surgery, advanced laparoscopy and robotics. Interestingly, the hypothesized learning curve for gaining sufficient confidence was more than 30 cases for major operations^[144,145].

In addition, more of the published techniques, although very promising in terms of outcomes and results, are not yet completely validated. An authors' comprehensive opinion of future developments in MIS for esophageal disease is reported in Table 1.

Centralization of the more challenging procedures and rigorous scientific approaches are needed before conventional open surgery can be abandoned completely.

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Gallstone ileus, clinical presentation, diagnostic and treatment approach

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Abstract

Gallstone ileus is a mechanical intestinal obstruction due to gallstone impaction within the gastrointestinal tract. Less than 1% of cases of intestinal obstruction are derived from this etiology. The symptoms and signs of gallstone ileus are mostly nonspecific. This entity has been observed with a higher frequency among the elderly, the majority of which have concomitant medical illness. Cardiovascular, pulmonary, and metabolic diseases should be considered as they may affect the prognosis. Surgical relief of gastrointestinal obstruction remains the mainstay of operative treatment. The current surgical procedures are: (1) simple enterolithotomy; (2) enterolithotomy, cholecystectomy and fistula closure (one-stage procedure); and (3) enterolithotomy with cholecystectomy performed later (two-stage procedure). Bowel resection is necessary in certain cases after enterolithotomy is performed. Large prospective laparoscopic and endoscopic trials are expected.

Key words: Intestinal obstruction; Bouveret's syndrome; Laparoscopic surgery; Endoscopic treatment; Gallstone ileus

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Core tip: A review of the symptoms and signs of gallstone ileus is presented. The findings, advantages and limitations of the different diagnostic modalities such as plain abdominal radiographs, upper gastrointestinal

series, ultrasound, computed tomography, magnetic resonance and endoscopy are reviewed. The different surgical options are discussed. Laparoscopic and endoscopic procedures are widely reviewed. Current data on morbidity and mortality are included.

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INTRODUCTION

Gallstone ileus is an infrequent complication of cholelithiasis and is defined as a mechanical intestinal obstruction due to impaction of one or more gallstones within the gastrointestinal tract. The term "ileus" is a misnomer, since the obstruction is a true mechanical phenomenon^[1]. Gallstone gastrointestinal obstruction would be an appropriate term.

BACKGROUND

In 1654, Thomas Bartholin^[2] described a cholecysto-intestinal fistula with a gallstone within the gastrointestinal tract in a necropsy study. In 1890, Courvoisier^[3] published the first series of 131 cases of gallstone ileus, with a mortality rate of 44%. In 1896, Bouveret^[4] described a syndrome of gastric outlet obstruction caused by an impacted gallstone in the duodenal bulb after its migration through a cholecysto- or choledochoduodenal fistula. This was the first preoperative diagnosis of the currently known Bouveret's syndrome.

EPIDEMIOLOGY

Gallstone ileus has shown a constant incidence of 30-35 cases/1000000 admissions over a 45-year period^[5]. This entity develops in 0.3%-0.5% of patients with cholelithiasis^[6]. It constitutes the etiologic factor in less than 5% of cases of intestinal obstruction, but up to one quarter of nonstrangulated small bowel obstructions in elderly patients^[7]. In a nationwide study at the United States from 2004 to 2009, only 0.095% of mechanical bowel obstruction cases were caused by a gallstone^[8]. Gallstone ileus has been observed with a higher frequency among the elderly^[1]. Halabi *et al*^[8], recently reported an age range from 60 to 84 years in American patients. A Japanese literature review reported a 13-year-old case as their youngest patient, while a Mexican series included a 99-year-old patient^[9,10]. Accordingly to the predominance of female patients in gallstone disease, the majority of gallstone ileus patients correspond to the female gender, with variable percentages from 72%-90%^[11,12].

PATHOPHYSIOLOGY

Gallstone ileus is frequently preceded by an initial episode of acute cholecystitis. The inflammation in the gallbladder and surrounding structures leads to adhesion formation. The inflammation and pressure effect of the offending gallstone causes erosion through the gallbladder wall, leading to fistula formation between the gallbladder and the adjacent and adhered portion of the gastrointestinal tract, with further gallstone passage^[13,14]. Less commonly, a gallstone may enter the duodenum through the common bile duct and through a dilated papilla of Vater^[15].

The most frequent fistula occurs between the gallbladder and the duodenum, due to their proximity^[11,16,17]. The stomach, small bowel and the transverse portion of the colon may also be involved^[1,13,14] (Table 1). This process might be part of the natural history of Mirizzi syndrome^[18]. Once the gallbladder is free of calculi, it may become a blind sinus tract and contract down to a small fibrous remnant^[19].

In 1981, Halter *et al*^[20] reported a case of gallstone ileus after endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincteromy (ES) and unsuccessful gallstone extraction. Three days later, the patient presented abdominal pain and vomiting. At laparotomy, a 3.5 cm gallstone was removed from the jejunum. To our knowledge, 13 cases of gallstone ileus have been reported after ERCP and ES. This adverse event may occur late after the endoscopic procedure, and should be considered in the differential diagnosis, especially in cases of delayed presentation^[21,22].

Spillage of gallstones during laparoscopic cholecystectomy is not infrequent. Although most of gallstones lost in a previous biliary surgery and lying free in the abdominal cavity are silent, they can cause an intraabdominal abscess and might ulcerate the intestinal wall and gain entrance to the bowel lumen and cause gallstone ileus^[23-26].

Once within the duodenal, intestinal or gastric lumen, the gallstone usually proceeds distally and may pass spontaneously through the rectum, or it may become impacted and cause obstruction. Less commonly if the gallstone is in the stomach, proximal migration can occur and the gallstone may be vomited^[14]. The size of the gallstone, the site of fistula formation and bowel lumen will determine whether an impaction will occur. The majority of gallstones smaller than 2 to 2.5 cm may pass spontaneously through a normal gastrointestinal tract and will be excreted uneventfully in the stools^[1,13,14]. Clavien *et al*^[6] reported an obstructing gallstones size range from 2 to 5 cm. Nakao *et al*^[11] found that impacted gallstones ranged in size from 2-10 cm, with a mean of 4.3 cm. Gallstones larger than 5 cm are even more likely to become impacted, although spontaneous passage of gallstones as large as 5 cm has occurred^[1,14,17]. The largest gallstone causing intestinal obstruction measured 17.7 cm in its largest diameter

Table 1 Frequency of biliary-enteric fistulas in patients with gallstone ileus

Fistula type	Range (%)
Cholecystoduodenal	32.5-96.5
Cholecystogastric	0-13.3
Cholecystojejunal	0-2.5
Cholecystoileal	0-2.5
Cholecystocolic	0-10.9
Choledochoduodenal	0-13.4
Undetermined	0-65

Data expressed in percentage ranges, according to ref. [6,10,11,16,25,30,34,36,55].

and was removed from the transverse colon^[14]. Multiple stones have been reported in 3%-40% of cases^[6].

The site of impaction can be almost in any portion of the gastrointestinal tract. If the gallstone enters the duodenum, the most common intestinal obstruction will be the terminal ileum and the ileocecal valve because of their relatively narrow lumen and potentially less active peristalsis. Less frequently, the gallstone may be impacted in the proximal ileum or in the jejunum, especially if the gallstone is large enough. Less common locations include the stomach and the duodenum (Bouveret's syndrome), and the colon^[1,7,13,14,17]. The size of the gallstone, a gallbladder inflammatory process compromising the duodenum and a cholecysto-duodenal fistula may cause a gallstone to become impacted in the duodenum^[27] (Table 2).

The presence of diverticula, neoplasms, or intestinal strictures such as secondary to Crohn's disease, decrease the lumen size and may cause the gallstone to impact at the narrowing site^[1,13,19]. Gallstone ileus has been reported at sites of anastomosis after partial gastrectomy and Billroth II reconstruction and after biliointestinal bypass in two cases^[28,29].

Ischemia may develop at the site of gallstone impaction, due to the pressure generated against the bowel wall and the proximal distention. Necrosis and perforation followed by peritonitis may occur^[13].

CLINICAL MANIFESTATIONS

The presentation of gallstone ileus may be preceded by a history of prior biliary symptoms, with rates between 27%-80% of patients^[6,7,10,12,16,30]. Acute cholecystitis may be present in 10%-30% of the patients at the time of bowel obstruction. Jaundice has been found in only 15% of patients or less. Biliary symptoms may be absent in up to one third of cases^[1,6,13,17,25,31].

Gallstone ileus may be manifested as acute, intermittent or chronic episodes of gastrointestinal obstruction. Nausea, vomiting, crampy abdominal pain and variable distension are commonly present^[1,9,13,17,25,32]. The intermittent nature of pain and vomiting of proximal gastrointestinal material, later becoming dark and feculent is due to the "tumbling" gallstone advancement^[12,15]. Therefore, there may be intermittent partial or complete

Table 2 Site of gastrointestinal obstruction in patients with gallstone ileus

Site	Range (%)
Duodenum	0-10.5
Stomach	0-20
Jejunum	0-50
Jejunum/proximal ileum	0-50
Ileum	0-89.5
Colon	0-8.1
Undetermined	0-25

Data expressed in percentage ranges, according to ref. [6,7,10-12,16,19,25,30,34,36,55].

intestinal obstruction, with temporary advancement of the gallstone and relief of symptoms, until the gallstone either passes through the gastrointestinal tract or it definitively becomes impacted and complete intestinal obstruction ensues^[13,17]. The character of the vomitus is dependent on the obstruction location. When the gallstone is in the stomach or upper small intestine, the vomitus is mainly gastric content, becoming feculent when the ileum is obstructed.

Particularly, Bouveret's syndrome presents with signs and symptoms of gastric outlet obstruction. Nausea and vomiting have been reported in 86% of cases, while abdominal pain or discomfort is referred in 71%. If the gallstone is not fully obstructing the lumen, the presentation will be of partial obstruction. Recent weight loss, anorexia, early satiety and constipation may be referred. Bouveret's syndrome has also been reported to be preceded by or manifest as upper gastrointestinal bleeding, secondary to duodenal erosion caused by the offending gallstone, with hematemesis and melena, in 15% and 7%, respectively^[17,27,33].

Physical examination may be nonspecific. The patients are often acutely ill, with signs of dehydration, abdominal distension and tenderness with high-pitched bowel sounds and obstructive jaundice. Fever, toxicity and physical signs of peritonitis may be noted if perforation of the intestinal wall takes place. The exam may be completely normal if no obstruction is present at the moment^[1,13,14,27].

DIAGNOSIS

The symptoms and signs of gallstone ileus are mostly nonspecific^[9,16,32]. The intermittency of symptoms could also interfere with a correct diagnosis, if clinical manifestations at the moment correspond to a partial obstruction or distal migration of the gallstone. The "tumbling phenomenon" may be the cause why the patient does not seek medical attention or admittance is postponed. Patients usually present 4 to 8 d after the beginning of symptoms and diagnosis is usually made 3 to 8 d after the onset of symptoms^[1,32]. Cooperman *et al.*^[34] found an average period of 7 d from the onset of symptoms until the hospitalization, and 3.7 d of hospitalization elapsed until surgical intervention. Periods of



Figure 1 Plain abdominal radiograph showing dilated small bowel loops and a high density endoluminal image suggestive of a gallstone (arrow). No pneumobilia is visualized.

several months of symptoms before seeking hospital attention has been reported^[30]. A correct preoperative diagnosis has been reported in 30%-75% of the cases^[6,12,30,35-37]. A high index of suspicion will be helpful, particularly in a female elderly patient with intestinal obstruction and previous gallstone disease; Bouveret's syndrome may be suspected in a patient with gastric outlet obstruction.

Plain abdominal radiograph

Plain abdominal radiographs are of major importance in establishing the diagnosis. In 1941, Rigler *et al*^[38] described four radiographic signs in gallstone ileus: (1) partial or complete intestinal obstruction; (2) pneumobilia or contrast material in the biliary tree; (3) an aberrant gallstone; and (4) change of the position of such gallstone on serial films. The presence of two of the three first signs, has been considered pathognomonic and has been found in 20%-50% of cases^[1,25]. Although pathognomonic, reports of Rigler's triad range from 0%-87%^[30]. A careful inspection for pneumobilia should be performed, since it is present in most patients with gallstone ileus, but sometimes it is identified only in retrospective observation^[25]. Pneumobilia may occur secondary to prior surgical or endoscopic biliary interventions. Therefore, the clinical presentation should be considered when evaluating this radiologic sign^[1]. In 1978, Balthazar *et al*^[39] described a fifth sign, which consists of two air fluid levels in the right upper quadrant on abdominal radiograph. The medial air fluid level corresponds to the duodenum and the lateral to the gallbladder. These authors found that this sign was present in 24% of patients at the time of admission. In Bouveret's syndrome, a dilated stomach is expected to be seen on plain abdominal radiograph, due to the gastric outlet obstruction^[40]. Cappell *et al*^[33], in a review of 64 cases of Bouveret's syndrome, found as relatively common findings pneumobilia (39%), calcified right upper quadrant mass or gallstone (38%), gastric distension (23%) and dilated bowel loops (14%) (Figure 1).

Upper gastrointestinal series

An upper gastrointestinal series may help to identify the

biliary enteric fistula and the level of obstruction^[1]. A secondary sign that may be useful is the identification of oral contrast material within the gallbladder^[41]. Cappell *et al*^[33], in a review of Bouveret's syndrome, upper gastrointestinal series included cholecystoduodenal fistula or pneumobilia (45%), a filling defect or mass in the duodenum (44%), cholecystoduodenal fistula (38%), gastric outlet or pyloric obstruction (27%), distended or dilated stomach (27%), gallstone in duodenum (21%), and duodenal obstruction (12%)^[33].

Abdominal ultrasound

When diagnosis is still doubtful, an abdominal ultrasound (US) will be indicated for gallbladder stones, fistula and impacted gallstone visualization. It may also confirm the presence of choledocholithiasis^[1,42]. The use of US in combination with abdominal films to increase the sensitivity of diagnosis has been advocated. US is more sensitive at detecting pneumobilia and ectopic gallstones. The combination of abdominal films and US has increased the sensitivity of diagnosis of gallstone ileus to 74%^[43]. The most frequent findings in Bouveret's syndrome are gallstone in or near the gallbladder (53%), pneumobilia or cholecystoduodenal fistula (45%), gallstone in duodenum (25%), dilated or distended stomach (15%), and a contracted gallbladder (13%)^[33] (Figure 2).

Computed tomography

Computed tomography (CT) is considered superior to plain abdominal films or US in the diagnosis of gallstone ileus cases, with a sensitivity of up to 93%^[44]. The frequency of Rigler's triad detection is higher under CT examination. In a retrospective study by Lassandro *et al*^[45], Rigler's triad was observed in 77.8% of cases by means of CT, compared to 14.8% with radiographs and 11.1% with US. Bowel loops dilatation was seen in 92.6% of cases, pneumobilia in 88.9%, ectopic gallstone in 81.5%, air-fluid levels in 37%, and the bilio-digestive fistula in 14.8%. Yu *et al*^[44] performed a prospective study where 165 patients with acute small bowel obstruction were evaluated for gallstone ileus, with retrospective identification of three diagnostic criteria: (1) small bowel obstruction; (2) ectopic gallstone, either rim-calcified or total-calcified; and (3) abnormal gallbladder with complete air collection, presence of air-fluid level, or fluid accumulation with irregular wall. Overall sensitivity, specificity and accuracy were 93%, 100%, and 99%, respectively. Rigler's triad was detected only in 36% of cases. These tomographic diagnostic criteria need further prospective validation. Current CT scanners may describe the location of the fistula, offending gallstones and gastrointestinal obstruction with better precision, and helping in therapeutic decisions^[46].

In Bouveret's syndrome, major findings on CT scan are obstruction due to a gastro-duodenal mass or lesion, pericholecystic inflammatory changes extending into the duodenum, gas in the gallbladder, pneumobilia or cholecysto-duodenal fistula, filling defects corresponding to one or more gallstones, thickened gallbladder wall,



Figure 2 Ultrasound findings in a patient with gallstone ileus. A: Hyperechoic images without acoustic shadow in a non-dilated common bile duct, suggestive of air in the bile duct (arrow). Right portal vein was identified by Doppler US; B: US showing hyperechoic images without acoustic shadow in a collapsed gallbladder (arrow) and duodenum, suggestive of endoluminal air (short arrow). Liver parenchyma (arrowhead); C: Fluid-filled dilated proximal jejunum bowel loop (arrowhead). US: Ultrasound.



Figure 3 Contrast-enhanced computed tomography findings in a patient with gallstone ileus. A: Portal phase IV-contrast enhanced computed tomography section reveals air in the hepatic duct (arrow), anterior to a permeable right portal vein (arrowhead); B: Communication between a non-distended gallbladder (arrowhead) and the duodenum (arrow), where presence of air is observed. Fluid-filled dilated jejunum loops and intestinal pneumatosis are seen (short arrow); C: Endoluminal round-shaped calcium-density images (arrows), and dilated small bowel loops (arrowhead) with pneumatosis (short arrow).

and a contracted gallbladder^[17,27].

CT scan may allow detection of a rim or totally calcified ectopic gallstone without oral contrast administration. This may be done even with non-enhanced CT. Identification of a rim-calcified gallstone may be more difficult with contrast-enhanced CT, compared to total calcified gallstones. Less calcified gallstones could be missed^[44]. Contrast-enhanced CT allows detection of edema and ischemia of the affected gastrointestinal tract site^[44,47]. Given the relevance of possible bowel ischemia, contrast-enhanced CT is of particular importance in management decision making (Figure 3).

Magnetic resonance cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) may be useful in selected cases where diagnosis is not clear after CT. A potential drawback of CT is that 15%-25% of gallstones appear as isoattenuating relative to bile or fluid. Pickhardt *et al.*^[48] described the use of MRCP for diagnosis of Bouveret's syndrome with isoattenuating gallstones. MRCP may be useful in these cases, due to the possibility to delineate fluid from gallstones, which appear as signal voids against the high-signal fluid. This is also a potential advantage in patients unable to tolerate oral contrast material. If sufficient fluid is present in the cholecystoenteric

fistula it could also be depicted. Therefore, MRCP may be particularly useful to confirm the gallstone ileus diagnosis in selected cases^[40]. Magnetic resonance for gastrointestinal obstruction evaluation is also a potential diagnostic option (Figure 4).

Esophagogastroduodenoscopy

In a review of 81 cases of Bouveret's syndrome in whom esophagogastroduodenoscopy (EGD) was performed, the gastroduodenal obstruction was revealed in all of them, but gallstone visualization was possible only in 56 (69%). Among those 56 cases, such gallstones were observed in the duodenal bulb in 51.8%, postbulbar duodenum in 28.6%, pylorus or prepylorus in 17.9%, and in one case the location was not reported. In 31% of cases the gallstone was not recognized because it was deeply embedded within the mucosa. When the gallstone is not visualized, the diagnosis should be strongly suspected when the observed mass is hard, convex, smooth, nonfriable, and nonfleshy, which are all characteristic of a gallstone and may improve the sensitivity of EGD. For such cases, US and CT are the preferred noninvasive diagnostic tests to confirm the endoscopic diagnosis, delineate the gastroduodenal anatomy, and demonstrate a cholecystoduodenal fistula^[33] (Figure 5).

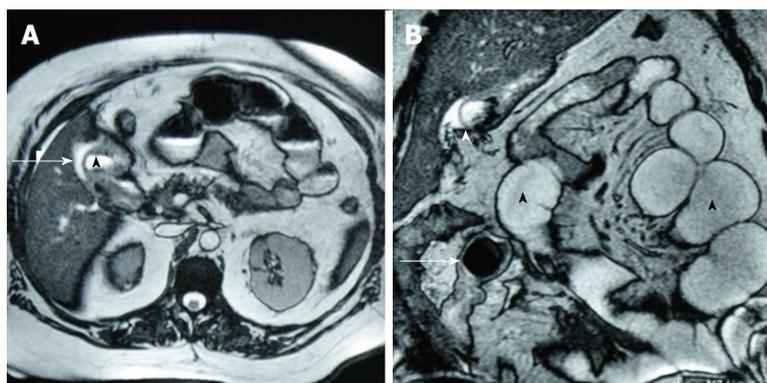


Figure 4 Magnetic resonance cholangiopancreatography findings in a patient with gallstone ileus. A: On T2-MRI, a hyperintense image is identified in the gallbladder bed (arrow), with communication with the duodenal second portion (arrowhead), suggestive of a cholecystoduodenal fistula; B: MRI coronal reconstruction showed dilated small bowel loops with endoluminal air (black arrowheads) and a signal-void round-shaped image, suggestive of a gallstone (arrow). Gallbladder communication with duodenum is observed (white arrowhead). MRI: Magnetic resonance imaging.



Figure 5 Esophagogastroduodenoscopy in a patient with Bouveret's syndrome revealed a gallstone in the duodenal bulb and the fistulous sinus. Courtesy of Gabriela Quintero-Tejeda, MD, Department of Gastrointestinal Endoscopy, Unidad Médica de Alta Especialidad, Hospital de Especialidades del Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social.

TREATMENT

The main therapeutic goal is relief of intestinal obstruction by extraction of the offending gallstone. Fluid and electrolyte imbalances and metabolic derangements due to intestinal obstruction, delayed presentation and pre-existing co-morbidities are common, and require management prior to surgical intervention^[1,19,23,32].

There is no consensus on the indicated surgical procedure. The current surgical procedures are: (1) simple enterolithotomy; (2) enterolithotomy, cholecystectomy and fistula closure (one-stage procedure); and (3) enterolithotomy with cholecystectomy performed later (two-stage procedure). Bowel resection is necessary in certain cases after enterolithotomy is performed.

Enterolithotomy has been the most commonly surgical procedure performed. Through an exploratory laparotomy, the site of gastrointestinal obstruction is localized. A longitudinal incision is made on the anti-mesenteric border proximal to the site of gallstone impaction^[5,6,23]. When possible, through gentle mani-

pulation the gallstone is brought proximally to a non-edematous segment of bowel. Most of the times, this is not possible due to the grade of impaction of the gallstone. The enterotomy is performed over the gallstone and it is extracted. Careful closure of the enterotomy is needed to avoid narrowing of the intestinal lumen and a transverse closure is recommended. Bowel resection is sometimes necessary, particularly in the presence of ischemia, perforation or an underlying stenosis^[6,23]. Manual propulsion of the gallstone through the ileocecal valve should be reserved for highly selected situations because of danger of mucosal injury and bowel perforation^[5,6,23]. Similarly, attempts to crush the gallstone *in situ* can damage the bowel wall and should be avoided^[23]. Multiple gallstones can generally be extracted through a single incision by clearing the gut and moving smaller gallstones towards bigger ones (Figure 6). In cases of sigmoid obstruction, transanal delivery is rarely possible. Sigmoid resection removing the gallstone and the underlying stenosis has been recommended^[6].

The main long-standing controversy in the management of gallstone ileus is whether biliary surgery should be carried out at the same time as the relief of obstruction of the bowel (one-stage procedure), performed later (two-stage procedure) or not at all.

In 1922, Pybus successfully extracted an obstructing gallstone from the ileum, closed the duodenal fistula and drained the gallbladder after removing two additional gallstones from it. In 1929, Holz extracted a gallstone from the sigmoid and after removing a second gallstone that was impacted in the duodenum, he closed a cholecystoduodenal fistula and removed the gallbladder. The author recommended this procedure for patients in satisfactory general condition. In 1957, Welch performed a successful one-stage surgery in a patient who was well prepared after recurrent gallstone intestinal obstruction. The authors suggested the feasibility of the operation under optimal conditions. In 1965, Berliner *et al*^[49] reported three cases managed in a similar manner, and mentioned that when the patient is adequately hydrated with serum electrolytes restored and the procedure

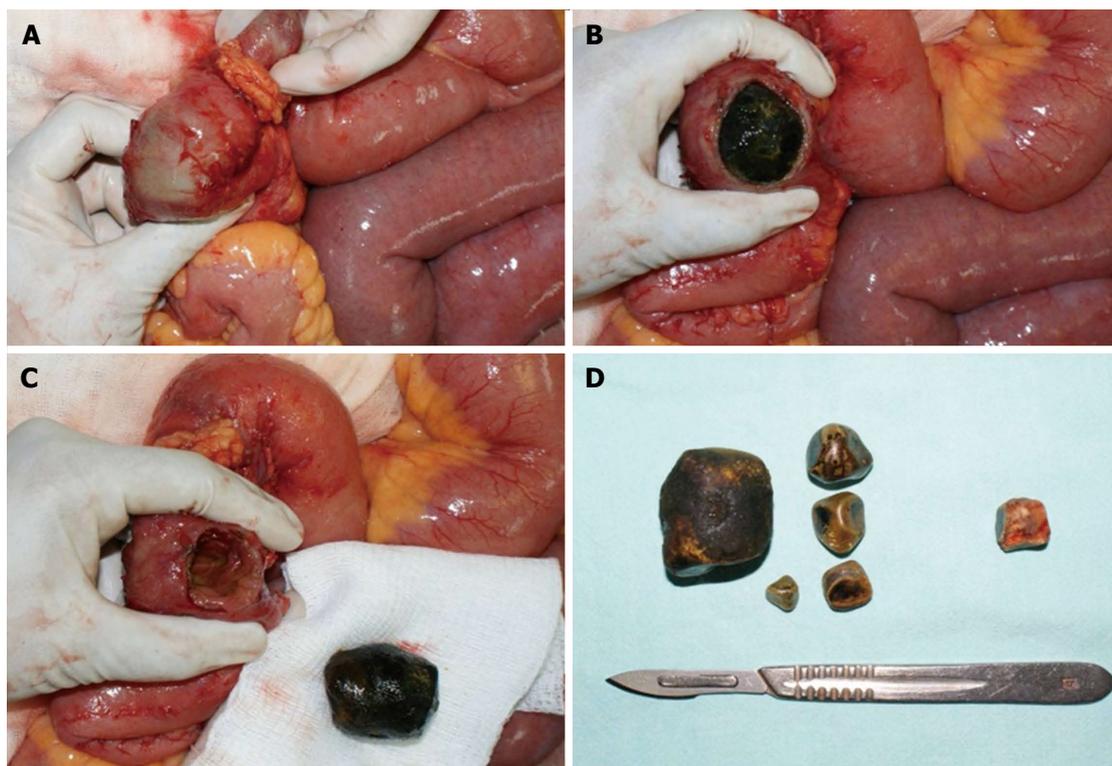


Figure 6 Surgical findings in a patient with gallstone ileus. A: An impacted gallstone was found in distal jejunum. A smaller gallstone proximal to the impacted one is observed; B: Enterotomy over the site of the impacted gallstone; C: Intestinal wall compromise due to gallstone impaction can be observed; D: The offending gallstone, plus four of smaller dimensions found in proximal jejunum. An obstructing gallstone was found and extracted from the common bile duct in the same patient (gallstone on the right).

does not represent a prohibitive operative risk, a one-stage procedure should be considered. In 1966, Warsaw *et al*^[12] reported a series of 20 patients, where enterolithotomy was combined with cholecystectomy and fistula closure in two cases, with cholecystostomy and closure of the fistula in one, and delayed cholecystectomy and closure of the fistula in two. There was no operative mortality. The authors recommend that the one-stage procedure should be considered in selected cases.

Cholecystoenteric fistula closure after the extrusion process has been reported, but if the cystic duct is permanently occluded and any part of the gallbladder mucosa remains viable, it probably remains patent^[15]. The risk of gallstone ileus recurrence is higher than previously reported. The commonly quoted recurrence incidence is 2%-5%, but up to 8% recurrence after enterolithotomy alone has been reported as well; half of these new onset events will present in the following 30 d^[50]. It must be considered that recurrence rates of 17%-33% have been reported^[6,51].

The possibility of recurrent cholecystitis and acute cholangitis has been highlighted^[6,49]. Warsaw *et al*^[12] reported recurrent symptoms or complications in 6 of 18 patients with unrepaired cholecystoenteric fistulas or retained gallbladders. Acute cholangitis has been reported in 11% of patients with cholecystoduodenal fistula and 60% with cholecystocolonic fistula^[6,34]. With a one-stage procedure, further gallstone-related events

are prevented^[12].

A long-term potential complication of biliary enteric fistula could be gallbladder cancer. Bossart *et al*^[52] found a 15% incidence of gallbladder cancer in 57 patients undergoing surgery for such fistulas, compared to 0.8% among all patients having cholecystectomy.

On the other hand, simple enterolithotomy has long been associated with a lower mortality^[7]. As Ravikumar *et al*^[53] observed, this study included patients from 70 published series spanning 40 years, with widely differing lengths of follow-up and evolving surgical techniques during this time period. Consideration should be taken of the fact that the severity of each case has influence on the outcome of any particular surgical procedure, and that mortality is not an absolute consequence of the surgical procedure itself. In the report by Clavien *et al*^[6], when patients were comparable in terms of age, concomitant diseases and APACHE II score, operative mortality and morbidity rates were not significantly different.

In 2003, Doko *et al*^[54] reported a 30 patient series with morbidity of 27.3% in patients undergoing enterolithotomy alone and 61.1% for a one-stage procedure. Mortality was 9% following enterolithotomy and 10.5% after a one-stage procedure. American Society of Anesthesiologists (ASA) scores were similar between the two groups but operating times were significantly longer for the one-stage procedure. Urgent fistula repair was significantly associated with postoperative complications.

The authors concluded that enterolithotomy is the procedure of choice, with a one-stage procedure reserved for patients with acute cholecystitis, gallbladder gangrene or residual gallstones^[6].

In 2004, Tan *et al.*^[55] reported a retrospective study of 19 patients treated by emergency surgery for gallstone ileus. The authors had no preference for either surgical procedure. Enterolithotomy alone was performed in 7 patients and enterolithotomy with cholecystectomy and fistula closure in 12 patients. In the first group, more patients had significant co-morbidity as identified by poorer ASA status (6 patients were ASA III and IV), poorer pre-operative status, and 4 patients were hypotensive in the pre-operative phase. All 12 patients in the one-stage procedure group were ASA I and II and none were hypotensive in the pre-operative phase. Operative time was significantly shorter in the enterolithotomy group (70 min vs 178 min). There were no significant differences in morbidity and there was no mortality in either group.

In 2008, Riaz *et al.*^[56] reported their retrospective experience with 10 patients diagnosed with gallstone ileus. The choice of the surgical procedure was largely determined by the clinical condition of the patient. Five patients underwent enterolithotomy alone (group 1), while the remaining 5 patients underwent cholecystectomy and fistula repair (group 2). In group 1, all patients were hypertensive and diabetic. All patients were hemodynamically-unstable, with metabolic acidosis and pre-renal azotemia. The ASA score was III or above in all patients. In group 2, only 2 patients were hypertensive and all were hemodynamically-stable at presentation with an ASA score of II. There was no operative mortality in both groups.

Many patients with gallstone ileus are elderly, with comorbidities, in poor general condition and have a delayed diagnosis, leading to dehydration, shock, sepsis or peritonitis. Relief of gastrointestinal obstruction by simple enterolithotomy is the safest procedure for these patients^[30,31].

At laparotomy, examination and careful palpation of the entire bowel, gallbladder and extrahepatic bile duct is recommended, in order to exclude gallstones, bile leakage, abscess or necrosis^[1,12,19,57]. Cholecystectomy and fistula repair reduce the need for reintervention and the incidence of complications related to fistula persistence, including recurrent ileus, cholecystitis or cholangitis, but it is justified only in selected adequately stabilized patients in good general condition, such as good cardiorespiratory and metabolic reserve, who are able to withstand a more prolonged operation, unless it has been clearly demonstrated that no gallstones remain in the gallbladder^[6,31,36,58].

Proponents of enterolithotomy alone argue that fistula closure is time consuming and technically demanding. Spontaneous fistula closure can occur when the gallbladder is gallstone-free and the cystic duct remains patent. Some authors have found no risk of cancer when fistula is not managed^[1,6,8].

According to different authors, enterolithotomy alone is the best option for most patients with gallstone ileus. The one-stage procedure should be offered only to highly selected patients with absolute indications for biliary surgery at the time of presentation and who have been adequately reanimated^[7,11,16,31,36,53].

The persistence or appearance of gallstone-related or gastrointestinal symptoms will prompt the need for evaluation. US and contrast gastrointestinal radiology may detect cholelithiasis and fistula persistence in patients who have been treated by enterolithotomy alone^[6,12]. Demonstration of gallstones, the appearance of symptoms, or a persistent cholecystoenteric fistula indicates the need for cholecystectomy, closure of the fistula, and common duct exploration^[12]. It has been emphasized that delayed cholecystectomy as a second procedure is clearly justified only in cases of symptom persistence^[7,31]. The two-stage procedure with scheduled follow-up biliary surgery is not common. Subsequent cholecystectomy and fistula closure are recommended to be performed 4 to 6 wk later^[7,16,32,55]. A mortality rate of 2.94% has been reported in this group of patients^[8].

Laparoscopy

In 1993, Montgomery^[59] reported 2 cases of mechanical intestinal obstruction, which were diagnosed laparoscopically and gallstone ileus was found. In both cases, the affected ileum segment was brought out of the abdominal cavity through a small incision, and through enterotomy the gallstone was removed. Both patients were discharged and only one presented a wound infection, which was successfully treated. In 1994, Franklin *et al.*^[60] reported a case of laparoscopically treated along with cholecystectomy and repair of a cholecystoduodenal fistula.

In 2003, El-Dhuwaib *et al.*^[61] reported a case of gallstone ileus that underwent an emergency laparoscopic enterolithotomy. During follow-up, a cholecystoduodenal fistula and bile duct stones were detected. An elective laparoscopic cholecystectomy with fistula repair, concomitant bile duct exploration, choledocolithotomy and primary bile duct closure were successfully performed. In 2007, Moberg *et al.*^[62] reported a series of 32 patients with gallstone ileus operated laparoscopically in 19 cases with 2 conversions, and by open surgery in 13 cases. There was no mortality. In 2013, Yang *et al.*^[63] reported a case of Bouveret's syndrome, which was successfully treated by laparoscopic duodenal lithotomy and subtotal cholecystectomy. In 2014, Watanabe *et al.*^[64] reported a case of gallstone ileus due to a 4 cm gallstone in the jejunum with presence of pneumobilia. Through single-incision laparoscopic surgery, enterolithotomy was performed. Cholecystoduodenal fistula closure was demonstrated 4 mo after the surgery. The patient had an uneventful postoperative course.

Although experience in minimally invasive surgical treatment of gallstone ileus is still developing, adequate management in low risk patients has allowed successful results. Dilated and edematous bowel represents a

more challenging scenario. According to a recent report, laparoscopy is used only in 10% of surgically managed gallstone ileus cases, with a high conversion rate (53.03%) to laparotomy^[68]. Early recovery and a low mortality are expected from laparoscopic procedures^[65].

Endoscopy

Gallstones causing gastroduodenal or colonic obstruction may be amenable to endoscopic detection and in certain instances to endoscopic extraction. In 1976, Stempfle *et al*^[66] reported a case of cholecystogastric fistula with passage of a gallstone to the stomach leading to massive hemorrhage of gastric mucosa. The gallstone was removed endoscopically and the imminent obstruction could be eliminated. Mucosal bleeding was managed with conservative method. Endoscopic visualization of radiologically detected gallstones in the duodenum has been reported, leading to definitive surgical treatment^[67].

In 1981, Finn *et al*^[68] reported a case of 73-year-old female with gallstone ileus which was diagnosed endoscopically and found 2 gallstones in the duodenal bulb. A cholecystoduodenal fistula was also demonstrated. Immediate surgery was performed. The role of colonoscopy in large bowel obstruction by a gallstone has been reported. In 1989, a report by Patel *et al*^[69] showed the technical difficulty after multiple attempts for gallstone extraction and further surgical extraction, but diagnosis was established. In 1990, Roberts *et al*^[70] reported the removal of a gallstone obstructing the sigmoid colon by means of colonoscopy. In 1985, Bedogni *et al*^[71] reported a successful gallstone extraction in a case of pyloroduodenal obstruction. The initial success rate of endoscopic management was less than 10%^[72]. After endoscopic mechanical lithotripsy (EML), electrohydraulic lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL) and endoscopic laser lithotripsy (ELL) have been used alone or in combination for gallstone endoscopic management.

In 1991, Moriai *et al*^[73] reported the combined use of EHL and EML for the treatment of a patient with two 3-cm gallstones in the stomach. The smaller fragments were removed orally. EHL of a gallstone causing gallstone ileus was first reported by Bourke *et al*^[74] in 1997. In 2007, Huebner *et al*^[75] reported two cases managed with EHL alone. This method has the risk of bleeding and perforation due to surrounding tissue damage. In 1997, ESWL was reported by Dumonceau *et al*^[76] who treated two patients with Bouveret's syndrome. All fragments were removed orally, except for one that was left in the stomach of the first patient and caused recurrent ileus. ESWL may need repeated sessions followed by endoscopy. Obesity and distended bowel interposition may be limitations^[77].

The use of Holmium: YAG laser lithotripsy has been reported. An attempt to fragment and retrieve a duodenal gallstone causing Bouveret's syndrome resulted in small bowel obstruction secondary to a fragment. The patient required surgical enterolithotomy^[78]. In 2005, Goldstein *et al*^[79] reported a case of a 94-year-

old patient with two gallstones in the duodenum, which could not be retrieved beyond the upper esophageal sphincter using a Roth net. A holmium: yttrium-aluminum-garnet (Holmium: YAG) laser was used for gallstone fragmentation, with subsequent successful removal^[79]. The main advantage of ELL is the precise targeting of the offending gallstone, with reduced risk of surrounding tissue injury^[80].

One of the potential limitations for endoscopic management of a gallstone is a location out of endoscopic reach. In 1999, Lübbers *et al*^[81] reported the case of a 91-year-old female patient who was unfit for surgery and after location of the gallstone in the upper jejunum, was managed by EML. In 2010, Heinzow *et al*^[82] reported the case of an 81-year-old female patient who suffered from gallstone ileus of the ileum. Peroral single-balloon enteroscopy allowed the successful endoscopic removal of the obstructing gallstone. Single and double balloon enteroscopy constitutes a recent means of endoscopically directed therapy.

A colonic location of an obstructing gallstone may be endoscopically managed in selected patients. In 2010, Zielinski *et al*^[83] reported a case of endoscopic EHL of a 4.1 cm gallstone in the sigmoid colon. A gallstone impacted at the ileocecal valve was successfully managed by Shin *et al*^[84] using EHL by means of colonoscopy in a patient with liver cirrhosis (Child-Pugh class B). The fragments were retrieved with snare and forceps.

These non-operative endoscopic methods should be considered in elderly and high risk patients^[6]. A potential complication of endoscopic treatment is the possibility of distal impaction of gallstone fragments^[17].

MORBIDITY

Previously, the most common postoperative complication has been wound infection. In 1961, Raiford^[15] observed a 75% global rate of wound infection. Localized peritonitis, respiratory complications, phlebitis, recurrent obstruction due to residual gallstones and cholangitis were also observed. In more recent series, the global rate of postoperative complications has been reported in the range of 45%-63%^[6,30,31,36,55]. Wound infection continues to be the most common complication, with rates of 27% and 42.5%, as reported by Clavien *et al*^[6] and Rodríguez Hermosa *et al*^[30] respectively. Several authors have reported no significant differences of postoperative complications between those patients treated by enterolithotomy or enterolithotomy, cholecystectomy and fistula closure^[6,31,36,55]. Martínez Ramos *et al*^[36] found a 100% complication rate among patients requiring intestinal resection. Global immediate complications were greater when the diagnosis was made during the surgical procedure than when it was made prior to surgery. If relapsing gallstones ileus is not considered, less common postoperative complications have been wound dehiscence, cardiopulmonary and vascular complications, sepsis, intestinal and biliary fistulas, and urinary tract infections^[6,31,55].

Currently, the most common postoperative complication is acute renal failure, which was seen in 30.45% of patients, followed by urinary tract infection (13.79%), ileus (12.42%), anastomotic leak, intraabdominal abscess, enteric fistula (12.27%), and wound infection (7.73%)^[8].

MORTALITY

Gallstone ileus is predominantly a geriatric disease, and as many as 80%-90% of patients have concomitant medical illnesses. Hypertension, diabetes, congestive heart failure, chronic pulmonary disease and anemia are the most common comorbidities^[8]. These associated conditions need to be considered, as they may affect the results of treatment^[1].

Mortality rates were reported as high as 44% at the late 1800's, while in the first half of the twentieth century these rates maintained between 40%-50%^[3,19]. In the 1990's, considerable reductions in mortality were observed to 15%-18%, to current rates of less than 7%^[7,8]. Specifically, simple enterolithotomy has long been associated with an 11.7% mortality compared to 16.9% for the one-stage procedure (enterolithotomy plus cholecystectomy and fistula closure)^[7].

As described by Kirchmayr *et al.*^[85], four main reasons might be responsible for the high number of lethal courses. First of all, gallstone ileus is a disease of the elderly. Second, concomitant diseases, such as cardiorespiratory diseases and/or diabetes mellitus are frequent. Third, because of uncommon symptoms diagnosis is difficult and a mean delay of 4 d from the beginning of symptoms to hospital admission is reported. Fourth, postoperative recovery is also hampered; age-related complications such as pneumonia or cardiac failure are more frequent than surgery associated complications.

In the study by Halabi *et al.*^[8] of 3268 gallstone ileus cases who underwent surgical management, an overall mortality rate of 6.67% was observed. The authors noted that fistula closure, performed during the initial procedure, was independently associated with a higher mortality rate than enterolithotomy alone. When bowel resection was indicated, it was also associated with a higher mortality rate than enterolithotomy alone. When analyzing by surgical procedures, the mortality rates were 4.94% for the enterolithotomy alone group, 7.25% for the enterolithotomy plus cholecystectomy and fistula closure group, 12.87% for the bowel resection group, and 7.46% for the bowel resection and fistula closure group. However, if consideration is made of the fact that bowel resection is not exactly an option but a requirement due to the bowel segment conditions instead, the mortality for those patients undergoing enterolithotomy alone or bowel resection is actually 6.53%.

In summary, gallstone ileus or gallstone gastrointestinal obstruction represents less than 1% of gastrointestinal obstruction cases, with a higher frequency

among the elderly. Computed tomography has proven to be the most accurate diagnostic modality, but diagnostic criteria validation is required. Surgical relief of obstruction is the cornerstone of treatment. Given the high incidence of comorbidities in these patients, a good judgement in selecting the surgical procedure is required. Enterolithotomy remains the mainstay of operative treatment. A one-stage cholecystectomy and repair of fistula is justified only in selected patients in good general condition and adequately stabilized preoperatively. Specific criteria for a one-stage procedure remain to be established. A two-stage surgery is an option for patients with persistent symptomatology after enterolithotomy surgery. Large prospective studies of laparoscopic and endoscopic-guided procedures are expected.

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Gastroesophageal reflux disease: A review of surgical decision making

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Abstract

Gastroesophageal reflux disease (GERD) is a very common disorder with increasing prevalence. It is estimated that up to 20%-25% of Americans experience symptoms of GERD weekly. Excessive reflux of acidic often with alkaline bile salt gastric and duodenal

contents results in a multitude of symptoms for the patient including heartburn, regurgitation, cough, and dysphagia. There are also associated complications of GERD including erosive esophagitis, Barrett's esophagus, stricture and adenocarcinoma of the esophagus. While first line treatments for GERD involve mainly lifestyle and non-surgical therapies, surgical interventions have proven to be effective in appropriate circumstances. Anti-reflux operations are aimed at creating an effective barrier to reflux at the gastroesophageal junction and thus attempt to improve physiologic and mechanical issues that may be involved in the pathogenesis of GERD. The decision for surgical intervention in the treatment of GERD, moreover, requires an objective confirmation of the diagnosis. Confirmation is achieved using various preoperative evaluations including: ambulatory pH monitoring, esophageal manometry, upper endoscopy (esophagogastroduodenoscopy) and barium swallow. Upon confirmation of the diagnosis and with appropriate patient criteria met, an anti-reflux operation is a good alternative to prolonged medical therapy. Currently, minimally invasive gastroesophageal fundoplication is the gold standard for surgical intervention of GERD. Our review outlines the many factors that are involved in surgical decision-making. We will review the prominent features that reflect appropriate anti-reflux surgery and present suggestions that are pertinent to surgical practices, based on evidence-based studies.

Key words: Gastroesophageal reflux disease; Decision-making; Fundoplication

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Core tip: Gastroesophageal reflux disease (GERD) is a common disorder with increasing prevalence. Excessive reflux of acidic gastric contents has a multitude of symptoms for the suffering patient including heartburn, regurgitation, cough, and dysphagia. Surgical interven-

tion is often necessary in those who fail medical therapy, are non-compliant or wish to discontinue long-term medical therapy, have complications secondary to GERD, or present with extra-esophageal symptoms. There are various types of anti-reflux operations that are successful in treating GERD. Laparoscopic fundoplication is the gold standard for surgical treatment. Robotic Nissen fundoplication is also advantageous with good outcomes.

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INTRODUCTION

The prevalence of gastroesophageal reflux disease (GERD) in the United States has appreciably increased in the last few decades, making it one of the most common chronic diseases^[1]. It is estimated that up to 20%-25% of Americans experience symptoms of GERD weekly^[2]. Interestingly, most patients that present to their primary care doctor with typical GERD symptoms, such as heartburn and regurgitation, never undergo formal diagnostic evaluation and are managed with non-surgical therapy such as proton pump inhibitors (PPI) long-term^[3]. In accordance with the American Gastroenterological Association and the American College of Gastroenterology, patients with symptoms suggestive of GERD should undergo an 8-wk empiric treatment regimen with a PPI^[4]. Non-responders should undergo esophagogastroduodenoscopy (EGD) as well as esophageal pH monitoring if EGD reveals no abnormalities^[4]. On the other hand, patients with extraesophageal symptoms are much more difficult to diagnose and should undergo pH monitoring sooner in the diagnostic algorithm^[5]. Unremitting GERD can result in complications including esophagitis with scarring and stricture formation, Barrett's esophagus and cancer, specifically adenocarcinoma. These types of symptoms may often require daily medication, which can be a significant adverse impact on the patients' quality of life^[6].

PATHOPHYSIOLOGY AND SYMPTOMATOLOGY

In simple terms, GERD results from failure of the distal esophageal reflux barrier^[7,8]. During normal physiologic swallowing, relaxation of the lower esophageal sphincter (LES) and crura occur which in turn allow the food bolus to enter the stomach. Furthermore, the LES and crura relax during belching to allow gas venting. If the LES relaxes separately from initiation of a swallow, these

relaxations are termed transient lower esophageal relaxations (TLESRs)^[7,8]. It has been shown that abnormal TLESRs result in an enlarged cross sectional area at the gastro-esophageal junction resulting in increased reflux of gastric contents and gas. These TLESRs are rather important as they likely result in 90% of reflux episodes^[7,9]. Hiatal hernias appear to increase the degree of reflux during TLESRs. In patients with severe reflux esophagitis, a hypotensive LES seems to be the etiology rather than abnormal TLESRs^[7,10]. If the LES pressure is < 10 mmHg, reflux tends to occur with more frequency. If the LES pressure is < 4 mmHg, however, free reflux occurs^[7,11,12].

The most common symptom of GERD is heartburn, which is said to be caused by the stimulation and activation of mucosal chemoreceptors in the distal esophagus^[3]. Other typical esophageal symptoms include regurgitation which, in addition to heartburn, reflect dysfunction of the reflux barrier. Extra-esophageal symptoms include cough, asthma, and chest pain. Additional testing, including combined impedance/pH monitoring, should be performed if GERD is thought to be the cause of any atypical symptom and/or the patient has been on long-term medical treatment and surgery is being considered^[8,13,14].

MANAGEMENT OF GERD

Surgical vs medical management of GERD

Medical options for patients with GERD include antacids, histamine-receptor antagonists or PPI therapy^[4]. Studies comparing medical management of GERD to surgical therapy have shown that anti-reflux operations are an effective alternative to medical treatments, even for patients with good symptom control on pharmacologic therapy^[15].

Furthermore, fundoplication results show significantly less acidic content and increased LES pressure compared to medical treatment alone. Fundoplication is associated with a high level of patient satisfaction and improved quality of life in patients with chronic GERD. According to the guidelines written by the American Society for Gastrointestinal and Endoscopic Surgeons (SAGES), surgical procedures for GERD are curative in 85%-93% of cases^[16]. In review of a meta-analysis comparing open vs laparoscopic surgery, a total of 16.2% of the patients in the open group and 14.7% in the laparoscopic group used acid suppression drugs post-operatively^[17]. As advancements in the field of laparoscopy have been made, minimal invasive operations have been established as the gold standard in the surgical treatment of this condition^[8].

Indications for anti-reflux surgery

The most frequent indication for anti-reflux operations symptoms refractory to pharmacological therapy^[18]. It is critical, however, to have physiological testing showing pathological acid reflux exists. SAGES guidelines suggest

that surgical intervention may be appropriate in patients who have failed medical management, decide for surgery despite successful medical management, have complications of GERD such as Barrett's esophagus and/or peptic stricture, have medical complications attributable to a large hiatal hernia, or have "atypical" symptoms such as asthma, hoarseness, cough, chest pain, dental erosions or aspiration and reflux documented on 24 h pH monitoring^[16]. It is important to note, however, that operative intervention to alleviate GERD should be performed after the diagnosis of GERD has been objectively confirmed and should only be considered in individuals who meet the aforementioned criteria. In the subset of patients who do indeed respond to pharmacologic therapy but are either unable or unwilling to take daily medication, anti-reflux surgery will likely prove quite beneficial. It has been estimated that up to 40% of patients do not respond to PPI therapy^[4]. There have been studies showing poor resolution of reflux symptoms after surgery in patients who do not respond to acid reducing medications. An eleven year follow-up study reported response and lack of response to acid reducing medications were associated with 77.1% and 56.0% success rates of laparoscopic Nissen fundoplication (LNF) respectively^[19]. Despite the potential of suboptimal results, failure of pharmacologic therapy in the treatment of GERD still remains an operative indication. In one study reviewing long-term outcomes after anti-reflux surgery, at 69 mo, the majority of patients maintained improvement or resolution of heartburn (90%), regurgitation (92%), and dysphagia (75%) when compared to before laparoscopic reflux surgery. The results were less satisfactory in patients with extraesophageal symptoms such as hoarseness (69%) and cough (69%)^[20]. Few absolute contraindications to an anti-reflux exist except the presence of esophageal cancer or Barrett's mucosa with untreated high-grade dysplasia. A long-term outcome 5-year follow-up study evaluating anti-reflux surgery in patients with Barrett's esophagus that included patients with low-grade dysplasia, short and long-segment Barrett's showed reflux symptoms were absent in 67 of 85 patients (79%) after surgery^[21]. In regards to resolution of Barrett's, low-grade dysplasia regressed to nondysplastic Barrett's in 7 of 16 (44%), and intestinal metaplasia regressed to cardiac mucosa in 9 of 63 (14%). High-grade dysplasia and adenocarcinoma were prevented in all 97 patients^[21].

Preoperative considerations

Preoperative objectives should identify the proper patients for anti-reflux surgery after appropriately evaluating symptoms and diagnostic studies. Proper selection of patients optimizes outcomes. Initial evaluation must include a thorough history and physical exam. It is important for the surgeon to focus on the duration of symptoms, type of reflux symptoms and causation/temporal relationship of symptoms. Studies have shown that patients with typical symptoms, in comparison to

those with atypical symptoms, have a better response to fundoplication. A 10-year follow-up study reported 85% percent of patients with typical symptoms had a successful outcome after LNF, compared to only 41% with atypical symptoms^[19]. Furthermore, patients who experience exaggerated symptoms when supine rather than standing tend to have better outcomes after fundoplication as well. In the supine position, transient lower esophageal relaxation periods increase. Studies have shown that fundoplication reduces TLRSR frequency by 50% and thus decrease reflux events^[22,23]. After a detailed history and physical examination is performed, important preoperative studies to consider are: (1) Upper endoscopy (EGD): Endoscopy has a high specificity (95%) for diagnosing GERD as the operator can note visual and histopathologic changes of the esophageal mucosa. Moreover, the operator is able to take biopsies of the mucosa that are essential in ruling out other etiologies or complications of reflux. Biopsies of the mucosa are necessary to diagnose and exclude other non-reflux esophageal disorders such as eosinophil esophagitis, *Helicobacter pylori*, Barrett's esophagus or esophageal cancer. As stated previously, if high-grade dysplasia or esophageal cancer is noted on endoscopy, the surgeon cannot perform anti-reflux surgery. If, however, low-grade dysplasia or intestinal metaplasia is noted, the surgeon should proceed with the procedure as studies have shown resolution and regression to cardiac mucosa. Despite its' high specificity, endoscopy lacks sensitivity in the diagnosis of GERD as up to half of patients with GERD will have normal endoscopic findings^[24]. EGD is also useful to visualize the presence of a hiatal hernia. If a hiatal hernia is discovered pre-operatively, the surgeon must repair the hiatal hernia prior to performing the wrap; (2) pH monitoring: As stated previously, non-responders to pharmacologic therapy should undergo EGD as well as esophageal pH monitoring. pH monitoring can be a very valuable tool to objectively establish a diagnosis of GERD and is the gold standard for pathologic acid reflux^[25]. A 24-h or 48-h intra-esophageal study can be done to evaluate the patient's pH levels during daily life, and thus assess reflux patterns as well as determining the patients' ability and frequency of clearing acid. Multiple devices are available for use in pH monitoring. Two specific devices include a 24 h transnasal catheter placement and BRAVO wireless esophageal pH probe monitoring, both of which have been proven effective to accurately diagnose GERD^[5]. It is necessary that the patient discontinue his/her acid suppression medication for a minimum of 1 wk for the pH monitoring to be accurate. If the patient is unable to stop the medication, referral for an impedance test should be done^[26]. Most studies have shown an elevated DeMeester score indicates pathological reflux. Impedance testing can distinguish between acidic and nonacidic reflux. Impedance testing, however, is prone to interpretational error so it is not optimal^[27]; (3) Esophageal manometry is used to identify dysmotility of the esophagus, for example, achalasia. Some surgeons

will determine the type of surgery necessary for the patient based on their manometry results (Nissen vs partial). However, there is overwhelming data showing even with poor motor function of the esophagus, a Nissen fundoplication provides the best results by effective blockade of reflux, which is most likely, the cause of poor dysmotility^[28,29]. Our group has shown that compared to patients with good motor function, patients with poor motor function tend to have longer short-term dysphagia, yet at the 3-mo follow-up period, both groups behaved similarly; and (4) Barium swallow: Perhaps not useful to all surgeons, a barium swallow can help to better understand the anatomy of esophagus and stomach. A barium swallow can prove valuable in patients with various anatomical abnormalities such as a shortened esophagus or hiatal hernias. Hiatal hernias affect the competence of the LES, in turn, impeding the ability to clear acid in the esophagus. It is prudent that the surgeon recognizes hiatal hernias preoperatively as it is necessary to repair them during any anti-reflux operation. A barium swallow study can also determine if the patient has esophageal dysmotility. For example, the diagnosis of achalasia is supported by barium swallow findings including dilation of the esophagus, a narrow esophago-gastric junction with "bird-beak" appearance, aperistalsis, and poor emptying of barium^[30].

SURGICAL TECHNIQUES USED TO TREAT GERD

Laparoscopic vs open technique for GERD

A laparoscopic, transabdominal approach is preferred for the vast majority of patients undergoing anti-reflux surgery. Rarely, transthoracic and open abdominal approaches are required and may be considered for patients undergoing revision of their former anti-reflux operations^[31]. However, reoperation surgery typically can be performed laparoscopically. Perioperative morbidity was found to be significantly lower (65%) after laparoscopic compared with open fundoplication^[32]. Laparoscopic fundoplication is associated with longer operative times but shorter hospital stays^[17]. In turn, conversion rates to open surgery were less than 5%^[17]. Laparoscopic fundoplication is preferred over open surgery because it is associated with shorter hospital stay, decreased pain, postoperative wound infections and abdominal wall hernia formation^[17]. Additionally, using the laparoscopic approach, surgeons have the advantage of seeing all the hiatal structures in a magnified fashion. In a 10-year randomized trial comparing LNF to conventional Nissen fundoplication (CNF or open technique), it was noted that twice as many patients required reoperation after CNF, including a much higher number of incisional hernia corrections. The 10-year effectiveness of LNF and CNF is comparable in terms of improvement of GERD symptoms, PPI use, quality of life, and objective reflux control seen on impedance studies. Thus, the long-term results from this trial

lend level 1 support to the use of LNF as the surgical procedure of choice for GERD^[33]. Regardless of the type of fundoplication performed, the aim of the operation is the same: Re-create and restore the normal physiologic functionality of the LES, reconstruction of the hiatus when necessary and repair of any hiatal hernia if present.

Partial vs total fundoplication

In the United States, in comparison to Europe, a 360° fundoplication is the most common anti-reflux operation performed. European surgeons, however, favor a partial fundoplication operation. Many prospective, randomized, controlled studies have evaluated both 360° and 270° fundoplication procedures and have shown similar short- and long-term efficacy^[34,35]. Despite these findings, proponents of the Nissen fundoplication argue its superiority over the partial fundoplication. Advocates for the partial fundoplication argue that their patients have fewer symptoms of bloating and retain their ability to vomit. In one randomized control study, there were noted to be a higher rate of postoperative dysphagia, flatulence, and bloating in total fundoplication as compared to partial fundoplication^[36]. There were not, however, significant differences between the two modalities in the continuing postoperative incidence of heartburn, esophagitis or persistent acid reflux. A similar proportion of patients experiencing excellent long-term outcomes were seen in both partial and Nissen fundoplication^[34,36]. Another study reported at 10 years, 89.5% patients who had undergone laparoscopic fundoplication were free of significant reflux (93.3% after Nissen, 81.8% after Toupet). Thus, Nissen patients did better than Toupet patients, although the difference was not statistically significant^[34].

Anterior (Dor) vs Nissen fundoplication

Prospective, randomized controlled studies comparing 120-degree anterior fundoplication vs Nissen fundoplication showed anterior fundoplication to be associated with less postoperative dysphagia, 74% in the Nissen group and 95% in the anterior fundoplication group after 24 mo follow up^[36]. However, this technique was shown to be less effective for controlling reflux over time. In addition, more patients required reoperations for reflux control after anterior fundoplication^[37].

Toupet vs Nissen fundoplication

There have been several randomized control studies comparing Toupet fundoplication to Nissen fundoplication. Studies have shown lower rates of post-operative dysphagia after a Toupet fundoplication when compared to results after a Nissen fundoplication - around 8.5% vs 13.5% respectively^[38]. There were no differences, however, in the percentage of patients affected by heartburn comparing the two procedures^[38]. Regarding the operative technique, recent findings have shown that the length of the wrap is important when performing a Toupet fundoplication. For example, a 3.0 cm Toupet vs 1.5 cm Toupet proved to better control reflux. The

Table 1 Comparison of advantages and disadvantages in different types of funduplications

	Advantages	Disadvantages
Nissen fundoplication	Very effective in controlling reflux over long periods of time	Increased flatulence, bloating and dysphagia
Anterior (Dor) fundoplication	Less postoperative dysphagia	Recurrent symptoms over time requiring more reoperations
Toupet fundoplication	Less postoperative dysphagia	Surgeons need to be mindful of length of wrap as it determines quality of reflux control

length of the wrap in a Nissen fundoplication, however, did not influence reflux control, rather mild dysphagia rates were higher for the 3.0 cm wrap (8.8%) compared to the 1.5 cm wrap (21.2%) at the 12-mo follow up^[39]. Five years after the operation, mild dysphagia rates in the Nissen fundoplication groups were equivocal, 9.7% in the 1.5 cm wrap and 7% in the 3.0 cm wrap^[39]. More level 1 evidence with longer follow up periods is required to determine whether Nissen fundoplication is superior to Toupet fundoplication in terms of patient outcomes (Table 1).

Use of robotic surgery in treating GERD

The use of robotic surgery for managing GERD has been shown to be a viable and safe option, with similar outcomes when compared to laparoscopy after one year follow up. Robot-assisted LNF is comparable to traditional laparoscopy in terms of complications, mortality and length of hospital stay. Robotic Nissen fundoplication is advantageous as the surgeon has improved ergonomics, visualization, comfort, and autonomy. The only disadvantages seen with robotic assisted surgeries were reported to have longer surgical times (131.3 min vs 91.1 min laparoscopically), and generally higher costs when compared to laparoscopic surgery^[40].

KEY OPERATIVE STEPS IN ROBOTIC NISSEN FUNDOPLICATION

Positioning

Supine position with arms out on arm boards.

Incision and exposure

Veress technique is used to enter the abdominal cavity 13 cm subxiphoid and 5 working ports are placed under direct visualization. A Genzyme liver retractor is placed to retract the left lobe of the liver superiorly and laterally. The patient is placed in steep reverse Trendelenburg, and the robot (DaVinci Xi) is docked and the working instruments are placed.

Procedure

Dissection begins with the takedown of the gastrohepatic ligament using a vessel sealer all the way to the right crus that is clearly dissected off the esophagus. The short gastrics are then taken all the way through the angle of His until the left crus is clearly defined. Right and left crus are clearly delineated, and the esophagus is identified. A Penrose drain is placed around the esopha-

gus and the posterior vagus after clearly identifying this window. Dissection is carried into the chest, allowing for complete reduction of the esophagus, and after which the hiatus is closed using V-Loc and 3-0 silk sutures.

The fundoplication is then performed around a 56 bougie taking a distal and proximal bite of the esophagus. The bougie is then removed. Posterior pexy is then performed to the right crus with 2 sutures. An anterior pexy is performed to the right and left crus.

Penrose is removed as is the Genzyme retractor.

The robot is undocked and the ports were removed under direct visualization.

The skin is approximated using fine absorbable sutures in a subcuticular manner.

Special situations

GERD in morbidly obese patients and surgical technique: There is a direct association between obesity and gastroesophageal reflux. The prevalence of GERD is higher with people that have higher body mass index (BMI), and linearly increases with increased BMI. Some studies have shown fundoplication surgeries for morbidly obese patients to have a higher rate of failures compared to normal weight patients^[19]. Other studies, however, have showed equivalent outcomes in obese and normal weight patients^[41,42]. One of the many lifestyle alterations suggested by physicians to aid in the treatment of GERD is weight loss. Morbidly obese patients following Roux-en-Y gastric bypass (LRYGB) have improved reflux symptoms after losing weight^[43]. One prospective study quoted 94% resolution of reflux symptoms 9-mo after patients underwent LRYGB^[44]. Essentially, the LRYGB procedure helps the patient lose weight and improve reflux symptoms as well. Thus, it is the procedure of choice for many surgeons treating morbidly obese patients with GERD.

Revisional surgery for failed anti-reflux surgery

The failure rate of fundoplication ranges from 3% to 16%^[45]. Not every patient who has failed anti-reflux surgery needs reoperation. It is important for the surgeon to determine whether a physiologic or anatomic failure can be ameliorated surgically. The most common indications for reoperation are a "slipped" fundoplication or herniation of the wrap into the mediastinum^[45,46]. Laparoscopic re-operative anti-reflux surgery is a viable and safe option for patients. While it is effective, re-operative surgeries have higher complication rates compared to primary repairs such as gastric or esophageal perforation^[45]. The re-operation should be done

in the same manner as the primary fundoplication. Revisional surgery, compared to primary repair, requires longer operative times (mean duration of reoperation was 177.4), is correlated with higher conversion rates to an open approach and has higher complication rates^[47]. Patient satisfaction after revisional surgery is generally high (89%) with resolution of heartburn symptoms in almost 80% of patients and resolution of regurgitation in 85% of patients, 18 mo after surgery^[48].

CONCLUSION

GERD is a very common disorder with increasing prevalence. Excessive reflux of acidic gastric contents has a multitude of symptoms for the suffering patient including heartburn, regurgitation, cough, and dysphagia. There are also associated complications of GERD including erosive esophagitis, Barrett's esophagus, stricture and adenocarcinoma. Surgical intervention is often necessary in those who fail medical therapy, are non-compliant or wish to discontinue long-term medical therapy, have complications secondary to GERD, or present with extra-esophageal symptoms. There are various types of anti-reflux operations that have been quite successful in treating GERD and restoring competence in an otherwise incompetent LES, while at the same time repairing a potential hiatal hernia. Laparoscopic fundoplication is the gold standard for surgical treatment of severe GERD and results in approximately 95% patient satisfaction. Robotic Nissen fundoplication is also very advantageous with good outcomes. In regards to the specific type of fundoplication, the Nissen fundoplication has overall improved outcomes when compared to partial wraps. Before entertaining a surgical approach, it is important that the surgeon take all necessary preoperative measures to ensure surgery is the appropriate choice for the patient. The surgeon must also take into consideration special situations such as obese patients or those that are in need of a revisional anti-reflux procedure.

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How to decide on stent insertion or surgery in colorectal obstruction?

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Abstract

Colorectal cancer is one of the most common cancers in western society and malignant obstruction of the colon accounts for 8%-29% of all large bowel obstructions. Conventional treatment of these patients with malignant obstruction requiring urgent surgery is associated with a greater physiological insult on already nutritionally replete patients. Of late the utility of colonic stents has offered an option in the management of these patients in both the palliative and bridge to surgery setting. This has been the subject of many reviews which highlight its efficacy, particularly in reducing ostomy rates, allowing quicker return to oral diet, minimising extended post-operative recovery as well as some quality of life benefits. The uncertainty in managing patients with malignant colonic obstructions has led to a more cautious use of stenting technology as community equipoise exists. Decision making analysis has demonstrated that surgeons' favored the use of stents in the palliative setting preferentially when compared to the curative setting where surgery was preferred. We aim to review the literature regarding the use of stent or surgery in colorectal obstruction, and then provide a discourse with regards to the approach in synthesising the data and applying it when deciding the appropriate application of stent or surgery in colorectal obstruction.

Key words: Self-expanding metallic stent; Stenting; Surgery; Colorectal cancer; Large bowel obstruction; Radiology

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Core tip: Despite the accumulation of data on stent insertion, the choice of stent or surgery as the most appropriate modality in the management of colorectal obstruction presents a constant decision dilemma. When cure is possible we want that, but with minimal

morbidity. In a group of patients who are prone to higher rates of morbidity and mortality, this can be problematic and full of uncertainty. This review takes an approach to review the primary and secondary outcomes established in the literature regarding the use of stent or surgery in colorectal obstruction, and then create discourse and a structured approach in regards to synthesising the data and applying it when deciding the appropriate application of stent or surgery in colorectal obstruction.

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INTRODUCTION

Despite the accumulation of data on stent insertion, the choice of stent or surgery as the most appropriate modality in the management of colorectal obstruction presents a constant decision dilemma. When cure is possible we want that, but with minimal morbidity. In a group of patients who are prone to higher rates of morbidity and mortality, this can be problematic and full of uncertainty.

This review takes an approach to review the primary and secondary outcomes established in the literature regarding the use of stent or surgery in colorectal obstruction, and then create discourse and a structured approach in regards to synthesising the data and applying it when deciding the appropriate application of stent or surgery in colorectal obstruction.

Colorectal cancer is one of the most common cancers in western society and malignant obstruction of the colon accounts for 8%-29% of all large bowel obstructions^[1]. Other causes of large bowel obstruction include uterine, ovarian, gastric, breast, bladder and kidney malignancies^[2]. Conventional treatment of these patients with malignant obstruction requiring urgent surgery is associated with a greater physiological insult on already nutritionally replete patients. This is associated with mortality in 15%-34% of patients and morbidity in 32%-64% of patients^[3]. Of late the utility of colonic stents has offered an option in the management of these patients. The first being used by Dohmoto *et al*^[4] in 1991. Tejero *et al*^[5] described the use of colonic stents as a "bridge to surgery" in 1994. This has been the subject of many reviews which highlight its efficacy, particularly in reducing ostomy rates, allowing quicker return to oral diet, minimising extended post-operative stay and some quality of life (QoL) benefits^[6]. Xinopoulos *et al*^[7] demonstrated that self-expanding metallic stent (SEMS) placement represents an alternative approach to colostomy for patients with inoperable malignant colonic strictures. The uncertainty in managing patients with malignant

colonic obstructions has led to a more cautious use of stenting technology as community equipoise exists^[8].

PATIENT AND DISEASE FACTORS

Regarding the location of obstructing colonic malignancy, Fiori *et al*^[9] in 2004 reported that 63.6% of obstructing malignancies occur in the rectum and 36.3% in the rectosigmoid/sigmoid colon. Sankararajah *et al*^[10] in 2005 observed 37% in the rectosigmoid, 21% in the sigmoid colon, 16% at the splenic flexure, 16% in the descending colon, 5% in the rectum and 5% in the ascending colon. van Hooft *et al*^[11] in 2008 observed 76% obstruction in the rectosigmoid and 24% obstruction in the descending colon. With the majority of obstructing pathology being on the left side, this makes these lesions amenable to endoscopic intervention. Sankararajah *et al*^[10] demonstrated malignant stricture length to be in the range of 3-7 cm meaning that all these lesions are within "stentable" range. Fiori *et al*^[9] and van Hooft *et al*^[11] collected data on patient ASA level with all patients included in their trials being ASA 1 to 3. The majority of the patients were in the ASA 2 category.

MORBIDITY OF SURGERY V STENT

While decision making with regards to the utility of stents in patients with metastatic disease may be easier for the treating clinician, this decision is more difficult to make for patients with local disease. A recent randomised controlled trial (RCT) by Young *et al*^[6] reported that in a population of patients with incurable metastatic large bowel obstruction, stent use was associated with faster return to diet, decreased stoma rates, reduced post-procedure stay, and some QoL benefits.

The decision with regards using a stent in patients with non-metastatic malignant bowel obstruction is one that is fraught with indecision due to the theoretical risk of perforation converting a once potentially curable disease to incurable^[12,13]. However this risk needs to be balanced with multiple other factors, principally being the patients pre-existing morbidities and the need for emergent surgical intervention. In this day, with highly trained endoscopists, the more imminent risk of perforation is much lower in some centres than the reported 4%.

Efficacy

The efficacy of SEMSs as a tool in the treatment of malignant colonic obstruction has been demonstrated well over the past few years. Many randomised control trials have supported their use and hence should be considered a valid option in the treatment of this condition (Table 1).

The 2011 review by Sagar *et al*^[14] reported an clinical relief of obstruction in the colonic stenting group to be approximately 0.66 d compared to 3.55 d in the emergency surgery group, with an overall success rate of 86%. In Ho's review in 2012, the placement of

Table 1 Summary of the studies included in this review

Ref.	Centres and aim	No. of patients (stenting/surgery)	Stenting morbidity	Surgery morbidity	Stenting mortality	Surgery mortality	Stenting efficacy
Fiori <i>et al</i> ^[9]	Single centre, palliation	11/11	0	1/11 (9%)	0	0	100%
Xinopoulos <i>et al</i> ^[27]	Single centre, palliation	15/15	0	0	0	0	93%
van Hooft <i>et al</i> ^[111]	Multicentre, palliation	11/10	11/11 (100%)	5/10 (50%)	3/11 (27%)	0	82%
Sankararajah <i>et al</i> ^[100]	Single centre	9/9	2/9 (22%)	6/9 (67%)	1/9 (11%)	1/9 (11%)	78%
Cheung <i>et al</i> ^[23]	Single centre, bridge to surgery	24/24	2/24 (8%)	17/24 (71%)	0	0	83%
van Hooft <i>et al</i> ^[24]	Multicentre, bridge to surgery	47/51	25/47 (53%)	23/51 (41%)	9/47 (19%)	9/51 (18%)	70%
Ho <i>et al</i> ^[15]	Single centre, bridge to surgery	20/19	7/20 (35%)	11/19 (35%)	0	3/19 (16%)	70%
Young <i>et al</i> ^[6]	Multicentre, palliative	26/26	10/26 (38%)	14/26 (54%)	0	0	79%

self expanding metallic stents took a median time of 35 min (range, 20-80 min). Seventy percent patients (14/20) had been stented successfully. Following stent placement, they resumed a diet after approximately day 2 and were discharged about day 4. Six out of 20 patients failed stenting with the main cause being the inability to pass the guide wire across the stenotic cancer (4/6 cases)^[15]. This technical success was also noted in the review by Khot *et al*^[16]. It may be overcome with the use of a pediatric nasogastroscope^[17].

Both Tan *et al*^[18] and Zhang *et al*^[19] reviews demonstrated that a higher primary anastomosis rate and lower morbidity rate was achieved in the group receiving colonic stents.

In the study by Ho *et al*^[15] stented patients were sent home significantly sooner than in the emergency surgery groups, with medial length of stays at 6 d vs 8 d respectively ($P = 0.028$). Furthermore, they demonstrated significantly better outcomes for the stenting group that went on to have elective surgery compared to the group randomized to have emergency surgery^[14].

A recent metaanalysis by Zhao *et al*^[20] emphasized that there is limited data on the long term survival of patients with malignant left sided colonic obstruction when comparing emergency surgery with semi-elective use of stents. With limited data, recommendation was made for more studies on the topic^[20].

BLOCKAGE

Blockage of stents principally affects patients who have long term stent insertion in the palliative setting. In the review by Khot *et al*^[16], the overall, reobstruction occurred in 52 of 525 (10%) cases with only three patients in the "bridge to surgery" group having reobstruction. The reasons of reobstruction in these patients included tumour in-growth in 32 (62%), stent migration in seven (13%) and faecal impaction in 13 (25%)^[16]. These issues with obstruction of the stent can be managed expectantly with surveillance being tailored to the patient's condition. In general, patients who are having the stent as a bridge to surgery would very rarely experience obstruction. Patients with palliative stent insertion who are not candidates for surgery would present the main group with tumor related blockage and this may be managed expectantly with re-stenting of the

lesion.

STOMA RATES

A major advantage of colonic stent placement is the reduction of stoma formation rates^[5,6,9,11,21]. This represents a significant improvement in the patient outcomes with relation to physical recovery and overall QoL issues. In the meta-analysis by Cennamo *et al*^[22], the permanent stoma creation rate was 38/152 (25%) in the stent group and 78/162 (48.1%) in the surgical group; the pooled analysis showed a significantly higher rate in the surgical group^[20]. In the RCT by Young *et al*^[6], none of the 19/26 patients in the stent group who were successfully stented required a stoma while 24/26 in the surgery group required a stoma to be fashioned ($P < 0.001$).

PERFORATION RATES

The decision of using a stent in patients with non-metastatic malignant bowel obstruction is one that is fraught with indecision due to the theoretical risk of perforation converting a once potentially curable disease to incurable. However this risk needs to be balanced with multiple other factors, principally being the patients pre-existing morbidities and the need for emergent surgical interventions. In four trials, no stent related perforation was noted (Young *et al*^[6] 2015, Cheung *et al*^[23] 2009; Fiori *et al*^[9] 2004; Sankararajah *et al*^[100] 2005). In two of the RCTs by Khot *et al*^[16] 2011 and van Hooft *et al*^[24], a perforation rate of 4% was noted. Khot *et al*^[16] states that this rate was significantly associated with balloon pre-dilatation. With Van Hooft's study the large number of centres^[24] involved in the study may not have allowed a standardisation in the technique and also local expertise may vary considering that some centres contributed one patient over the two year period.

DEATH

In malignant obstruction of the colon, emergency surgery is associated with a high mortality rate of 10%-30%, when compared to < 5% rate in elective surgery for colorectal cancer^[25,26]. Three meta-analyses^[14,18,19],

Table 2 Surgeons' treatment preferences in different clinical scenarios (Suen *et al*^[8])

Clinical scenarios	Level of clinical certainty			Evidence of community equipoise?
	Surgery (%)	Undecided (%)	Stent (%)	
1 70yo; partial obstruction; metastatic cancer; ASA score 4	8	12	80	N
2 70yo; complete obstruction; metastatic cancer; ASA 4	9	8	82	N
3 50yo; partial obstruction; metastatic cancer; ASA 4	15	10	75	N
4 50yo; complete obstruction; metastatic cancer; ASA 4	12	8	80	N
5 70yo; partial obstruction; metastatic cancer; ASA 1	51	19	30	Y
6 70yo; complete obstruction; metastatic cancer; ASA 1	40	13	47	Y
7 50yo; partial obstruction; metastatic cancer; ASA 1	60	17	23	Y
8 50yo; complete obstruction; metastatic cancer; ASA 1	51	14	35	Y
9 70yo; partial obstruction; curable cancer; ASA 4	66	15	19	Y
10 70yo; complete obstruction; curable cancer; ASA 4	41	13	46	Y
11 50yo; partial obstruction; curable cancer; ASA 4	73	10	17	N
12 50yo; complete obstruction; curable cancer; ASA 4	50	11	39	Y
13 70yo; partial obstruction; curable cancer; ASA 1	96	4	0	N
14 70yo; complete obstruction; curable cancer; ASA 1	79	12	9	N
15 50yo; partial obstruction; curable cancer; ASA 1	96	4	0	N
16 50yo; complete obstruction; curable cancer; ASA 1	87	9	4	N

did not show any advantage in terms of post-operative mortality between the emergency surgery and stenting groups. In the recent RCT by Young *et al*^[6], similar mortality figures were noted in both groups, noting that this patient population was palliative. A review of the United Kingdom National Audit showed that patients undergoing surgery for left-sided colonic obstruction had an operative mortality rate of 12.9%^[27]. The mortality rate with stenting being a lot lower at 1%, giving evidence that it is a safe method to decompress a patient as a bridge to surgery^[16].

COST

The cost of stents utility needs to be weighed up against many factors. They may represent an expensive option in isolation, however overall they represent a cost-effective option in the treatment of malignant obstruction of the colon. A study from the United Kingdom demonstrated the cost of a palliative stent was fifty percent less than surgical decompression and that the expense of 'bridge to surgery' was reduced by twelve percent with compared to a two stage procedure^[28]. In the review by Fiori *et al*^[9], the median hospital stay was 2.6 d for stent group and the median hospital stay was 8.1 d for the stoma group.

Other factors such as QoL, faster return to normal bowel function and significantly less physiological insult make stenting a much more cost-effective option. Further, the additional costs of outpatient stoma care should also not be forgotten^[16].

QOL

Increasing evidence has been published with regards to the QoL of patients undergoing stents and surgical intervention for the management of malignant bowel obstruction. In the study by van Hooft *et al*^[24] (2011), primary outcome of global health status was recorded and no significant difference was noted between the two groups. More recently, Young *et al*^[6] (2015) observed

that 15/26 (58%) patients in the stent group patients were recorded as having an increased QoL from baseline to one week compared to 7/26 (27%) of the surgery group ($P = 0.02$). The surgery group had significantly lowered QoL compared to the stent group from baseline to 1 and 2 wk ($P < 0.001$ and $P < 0.012$), and from baseline to 12 mo ($P = 0.01$) in favor of the stent group, while both reported reduced QoL^[6]. There were no significant differences in whether the patient had an increased or decreased QoL at any other time point.

DECISIONS

The treatment of patients with stenting technology is one that has traditionally being fraught with concern by the treating clinician. A recent study by Suen *et al*^[8] demonstrated that there would be limitations in conducting a future randomised controlled trial to assess the use of colonic stenting especially in the curative setting. Surgeons' favored the use of stents in the palliative setting preferentially when compared to the curative setting where surgery was preferred (Table 2).

In the management of physiologically poor patients (ASA > 3) with complete bowel obstruction, SEMS is the preferred initial intervention of choice. This allows the patient to be physiologically optimised for subsequent interventions and also increases the chance of a one-stage resection. The morbidity of emergency surgery can be as high as 51% with an associated mortality rate of 16%^[29]. With the greatest concern of colonic perforation being reported at 4% in previous trials, and modern day trials are quoting this at 0% with increasingly experienced interventionalists and safe methodology^[6]. This low rate of perforation and the benefits of stenting with lower stoma formation rates, lower perioperative morbidity and quicker recovery/return to community should make SEMS a valid tool in the management of malignant complete bowel obstruction^[23].

In the fit patient with curable disease, surgery is more often preferred as the intervention of choice due

to the improved physiologic parameters aiding in a better outcome and potential for one stage resection.

Considering the myriad of clinical scenarios and variables, the overall judgement, stenting technology offers an alternate tool to the clinician in the management of large bowel obstruction, with safe and effective outcomes.

The present body of evidence regarding stent insertion demonstrates its role, but to more clearly define its use in areas of uncertainty and community equipoise would require large multi-centre RCT's. Such trials may be necessary, but will be hard to complete with the difficulties of recruiting patients to trials where treating clinicians still hold conservative views as to the merits of stent or surgery.

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Lymphatic spreading and lymphadenectomy for esophageal carcinoma

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Abstract

Esophageal carcinoma (EC) is a highly lethal malignancy

with a poor prognosis. One of the most important prognostic factors in EC is lymph node status. Therefore, lymphadenectomy has been recognized as a key that influences the outcome of surgical treatment for EC. However, the lymphatic drainage system of the esophagus, including an abundant lymph-capillary network in the lamina propria and muscularis mucosa, is very complex with cervical, mediastinal and celiac node spreading. The extent of lymphadenectomy for EC has always been controversial because of the very complex pattern of lymph node spreading. In this article, published literature regarding lymphatic spreading was reviewed and the current lymphadenectomy trends for EC are discussed.

Key words: Lymphadenectomy; Lymphatic spreading; Anatomical lymphatic system; Lymph node metastasis; Esophageal cancer

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Core tip: Esophageal carcinoma (EC) is a highly lethal malignancy with a poor prognosis. One of the most important prognostic factors in EC is lymph node status. Therefore, lymphadenectomy has been recognized as a key that influences the outcome of surgical treatment for EC. However, the lymphatic drainage system of the esophagus is very complex, with cervical, mediastinal and celiac node spreading. The extent of lymphadenectomy for EC has always been controversial because of the very complex pattern of lymph node spreading. In this article, published literature regarding lymphatic spreading was reviewed and the current lymphadenectomy trends for EC are discussed.

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INTRODUCTION

Esophageal carcinoma (EC) is one of the most common cancers and an important cause of cancer-related deaths in the world. It is an aggressive disease with a poor prognosis and a rapidly increasing incidence. The overall 5 years survival is 10%, ranging from 15% to 40% after surgery. Although multimodal therapy, including neoadjuvant chemotherapy or chemoradiotherapy with esophagectomy, has improved the long-term survival, surgery is also regarded as the standard treatment for resectable EC^[1-4]. Lymph node status has been recognized as the most important independent factor that influences the prognosis of EC. The 7th edition of the TNM staging system showed that an increasing number of metastatic lymph nodes is associated with a poorer prognosis^[5,6]. Therefore, the outcome of surgery depends on lymphadenectomy as well as the primary tumor invasion in EC.

However, the extent of lymphadenectomy in EC is still considerably controversial. There have been two primary opinions in recent years. Some agree with a three-field lymphadenectomy and hold that it is essential to achieve improved postoperative survival by resectioning adequate lymph nodes in the neck because cervical lymph node metastases have been documented as approximately 20% to 40%. Others argue that two-field lymphadenectomy is enough to dissect all the possible metastatic lymph nodes, including recurrent nerve chain lymph nodes from the superior mediastinum up to the neck, with less perioperative complications and the same outcome^[7-10]. A consistent lymphadenectomy strategy has yet to be established.

In this review, we hope to offer some references about the extent of lymphadenectomy through describing the pattern of the lymphatic spreading.

THE ANATOMICAL LYMPHATIC SYSTEM OF THE ESOPHAGUS

The lymphatic drainage system of the esophagus is very complex because of an abundant lymph-capillary network in the lamina propria and muscularis mucosa, deep to the basement membrane. In total, lymphatic spreading has two modes, including penetrating the esophageal wall transversally and shifting longitudinally upwards (cervical lymph glands) and downwards (abdominal lymph glands). However, the longitudinal lymphatic flow is much more abundant than the transverse flow^[11,12]. In detail, there are three pathways for lymph node metastasis in EC. One is spreading longitudinally along the submucosal lymphatic networks to regional and non-regional lymph nodes; another passes transversely through the muscularis propria to regional lymph nodes; and the last penetrates perpendicularly through the muscularis mucosa to the thoracic duct and the venous system^[13]. Moreover, some studies show the presence of lymphatic drainage

and an anatomical correlation between the right recurrent laryngeal nerve nodes and cervical lymph nodes in EC, which suggests that tumor cells from the midthoracic level reach the right recurrent laryngeal nerve nodes through submucosal lymphatic vessels in the early stage. Meanwhile, it seems that lymphatic routes communicating with periesophageal lymph nodes generally originate from the intermuscular area of the muscularis propria and connections between the submucosal and intermuscular areas do not exist. Thus, once the primary tumor infiltrates the submucosa of the esophagus, the lymph node metastasis might apparently increase^[14-16].

PATHWAYS OF ESOPHAGEAL LYMPHATIC SPREADING

According to many published data, the upper mediastinal and perigastric areas are the most common areas for lymph node metastasis in EC. However, lymph node metastasis in different areas may vary with the location of the primary tumor^[17,18].

For upper thoracic EC, tumor cells usually spread upwards to upper mediastinal and cervical nodes. As for middle thoracic EC, lymphatic flow drains primarily both up and down into the cervical, upper mediastinal, periesophageal and perigastric nodes. With regard to lower thoracic EC, the perigastric area is the most important^[17,18]. Another study of endoscopic injection of technetium-labeled rhenium colloid into the esophageal wall also demonstrated that lymphatic flow of the upper and middle third of the esophagus drains mainly to the neck and upper mediastinum, with the lower third draining mainly into the abdomen^[19]. These studies generally reach a consensus.

On the other hand, Akiyama *et al.*^[20] showed that the frequency of cervical and upper mediastinal lymph node metastasis, including recurrent laryngeal nerve chains, was 46.3% in cases of thoracic EC. Shiozaki *et al.*^[21] reported that the rates of cervical lymph node metastasis with positive recurrent laryngeal nerve nodes was 22.2%, 51.9% and 50.0% in upper, middle and lower third thoracic EC, respectively. The rate of the recurrent laryngeal nerve lymph node metastasis with positive cervical lymph nodes was 51.2%, in contrast to 13.9% of patients with negative cervical nodes^[22]. Tabira *et al.*^[23] demonstrated that the 5 years survival was 21% with recurrent laryngeal nerve nodes metastasis, in contrast to 47% with negative recurrent nerve nodes. Therefore, it is generally accepted that recurrent laryngeal nerve chain nodes, especially the right side, should be intensively dissected in surgery for EC to improve survival, regardless of the location of the tumor^[20-24].

In addition to the location, the tumor histological type and invasion depth may be worth considering, well known as influencing factors on the prognosis for EC^[25-29]. In contrast to esophageal squamous cell carcinoma

ma with lymphatic spreading more widely, the lymphatic flow of esophageal adenocarcinoma is primarily into the lower posterior mediastinum, the pericardial region and along the lesser gastric curvature. Distant metastasis is rarely found^[28,30]. Based on the anatomical lymphatic drainage system, lymph node metastasis in EC is usually present in the upper mediastinum and perigastric area, known as skip metastasis, with the tumor not penetrating through the submucosa. If the tumor reaches the muscularis propria, the rate of periesophageal lymph node metastasis will increase rapidly for the middle and lower thirds of the mediastinum^[18].

LYMPHADENECTOMY FOR EC

Lymph node metastasis is the most important prognostic factor in EC and the number of metastatic nodes is closely related to survival. More and more studies have reported that the number of positive nodes independently determines survival rather than the area of metastatic lymph node in EC^[5,31-35]. Tachimori *et al.*^[18] showed that the overall postoperative survival did not differ between the areas of metastatic lymph nodes. According to their multivariate analyses, the number of metastatic nodes was the most predictive factor for survival, not the area. Similarly, Zhang *et al.*^[31] reported that the number of metastatic lymph nodes was significantly associated with survival for esophageal squamous cell carcinoma. The 5 years survival rates of patients with none, one and two or more positive lymph nodes were 59.8%, 33.4% and 9.4%, respectively. Therefore, the 7th edition of the TNM staging system identified the number of metastatic lymph nodes for N stage in EC^[6]. Apparently, the more lymph nodes are dissected, the lower the possibility of missing positive lymph nodes. The 7th edition also intensively requested that at least twelve lymph nodes should be removed for an accurate and reliable N classification in EC on account of several detailed research outcomes^[36,37]. However, only considering the number regardless of the area of metastatic lymph nodes is not enough. For the same number of positive lymph nodes, the prognosis between one and more distribution areas is different^[38,39].

Considering both outcome of lymphadenectomy and perioperative complications, the controversy about the extent of lymphadenectomy for EC has developed: Two or three-field?

The three-field lymphadenectomy was initiated in Japan. According to a prospective randomized trial, high neck recurrence rates in patients with esophageal squamous cell cancer were reported, suggesting that it was necessary to add neck dissection^[40]. After that, it was known that lymph from the upper third of the esophagus mainly flows upwards to the superior mediastinum and neck, whereas lymph from the middle and lower third of the esophagus flows downwards *via* the mid and inferior mediastinum to the left gastric and celiac nodes^[41]. A nationwide study showed that

the rate of lymph node metastasis was significantly increased with adding cervical dissection of three-field lymphadenectomy (58.7% of two-field vs 72.9% of three-field). Moreover, not only the rate of cervical nodes metastasis, but also the rate of mediastinal nodes metastasis was evidently increased^[42]. Meanwhile, Lerut *et al.*^[8] showed that the overall morbidity was 58%, 5 years disease-free survival was 46.3% and 5 years overall survival was 41.9% after three-field lymphadenectomy. Other research reported that the 5 years survival rate after three-field dissection was in the range of 40%-50%^[42,43]. However, some demonstrated that no survival benefit was found in patients undergoing cervical nodal dissection compared to esophagectomy with three-field vs two-field lymphadenectomy^[44]. Several recent meta-analyses suggested a priority of three-field lymphadenectomy for EC, especially for tumors with lymph node metastasis. However, the incidence of complications such as anastomotic leakage and recurrent laryngeal nerve palsy increased following three-field lymphadenectomy^[45,46].

CONCLUSION

Lymph node metastasis is a key factor that affects both surgical treatment and prognosis in patients with EC. Thus, reasonable lymphadenectomy becomes very important, offering a better treatment outcome and accurate staging. However, lymphatic channels within the esophagus are very complex, resulting in variable lymphatic spread and skip metastases in EC. Generally, upper mediastinal and perigastric areas are worth more consideration. Based on current studies, it seems that three-field lymphadenectomy for EC is being gradually accepted by more and more people, with more extensive lymphadenectomy and higher survival. However, there are more postoperative complications in three-field lymphadenectomy compared to two-field. Therefore, more studies have recently focused on identifying optimal patients for each pattern of lymphadenectomy. Considering complications, tumor stage and lymphatic spreading of the esophagus, limiting factors in the application of three-field lymphadenectomy, may be a poor physical condition, systemic disease stage and lower mediastinal, including the esophagogastric junction, carcinoma of the esophagus. Although more strict clinical trials are needed to compare two and three-field lymphadenectomy, it is essential to attempt to decrease surgical traumatic injury of esophagectomy with lymphadenectomy while ensuring the extent of lymph node dissection in EC.

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Single-incision laparoscopic surgery for colorectal cancer

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Abstract

AIM: To determine the effect of single-incision laparoscopic colectomy (SILC) for colorectal cancer on short-term clinical and oncological outcomes by comparison with multiport conventional laparoscopic colectomy (CLC).

METHODS: A systematic review was performed using MEDLINE for the time period of 2008 to December 2014 to retrieve all relevant literature. The search terms were "laparoscopy", "single incision", "single port", "single site", "SILS", "LESS" and "colorectal cancer". Publications were included if they were randomized controlled trials, case-matched controlled studies, or comparative studies, in which patients underwent single-incision (SILS or LESS) laparoscopic colorectal surgery. Studies were excluded if they were non-comparative, or not including surgery involving the colon or rectum. A total of 15 studies with 589 patients who underwent SILC for colorectal cancer were selected.

RESULTS: No significant differences between the groups were noted in terms of mortality or morbidity. The benefit of the SILC approach included reduction in conversion rate to laparotomy, but there were no significant differences in other short-term clinical outcomes between the groups. Satisfactory oncological surgical quality was also demonstrated for SILC for the treatment of colorectal cancer with a similar average lymph node harvest and proximal and distal resection margin length as multiport CLC.

CONCLUSION: SILC can be performed safely with similar short-term clinical and oncological outcomes as multiport CLC.

Key words: Single-incision laparoscopic surgery; Single-incision laparoscopic colectomy; Colorectal cancer

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Core tip: The aim of this review is to determine the effect of single-incision laparoscopic colectomy (SILC) for colorectal cancer by comparison with multiport conventional laparoscopic colectomy (CLC). A total of 15 studies with 589 patients who underwent SILC for colorectal cancer were selected. No significant differences between the groups were noted in terms of

short-term clinical and oncological outcomes, but there was a reduction in the conversion rate to laparotomy in the SILC group. We concluded that SILC can be performed safely with similar short-term clinical and oncological outcomes as multiport CLC.

Hirano Y, Hattori M, Douden K, Ishiyama Y, Hashizume Y. Single-incision laparoscopic surgery for colorectal cancer. *World J Gastrointest Surg* 2016; 8(1): 95-100 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i1/95.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i1.95>

INTRODUCTION

Many surgeons have attempted to reduce the number and size of ports used in laparoscopic surgery in order to decrease parietal trauma and improve cosmetic results, and single-incision laparoscopic surgery (SILS), in which the laparoscopic procedures are completed using trocars placed in a single umbilical incision, has recently been developed^[1].

Since the oncologic safety of laparoscopic colectomy in cancer patients has been proven in randomized trials^[2], laparoscopic surgery has steadily become a safe and practical treatment option for these patients, even those with malignant disease of the colon and rectum.

Single-incision laparoscopic colectomy (SILC) is a challenging procedure. Although it seems to be safe and feasible, there is insufficient clinical evidence to confirm this. Moreover, it is unclear whether SILC is able to achieve satisfactory oncologic results in colorectal cancer patients compared to multiport conventional laparoscopic colectomy (CLC).

The aim of this systematic review is to compare the short-term clinical and oncological outcomes following SILC and multiport CLC.

MATERIALS AND METHODS

Data search

An electronic search was performed using MEDLINE databases from 1966 to 2014. The search terms were "laparoscopy", "single incision", "single port", "single site", "SILS", "LESS", and "colorectal cancer". The authors performed the electronic searches in December 2014. Publications were included if they were randomized controlled trials, case-matched controlled studies, or comparative studies, in which patients underwent single-incision (SILS or LESS) laparoscopic colorectal surgery. Studies were excluded if they were non-comparative, or not including surgery involving the colon or rectum.

Articles were selected if the abstract contained data on patients who underwent SILC for colorectal diseases in the form of randomized controlled trials (RCTs) and other controlled or comparative studies. Conference abstracts were excluded. To avoid duplication of data,

articles from the same unit or hospital were excluded. Reports including benign colorectal diseases or reports with fewer than 10 cases of SILC and review articles were excluded from this study. Data extracted for this study were taken from published reports, and authors were not contacted to obtain additional information. The flow chart of the selection process is summarized in Figure 1.

Results of the literature research

By using the above search strategy, a total of 162 potentially relevant citations were found. After the exception of 125 duplicate citations, we excluded 86 articles irrelevant to the surgical specialty and 26 relevant articles by reviewing titles and abstracts. Fourteen publications were selected for review of the full text^[3-17] and 11 articles including benign colorectal diseases were excluded from this study. There were 13 comparative studies, including 5 case-matched ones, between SILC and conventional laparoscopic procedures. There were two RCTs in the selected literature^[10,11].

RESULTS

The literature search identified one randomized controlled trial and 13 case-matched control or comparative studies^[3-17]. In total, 1559 colorectal resections were included, 589 by SILC and 970 by CLC. Table 1 describes basic demographic data from each study, including patient age, male-female ratio, body mass index, and colorectal surgical procedure breakdown (right, left, or total). There were no differences in patient characteristics in all studies.

The incidence of postoperative mortality was reported in 13 studies, 0% and 0.11% in the SILC and CLC groups, respectively. The incidence of postoperative morbidity was reported in 14 studies, 15.1% and 18.1% in the SILC and CLC groups, respectively.

The average operative time was described in 14 of the included studies. Takemasa *et al.*^[16], in their case-matched series, reported that operation time was significantly shorter in the group treated by right-sided SILC ($n = 69$) than in the group treated by right-sided CLC ($n = 69$) (168 ± 32 min vs 179 ± 32 min, respectively, $P = 0.046$). The average estimated blood loss was described in 14 studies; there were no significant differences in all reports.

Thirteen studies described conversion to open surgery, which was 0.92% in the SILC group and 3.04% in the CLC group. An additional 13.3% of SILC procedures required the insertion of an additional port to allow completion of the operation (Table 2).

Fourteen studies reported the average length of hospital stay. Poon *et al.*^[11] reported that the median hospital stay in the SILC group was shorter than that in the CLC group in their study.

Poon *et al.*^[11] found that the SILC group had a consistently lower median pain score than the CLC group during the whole postoperative course, and the

Table 1 Patient demographics

Year	First author	Number of patients		Age (yr)		Gender				Body mass index (kg/m ²)		Operative procedure			
		SILC	CLC	SILC	CLC	SILC		CLC		SILC	CLC	SILC		CLC	
						Male	Female	Male	Female			Right	Left	Right	Left
2011	Kim SJ	73	106	65	63	-	-	-	-	22.7	25.6	20	26	28	67
2011	McNally ME	27	46	67	73	13	21	13	21	27	26	14	8	35	8
2011	Papaconstantinou HT	26	26	65	66	11	11	11	11	28	28	19	4	19	4
2012	Curro G	10	10	60	59	4	3	4	3	25	26	10	0	10	0
2012	Egi H	10	10	68.5	68	4	4	4	4	22.5	21.9	10	0	10	0
2012	Fujii S	23	23	63.9	65.2	10	13	10	13	21.6	22.9	9	14	9	14
2012	Huscher CG	16	16	70	70	-	-	-	-	-	-	8	8	6	10
2012	Lu CC	27	68	60.26	64.29	16	36	16	36	-	-	8	18	16	45
2012	Poon JT	25	25	67	67	14	18	14	18	23.3	23.6	8	17	9	16
2013	Kwag SJ	24	48	59.5	59	9	18	9	18	24.4	24	0	24	0	48
2013	Mynster T	18	36	70	73	8	16	8	16	24	24	7	11	14	22
2013	Pedraza R	50	50	64.6	66.3	25	27	25	27	27.2	31	33	14	33	14
2013	Yun JA	66	93	61	59	33	55	33	55	23.82	24.23	66	0	93	0
2014	Takemasa I	150	150	64.3	65.5	75	71	75	71	21.7	22.4	69	81	69	81
2014	Lim SW	44	263	63.9	63.8	28	170	28	170	23.7	23.8	11	15	15	82
	Total	589	970	-	-	250	463	250	463	-	-	292	240	366	411

SILC: Single-incision laparoscopic colectomy; CLC: Conventional laparoscopic colectomy.

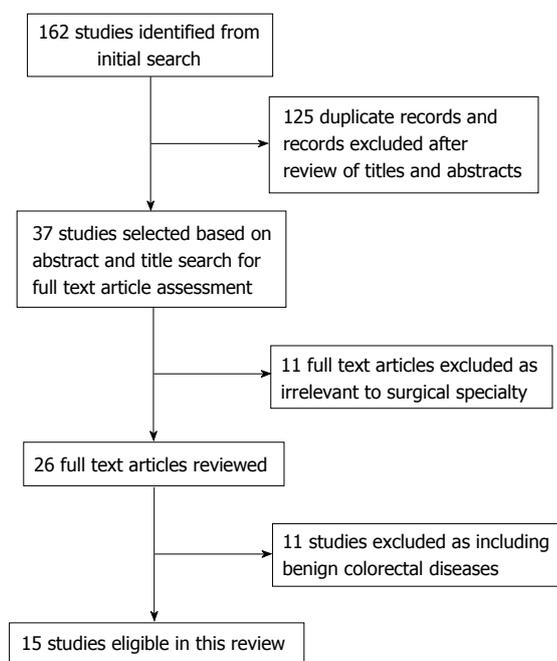


Figure 1 Flow chart of the selection process for studies included in the systematic review.

difference was statistically significant on day 1 [0 (0-5) vs 3 (0-6), respectively, $P = 0.002$] and day 2 [0 (0-3) vs 2 (0-8), respectively, $P = 0.014$]. Takemasa *et al.*^[16] also revealed that postoperative pain was significantly lower with SILC than that with CLC in their case-matched study (4.2 ± 2.7 vs 5.1 ± 3.3 , respectively, $P = 0.01$). Lu *et al.*^[9], however, reported that postoperative pain scores were significantly higher in the SILC group than those in the CLC group (3.07 ± 1.14 vs 2.41 ± 0.63 , respectively, $P < 0.001$).

Kim *et al.*^[3] showed that postoperative recovery was faster in the SILC group in terms of shorter time duration before first flatus (SILC vs CLC; 2.5 ± 1.2 d

vs 3.2 ± 1.8 d, $P = 0.004$), earlier initiation of free oral fluids (1.8 ± 2.2 d vs 2.6 ± 1.7 d, $P = 0.000$) and of a solid diet (4.2 ± 2.9 d vs 6.5 ± 2.7 d, $P = 0.000$), less frequent usage of parenteral narcotics (2.2 ± 3.2 times vs 3.5 ± 4.0 times, $P = 0.029$), and shorter hospital stay (9.6 ± 9.6 d vs 15.5 ± 9.8 d, $P = 0.000$) (Table 3).

With regard to oncologic clearance, 14 studies reported average lymph node harvest. The length of proximal resection margin was reported in 7 studies, and that of distal was reported in 8 studies. The mean number of harvested lymph nodes and proximal and distal resection margins did not differ significantly between the two groups. Papaconstantinou *et al.*^[5] reported that the mean follow-ups were 13 and 21 mo for the SILC and CLC groups, respectively ($P < 0.001$), with 2 (8%) recurrences in each group, and no port-site recurrences or deaths. Disease-free survival at 1 year was 92% for both groups. Yun *et al.*^[15] reported that the mean follow-up periods were 24.5 mo for the SILC group and 26.4 mo for the CLC group ($P = 0.098$), with 6 recurrences in the SILC group (9.1%) and 3 recurrences in the CLC group (3.2%) ($P = 0.120$). One death occurred in the CLC group. Disease-free survival at 24 mo did not differ significantly between the 2 groups (89.7% vs 96.3%, $P = 0.120$) (Table 4).

DISCUSSION

Natural orifice transluminal endoscopic surgery (NOTES) has recently been developed as a new less invasive type of surgery; however, NOTES is technically challenging, and the currently available instruments need to be improved. As a bridge between traditional laparoscopic surgery and NOTES, SILS was developed to further minimize the invasiveness of laparoscopic surgery by reducing the number of incisions required. SILS can be performed by refining existing technology, and it does not require the surgeon to learn any new skills.

Table 2 Postoperative mortality, morbidity, conversion rate and additional port insertion rate *n* (%)

First author	Mortality		Morbidity		Conversion to open procedure		Additional port insertion SILC
	SILC	CLC	SILC	CLC	SILC	CLC	
Kim SJ	0	1 (1.37)	23 (31.5)	39 (36.8)	1 (1.36)	3 (2.83)	-
McNally ME	0	0	5 (18.5)	16 (34.8)	0	6 (13.0)	5 (18.5)
Papaconstantinou HT	-	-	-	-	0	1 (7.7)	3 (11.5)
Curro G	0	0	2 (20.0)	1 (10)	0	0	-
Egi H	0	0	0	0	0	1 (10)	-
Fujii S	0	0	3 (13.0)	5 (21.7)	0	1 (4.35)	-
Huscher CG	0	0	3 (18.8)	5 (31.3)	0	0	1 (6.3)
Lu CC	0	0	2 (7.4)	3 (4.41)	-	-	-
Poon JT	0	0	4 (16.0)	3 (12)	0	0	-
Kwag SJ	0	0	2 (8.33)	4 (8.33)	0	0	7 (29.2)
Mynster T	0	0	3 (16.7)	6 (16.7)	1 (5.56)	4 (11.1)	3 (16.7)
Pedraza R	-	-	7 (14.0)	4 (8)	0	1 (4)	5 (27.8)
Yun JA	0	0	6 (9.09)	14 (15.1)	1 (1.52)	5 (5.37)	-
Takemasa I	0	0	18 (12.0)	25 (16.7)	2 (1.33)	5 (3.33)	12 (8.0)
Lim SW	0	0	7 (15.9)	46 (17.5)	0	0	10 (22.7)
Total	0	1 (0.11)	85 (15.1)	171 (18.1)	5 (0.89)	27 (2.99)	46 (13.0)

SILC: Single-incision laparoscopic colectomy; CLC: Conventional laparoscopic colectomy.

Table 3 Other short-term clinical outcomes

First author	Operative time (min)		Estimated blood loss (mL)		Length of hospital stay (d)	
	SILC	CLC	SILC	CLC	SILC	CLC
Kim SJ	274	254	282	418	9.6	15.5
McNally ME	114	135	50	50	3	5
Papaconstantinou HT	144	144	57	87	3.6	5
Curro G	170	160	35	50	6	6
Egi H	192	222	48	51.5	8	10.5
Fujii S	174	179	9	109	8.2	12.7
Huscher CG	147	129	200	-	6	7
Lu CC	180	184	35	50	7	7
Poon JT	155	124	50	80	4	5
Kwag SJ	251	237	135	144	7.1	8.1
Mynster T	167	189	0	38	3	3
Pedraza R	127.9	126.7	64.4	87.2	4.5	4
Yun JA	155	174	-	-	8	9
Takemasa I	172	173	32	37	8.2	8.7
Lim SW	185	139.2	82.3	70.1	8.2	8.8

SILC: Single-incision laparoscopic colectomy; CLC: Conventional laparoscopic colectomy.

Table 4 Oncological outcomes

First author	Harvested LN		Proximal resection margin (cm)		Distal resection margin (cm)	
	SILC	CLC	SILC	CLC	SILC	CLC
Kim SJ	29.3	23.2	33.4	17.9	17.2	13
McNally ME	15	17	-	-	-	-
Papaconstantinou HT	18	17	9.3	9.3	10.5	9.3
Curro G	25	24	-	-	-	-
Egi H	15	16.5	-	-	-	-
Fujii S	19.9	23.3	8.8	8.5	9.5	7.6
Huscher CG	18	16	-	-	8	6
Lu CC	-	-	-	-	7	6
Poon JT	16	20	8	8	5.5	6
Kwag SJ	19.6	20.8	11.2	11.4	7.5	9.2
Mynster T	17	20	-	-	-	-
Pedraza R	21.4	19.2	-	-	-	-
Yun JA	24	27	14.4	15	16.6	15.8
Takemasa I	22.2	22.4	-	-	-	-
Lim SW	23.2	27.4	10.5	11.2	6.6	5.5

SILC: Single-incision laparoscopic colectomy; CLC: Conventional laparoscopic colectomy.

SILC for colon cancer was first described by Bucher *et al.*^[18] and Remzi *et al.*^[19] in 2008. Although many authors have reported that SILC provides a better cosmetic result with similar perioperative results, the procedure remains somewhat controversial. Several studies of SILC were designed to include both cancerous and noncancerous lesions, such as adenoma, diverticulitis, and inflammatory disease. The aim of this review of 14 studies was to compare short-term clinical and oncological outcomes from SILC with those of CLC only for colorectal cancer.

The major findings of the analysis showed no significant differences between the groups in terms of mortality or morbidity. Operative time was also similar between the groups. The benefits of a minimally invasive approach were enhanced within the SILC group as reflected by a reduction in estimated blood loss and length of hospital stay. The incidence of conversion to an open procedure was also significantly reduced in the SILC group (SILC 0.92% vs CLC 3.04%, $P = 0.016$); however, 13.3% of SILC procedures required the insertion of an additional port to allow completion of the operation. The oncological safety of SILC for the treatment of colorectal cancer, as evidenced by similar average lymph node harvest as well as proximal and distal resection margin length, was comparable to that of CLC.

The patient populations for both groups were similar in terms of age, body mass index, and right vs left colorectal procedures. However, male gender was significantly less in the SILC group, which implies a degree of selection bias may have been present in the studies included and thus represents a significant confounder in the interpretation of the short-term outcomes presented.

Reduction of postoperative pain is an important benefit associated with a minimally invasive approach to surgery. The transition from an open to a laparoscopic procedure was revolutionary and associated with large improvements in postoperative pain. Although Poon *et al.*^[11] and Takemasa *et al.*^[16] revealed reduction of pain scores following SILC compared to CLC in their studies, the evolution from a conventional multiport laparoscopic approach to a single-incision technique is less dramatic and may only result in incremental improvements in postoperative pain.

The oncological surgical quality of a SILC approach was demonstrated by a similar average lymph node harvest and proximal and distal resection margins compared to those of CLC. With regards to survival, Papaconstantinou *et al.*^[5] reported that the mean follow-ups were 13 and 21 mo for the SILC and CLC groups, respectively, and that the recurrence rates and disease-free survivals (DFSs) at 1 year were equivalent in both groups. Yun *et al.*^[15] showed that the mean follow-up periods were 24.5 mo for the SILC group and 26.4 mo for the CLC group, and that the recurrence rates and DFSs at 2 years did not differ significantly between the two groups. Comparison of long-term survival follow-

ing SILC and CLC for colorectal cancer is clearly an important area for future research.

Despite this present review being the largest analysis on comparison between SILC and CLC for colorectal cancer to date, there are important limitations that must be acknowledged. Currently, only 2 RCTs have been published on this subject, and therefore, important confounding factors, including patient medical comorbidities, may not be evenly distributed between the groups, thus influencing the results generated. Furthermore, there was a wide range in surgical techniques and devices used that were included in the SILC group.

In conclusion, SILC for colorectal cancer can be performed safely with similar short-term clinical and oncological surgical outcomes to multiport CLC. In the future, RCTs with a large number of cases are necessary to determine the role of SILC in long-term clinical and oncological outcomes.

COMMENTS

Background

Single-incision laparoscopic surgery, in which the laparoscopic procedures are completed using trocars placed in a single umbilical incision, has recently been developed, since the oncologic safety of laparoscopic colectomy in cancer patients has been proven in randomized trials, laparoscopic surgery has steadily become a safe and practical treatment option for these patients, even those with malignant disease of the colon and rectum. Single-incision laparoscopic colectomy (SILC) is a challenging procedure. Although it seems to be safe and feasible, there is insufficient clinical evidence to confirm this. Moreover, it is unclear whether SILC is able to achieve satisfactory oncologic results in colorectal cancer patients compared to multiport conventional laparoscopic colectomy (CLC).

Innovations and breakthroughs

Aim to determine the effect of SILC for colorectal cancer on short-term clinical and oncological outcomes by comparison with multiport CLC.

Applications

SILC for colorectal cancer can be performed safely with similar short-term clinical and oncological surgical outcomes to multiport CLC. In the future, randomized controlled trials with a large number of cases are necessary to determine the role of SILC in long-term clinical and oncological outcomes.

Peer-review

The article is very interesting and good enough, focused details are well described and may show a step forward in the field of minimally invasive surgery.

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Successful living donor intestinal transplantation in cross-match positive recipients: Initial experience

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Abstract

Sensitized patients tend to have longer waiting times on the deceased donor list and are at increased risk of graft loss from acute or chronic rejection compared to non-sensitized candidates. Desensitization protocols are utilized to decrease the levels of alloantibodies and to convert an initial positive cross-match to prospective donors into a negative crossmatch. These procedures are mostly available in the setting of living donation. Due to the elective nature of the procedure, desensitization protocols can be extended until the desire result is obtained prior to transplantation. We present two cases of successful desensitization protocol applied to living donor intestinal transplant candidates that converted to negative cross-match to their donors. We present two cases of intestinal transplant candidates with a potential living donor to whom they are sensitized. Both cases underwent successful transplantation after desensitization protocol. No evidence of humoral rejection has occurred in either recipient. Living donor intestinal transplantation in sensitized recipients against the prospective donors provides the ability to implement a desensitization protocol to convert to negative cross-match.

Key words: Living donor; Positive crossmatch; Intestinal

transplant; Desensitization protocol; Donor specific antibody; Plasmapheresis

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Core tip: Intestinal transplant candidates are frequently sensitized and waiting longer on the list. Living donation of intestine has been successful and allows for time to immunologically prepare sensitized recipient prior to transplant to achieve higher degree of success.

Garcia-Roca R, Tzvetanov IG, Jeon H, Hetterman E, Oberholzer J, Benedetti E. Successful living donor intestinal transplantation in cross-match positive recipients: Initial experience. *World J Gastrointest Surg* 2016; 8(1): 101-105 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i1/101.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i1.101>

INTRODUCTION

Allosensitization represents a common problem for patients awaiting small bowel transplantation. In this patient population, allosensitization occurs often consequent to multiple blood transfusions administered during complex abdominal procedure, eventually leading to short bowel syndrome.

The presence of donor specific antibodies to the human leukocyte antigens (HLA) antibodies augments the risk of either acute or chronic immune mediated graft loss^[1]. In kidney transplantation, removing anti-HLA antibodies by a combination of plasmapheresis, immunoglobulins (IVIG) and immunosuppression have been successfully applied to prevent antibody-mediated rejection (AMR). However, this approach can logistically only be applied in the context of elective living donor transplantation.

Outcomes after living donor small bowel transplantation in experienced centers are comparable to those obtained with cadaver grafts^[2]. The elective nature of living donor intestinal transplantation offers the opportunity for the use of desensitization protocols in highly sensitized patients. Herein, we present the first report of two successful small bowel transplants after desensitization protocol in recipients with a positive cross-match (CM) to their prospective living donors.

CASE REPORT

Case one

A 13-year-old Caucasian male was diagnosed of pseudo-papillary tumor of the head of the pancreas with vascular encasing of portal vein and superior mesenteric artery. He underwent a Whipple procedure with vascular resection and reconstruction. Twelve months later, the patient presented with acute bowel ischemia secondary to superior mesenteric artery thrombosis and underwent

nearly total enterectomy and extended right colectomy. The patient was placed on total parenteral nutrition (TPN) as he was left with less than 5 cm of intestine. Given the young age of the patient and the high sensitization we suggested living donor small bowel transplant.

The other of the patient, 36-year-old in perfect health without previous abdominal surgeries, volunteered as a potential donor for intestinal transplantation. The donor evaluation process was carried out according to our standard protocol previously reported^[3].

Due to the multiple blood transfusions required during the events leading to transplantation, his Panel Reactive Antibodies (PRA) was 67% for class I and 100% for class II. He had strong donor specific antibodies (DSA) at locus A × 11:01 (MFI = 7359). The initial CM was positive by flow cytometry technique with pronase treatment at + 55 channel shifts for T cell and + 40 for B cell (negative CM less than + 17 channel shift); the standard cytotoxic CM was negative. The patient underwent seven plasma exchange treatments before the planned transplant procedure, each followed by IVIG at the dose of 100 mg/kg. The final flow cytometry CM remained weakly positive, with + 19 channel shifts for T cell and + 23 channel shift for B cell; the standard CM stayed negative. At the time of transplant our recipient was 36.7 kg (the 10th percentile in the growth chart) and fully dependent on total parenteral nutrition. The transplant event was successful; the 180 cm ileal graft was revascularized through anastomosis to the aorta and the vena cava. Proximally, the bowel graft was anastomosed to the stomach and distally to the residual colon; a loop ileostomy was created for graft monitoring.

Induction immunosuppression consisted of methylprednisolone taper along with of five doses of thymoglobulin (100 mg/kg) and 5 plasmapheresis treatments every other day followed by IVIG (125 mg/kg based on ideal body weight) on alternative days. He was closely monitored with ileoscopy and graft biopsy for surveillance of rejection weekly for a month, biweekly for another 2 mo and monthly thereafter. There was no evidence of rejection in any of the biopsies over two years follow-up.

Two months post-transplant, his course was complicated by an Epstein barr virus positive post-transplant lymphoproliferative disorder (PTLD) involving lymph nodes in both sides of the diaphragm. He was successfully treated with reduction of immunosuppression, antiviral therapy, Rituximab (375 mg/m²) weekly for total of 6 doses and Cytoxan (600 mg/m²) every 21 d for a total of 6 doses.

Nine months after transplant, he had successful ileostomy reversal and his TPN was completely discontinued. He is currently fully supported by unrestricted oral diet and his most recent weight is 51.7 kg (the 18th percentile of his peers) at 2 years follow up; he remains in remission from PTLD. His maintenance immunosuppression consists of prednisone 5 mg daily and low dose Tacrolimus with target levels of 4-6 ng/mL.

Case two

A 56-year-old Caucasian female with history of scleroderma complicated by intestinal pseudo-obstruction, underwent several intestinal resections and diverting ileostomy. Unfortunately, an injury to the superior mesenteric vessels occurred during one of the surgical procedures, resulting in near total enterectomy and extended right colectomy. At the time of presentation to our center, she was TPN-dependent for 6 mo, with high output tube duodenostomy; she was underweight at 42.2 kg with a body mass index (BMI) of 17 kg/m².

Her daughter, a healthy 36-year-old female ABO compatible, with a BMI of 24 kg/m², volunteered as a potential donor. The recipient was sensitized with a PRA class I 80% and class II 26%; no DSAs were identified. While the standard cytotoxic CM was negative, the flow cytometry CM was negative for T cell but positive for B cell with + 69 channel shifts. Desensitization was conducted by three plasma exchange treatments prior to transplant followed by IVIG, obtaining a completely negative flow cytometry and standard CM at the time of transplant.

A donor ileal graft of 190 cm was transplanted successfully in the recipient with our standard technique. Thymoglobulin (3 mg/kg) was given intraoperative and followed by three more doses (1.5 mg/kg) on alternate days to plasmapheresis; Tacrolimus was initiated the day prior to procedure with rapid taper of steroids to 10 mg daily by post-operative day 5. Endoscopic surveillance at previously described intervals during the initial 6 mo follow up revealed no evidence of rejection. The patient has had successful ileostomy reversal at 6 mo and is tolerating oral intake; she is no longer on supplemental TPN.

DISCUSSION

Small bowel transplantation is an accepted treatment for patient with irreversible intestinal failure with life-threatening complications of TPN. At the end of 2014, there were approximately 250 patients listed for bowel transplantation in the United States. For candidates wait-listed in 2010, the median time to transplant was 14.9 mo for those younger than 18 years and only 2.8 mo for those aged 18 years or older^[4]. The United Network of Organ Sharing does not report separately the waiting time on sensitized candidates for bowel transplantation, but experience in kidney recipients suggests potentially longer waiting times^[5]. Importantly, transplant outcomes performed on recipients receiving total parenteral nutrition for less than one year are significantly better than those on TPN of a year or longer^[6].

In the current literature there are limited publications concerning small bowel transplantation in CM positive recipients. While intestinal transplantation has a higher rejection rate than most other solid organs (42% in the first year)^[4], antibody mediated rejection (AMR) is not well characterized and understood in this set of patients.

In other solid organs, the presence of C4d staining in the biopsies is indicative of AMR but this may not apply to intestinal transplants^[7].

Recently, virtual crossmatch has been successfully used to facilitate allocation of intestinal grafts specifically in the subgroup of sensitized candidates^[8]. With this strategy, the group at Georgetown University has achieved 80% successful allocation with negative cross-match in sensitized recipients compared to 86.7% in non-sensitized, minimizing the discard rates of suitable organs originating out of state. However, sensitized patients with elevated PRA achieving a negative CM showed a survival disadvantage. The 1-year graft survival was lower in the sensitized group at 66.7% compared to 85.2% in the group with low PRA^[8]. Although the authors did not observe a statistically significant difference between the two groups, likely due to a small sample size, the discrepancy is clinically concerning. The study also did not comment on specific therapy to reduce the levels of alloantibodies.

Experience in other solid organ transplantation such as kidney or heart indicates that outcomes in sensitized recipients are inferior to those observed in non-sensitized patients. Sensitized patients exhibit higher rejection rates, lower graft and patient survival^[9]. Similarly, in intestinal transplantation, the risk of AMR has been reported to be higher in sensitized recipients and in those developing *de-novo* DSA. Diagnosis of AMR should be based on clinical suspicion in the presence of DSA or increased PRA since intestinal biopsy may not be conclusive^[10,11]. Independent risk factors for worse outcomes in intestinal transplantation are: recipient PRA more than 20%, liver-sparing grafts and absence of recipient splenectomy^[12]. Persistence of DSA after transplantation or *de-novo* formation of DSA result in increased risk of graft loss due to rejection (58% and 47% respectively). The risk of graft loss in patients without DSA was 8% and 13% in those clearing DSAs after transplant. Liver containing grafts are immunoprotective, effectively clearing pre-formed antibodies and reducing the risk of *de-novo* formation, but the recipients with persistent DSA after transplantation correlated with lower graft survival despite the presence of the liver^[13]. Additionally, the rates and aggressiveness of rejection are worse in isolated intestine vs transplant containing liver graft^[14].

Contrary to these results, Kubal *et al.*^[15] recently reported similar 3-year survival rates in small bowel transplantation (67% in positive CM vs 65% in negative CM). The also did not found a significant difference in the incidence of acute rejection between liver sparing and liver containing grafts (30% vs 29%). Additionally, the use of anti-interleukin-2 antibody as part of the induction therapy was noted to significantly reduce the rate of rejection overall.

Protocols to desensitize recipients continue to evolve and emerging therapeutic strategies allow successful positive CM transplantation^[16]. The application in small bowel transplantation is not widely reported but the use of Bortezomib during induction in sensitized candidates has been suggested^[13]. Performing surveillance DSA

to identify patients at risk, especially those without a concomitant liver, and rapidly initiate treatment with a combination of plasmapheresis, IVIG may optimize outcomes^[17,18]. The use of Bortezomib to treat resistant rejection was successful in one case report^[19].

The only Desensitization protocol reported in wait list candidates to intestinal transplantation used escalating doses of IVIG according to the level of response in reducing the PRA level and included plasmapheresis or mycophenolate mofetil as the final step. The rate of rejection was found to be similar to non-sensitized recipients and the waiting time was also reduced on patients responding to the protocol^[20].

Our center is experienced in living donor small bowel transplantation and the elective nature of the procedure offers several advantages, especially in the sensitized candidates. We can optimize the immunological condition prior to transplantation with current desensitization protocols existing in other solid organs, mostly in kidney transplantation. As noted before, the risk antibody mediated rejection is increased in patients with elevated PRA, *de-novo* DSA formation and those with positive B cell CM. We realize that the CM was weak prior to desensitization, especially in the second case, and resulted in easier conversion to a negative CN. The one-year follow-up on both patients without rejection episodes are encouraging and suggest that pretransplant plasmapheresis may effectively prevent humoral rejection in sensitized intestinal transplant recipients. We acknowledge this is a very short follow and follow up DSA surveillance studies may be necessary to confirm the success of this protocol.

In conclusion, living donation offers the possibility to initiate therapy to optimize the immunological condition at the time of transplant, converting to a negative CM sensitized intestinal transplant recipients to their prospective donors.

COMMENTS

Case characteristics

Two patients with short bowel syndrome treated with living donor intestine transplantation.

Clinical diagnosis

Both cases present highly sensitized making their chances for a deceased donor transplant unlikely.

Differential diagnosis

Sensitization can be from autoantibodies or atypical antibodies and not identified in by donor specific antibodies (DSA) studies.

Laboratory diagnosis

Cross-match and DSA studies performed.

Pathological diagnosis

Biopsies taken from the intestinal mucosa were normal.

Treatment

They underwent desensitization protocol and elective intestine transplant.

Related reports

Intestinal transplant candidates are frequently sensitized and tend to wait for an organ longer than non-sensitized patients. Living donation is a scheduled procedure allowing for desensitization protocol to be completed prior to transplantation. This is not available when a deceased organ is offered. Desensitization protocols are applied frequently for sensitized patients before receiving a kidney transplant from live donors. The application to prospective recipient of intestine is novel.

Term explanation

Desensitization protocols can turn positive crossmatch into negative and allow for successful transplantation.

Experiences and lessons

This is a two cases report with limited follow up, but successful so far in both recipients. Post-transplant lymphoproliferative disorder is a risk in patients receiving high immunosuppression as the desensitization protocol.

Peer-review

This is a manuscript that presents a valuable potential solution to the shortage of small bowel grafts, particularly in the setting of patients who are sensitized. The authors provide an interesting hypothesis for larger studies.

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2016 Laparoscopic Surgery: Global view

Laparoscopic complete mesocolic excision with central vascular ligation in right colon cancer: A comprehensive review

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Abstract

Aim of the study is to comprehensively review the

latest trends in laparoscopic complete mesocolic excision (CME) with central vascular ligation (CVL) for the multimodal management of right colon cancer. Historical and up-to-date anatomic-embryological concepts are analyzed in detail, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. The rationale behind Laparoscopic CME with CVL is thoroughly investigated and explained. Attention is paid to the current surgical techniques and the quality of the surgical specimen, yielded through mesocolic, intramesocolic and muscularis propria plane of surgery. We evaluate the impact on long term oncologic outcome in terms of local recurrence, overall and disease-free survival, according to the plane of resection achieved. Conclusions are drawn on the basis of the available evidence, which suggests a pivotal role of laparoscopic CME with CVL in the multimodal management of right sided colonic cancer: performed in the right mesocolic plane of resection, laparoscopic CME with CVL demonstrates better oncologic results when compared to *standard* non-mesocolic planes of surgery, with all the advantages of laparoscopic techniques, both in faster recovery and better immunological response. The importance of minimally invasive *meso-resectional* surgery is thus stressed and highlighted as the new frontier for a modern laparoscopic total right mesocolectomy.

Key words: Right sided colonic cancer; Complete mesocolic excision; Central vascular ligation; Laparoscopy; Quality of surgical specimen; Oncologic outcome

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Core tip: Laparoscopic complete mesocolic excision

(CME) with central vascular ligation (CVL) is based on resection of the colon within its intact and inviolate mesocolon with high tie ligation, so to improve the quality of the resection specimen produced; up-to-date anatomo-embryological concepts are analyzed in detail, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. The rationale behind the CME with CVL is explained and particular attention is paid to the current surgical techniques. The impact on local recurrence, disease-free and overall survival is reviewed. Current literature about laparoscopic CME with CVL demonstrated better quality of the surgical specimen produced and significant survival advantage when compared to standard non-mesocolic resections, stressing the importance of meso-resectional surgery, especially when performed with minimally invasive techniques: higher surgical quality, faster recovery and better immunological response may in fact contribute to better long term oncologic outcome.

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INTRODUCTION

At the end of the 19th century, Emil Theodor Kocher^[1,2], was the first to theorize oncologic resections based on removal of the involved organ along with its lymphatic drainage; this concept was shortly after substantiated by Miles *et al*^[1] and Jemison *et al*^[2] for rectal and colonic cancer respectively. Yet, the real revolution in oncologic surgery was performed seventy years later by Heald *et al*^[3], who introduced the concept of total excision of the mesorectum (TME), the primitive embryological dorsal mesentery of the rectum: Dissection in the mesorectal plane yields an intact fascial-lined specimen containing all the vasculo-lymphatic pathways and lymph nodes, and reduces the risk of an involved circumferential resection margin (CRM)^[3,4]. The embryological right plane of dissection, graded by the pathologist, has been shown to be independently related to the risk of local recurrence, disease free and overall survival^[5,6], so to promptly became the central part of any multimodal treatment of rectal cancer^[7].

In 2009, Hohenberger *et al*^[8] translated the concept of TME to colonic cancer, noting that traditionally more favorable oncologic results of colon neoplasia was eventually overtaken by rectal cancer: Multimodal strategies, not yet applied to colonic tumors, and a more radical surgical approach performed along embryonic planes of development with higher quality

specimens, produce better oncologic outcome; thus, complete mesocolic excision (CME) with central vascular ligation (CVL) was theorized, standardized and eventually validated by several studies^[9,10].

The concept of complete excision of the involved organ along with its primitive mesentery, associated to central ligation of the supplying blood vessels, is progressively gaining acceptance as the next step towards a modern surgical oncology; surgical resection of the primitive embryological mesentery is in fact pivotal for optimal local clearance. The primitive mesentery is the embryological envelope where the neurolymphovascular structures develop within a double-layered mesenchymal fibrofatty tissue and the initial pathway for cancerous diffusion: Its intact, complete excision is thus essential to clear residual disease in the surgical field, with consequent impact on local control.

Furthermore, CVL allows for an extensive lymph node dissection along the feeding vessels, with significant effect on regional recurrence and systemic dissemination, as shown by improved survival in stage I-III colonic cancers treated with enhanced lymph node harvesting^[11,12].

Blending Complete Mesocolic Excision with CVL is thus the logical step in gaining the highest loco-regional control, removing both the intact mesocolon and the apical nodes, with relevant impact on long term outcome. To take advantage of minimally invasive techniques, laparoscopic approach to CME with CVL seems the natural consequence in the evolution of this procedure.

ANATOMO-EMBRYOLOGICAL CONCEPT OF THE MESOCOLON

The mesocolon is the adult remnant of the primitive dorsal mesentery^[13-19]. In the 5 mm embryo (approximately 32 d), the colon develops within a dorsal mesentery for all its length; an approximately 270° counterclockwise rotation of the primitive mid-gut along the axis of the superior mesenteric artery (SMA) causes the folding of the dorsal mesentery, originating the future mesocolon^[13-19].

In 1885, Treves^[20] stated that the right mesocolon fuses with the primitive posterior parietal peritoneum, with the consequent obliteration of the space between these embryonic structures. This view of mesenteric obliteration through a process of fusion was than refuted in the early '900 by the study of Carl Toldt^[21] and Congdon^[22], who affirmed that the mesentery of the colon persists in adulthood not only at the level of the transverse and sigmoid colon, but all along its length, being separated from the posterior parietal peritoneum by a loose areolar connective plane referred to as Toldt's fascia. Later on, Goligher^[23] described the possibility of stripping back the colon and its meso towards the midline, restoring the primitive embryological disposition

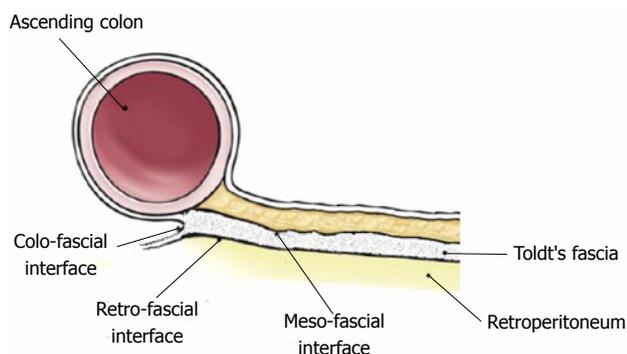


Figure 1 Depiction illustrating the relationships between the mesocolon, Toldt's fascia (schematically exaggerated for descriptive purpose) and the retroperitoneum. Meso-fascial interface is the apposition between the Toldt's fascia and the overlaying mesocolon; Retro-fascial interface is the apposition between the Toldt's fascia and the underlying retroperitoneum.

before its rotation, confirming the Toldt's and Congdon's remarks.

Contemporary view of the mesenteric organ

The increasing focus on the quality of the surgical specimen as an independent variable in the outcome of cancer surgery stresses the need for a more detailed knowledge of the mesocolon anatomy.

Recent papers demonstrated that the mesocolon persists in adulthood as a distinct anatomic structure, continuous from the ileocecal valve to the rectosigmoid junction, with well defined mesocolic, fascial, and retroperitoneal components and related mesofascial (the apposition between the Toldt's fascia and the overlaying mesocolon) and retrofascial (the apposition between the Toldt's fascia and the underlying retroperitoneum) interfaces (Figure 1): These latter are crucial for surgical planes in mesocolic and colonic mobilization^[24,25].

Furthermore, recent studies^[26,27] investigated the mesocolon by light and electron microscopy: Its structure is homogeneous across all locations and is composed of adipocyte lobules separated by thin fibrous septae layered by mesothelium, with lymphatic channels within this lattice; unexpectedly, a further connective, highly cellular submesothelial layer exists between surface mesothelium and the adipocytes.

A detailed appraisal of the lymphatic network within the mesocolon by immunohistochemical analysis^[28], showed that lymphatic vessels occur within both submesothelial connective tissue and interlobular septations, on average every 0.14 mm and within 0.1 mm from the mesocolic surfaces, generating a rich lymphatic network; the authors stressed that breaching the mesocolic surface extensively disrupts this lymphatic network. In the same study, lymphatic vessels were also identified within the Toldt's fascia, with no direct communication with those in the mesocolon, and whose clinical significance (independent or integral part of the mesocolon) should be investigated with further dedicated works: In fact, in mesofascial separation,

mesocolon and fascia are surgically separated with the Toldt's fascia left *in situ* (Figure 2A), whereas in retrofascial separation the mesocolon/fascia complex is separated from the underlying retroperitoneum (Figure 2B); both separations are integral to CME as shown by Hohenberger *et al*^[8], but the exact role of lymphatic channels within the Toldt's fascia could define only retrofascial separation as an oncologically correct plane of resection.

Time for a new terminology?

Some authors^[29-32] advocated the need for a new terminology in describing the mesocolon and its related surgical procedures: Visceral and parietal fascia, pre-renal fascia, parietal plane, somatic fascia may ingenerate confusion and should be standardized in the modern view of the mesenteric organ.

A surgical plane is defined as the interface between two contiguous structures, and in resectional colonic surgery the planes are (1) mesofascial; (2) retrofascial; and (3) colofascial, as shown in Figure 1. In keeping with this, a terminology of total or partial right (left) mesocolectomy has been proposed, being more informative than right (left) hemicolectomy or ileocolic resection because entirely derived for the current anatomical appraisal of the mesenteric organ anatomy.

THE RATIONALE BEHIND

There are three essential components of CME with CVL: (1) development of a mesofascial or retrofascial plane to mobilize an intact and inviolate mesocolon as an intact package; (2) CVL with high tie to maximize the vertical lymph node dissection (central spread); (3) adequate length of bowel to remove pericolic lymphnodes, maximizing the longitudinal lymphnode harvesting (longitudinal spread).

CME allows for removal of the entire envelope of the primitive dorsal mesentery along the anatomic-embryological avascular cleavage planes, and is therefore fundamental for a true radical R0 resection, as the meso contains the whole potential routes of metastatic spread through lympho-vascular, neuroperineural and fibro-fatty tissues^[8-10]. The mesocolon must be excised as an intact, inviolate package as any breach of its surface and underlying structures threatens the radial margin and disrupts the lymphatic network of the meso-structure with consequent *spillage* of neoplastic cells within the surgical field, enhancing the risk of local recurrence. This concept stresses further the need for a correct surgical plane of resection to maximize the local clearance, exactly the same way we conceptually perform TME for rectal cancer: To reduce to reduce the risk of an involved CRM and minimize the risk of local failure^[7].

CVL is essential in obtaining an adequate regional control and impact on survival. The latest 2010 JSCCR guidelines recommends D2 dissection for clinically

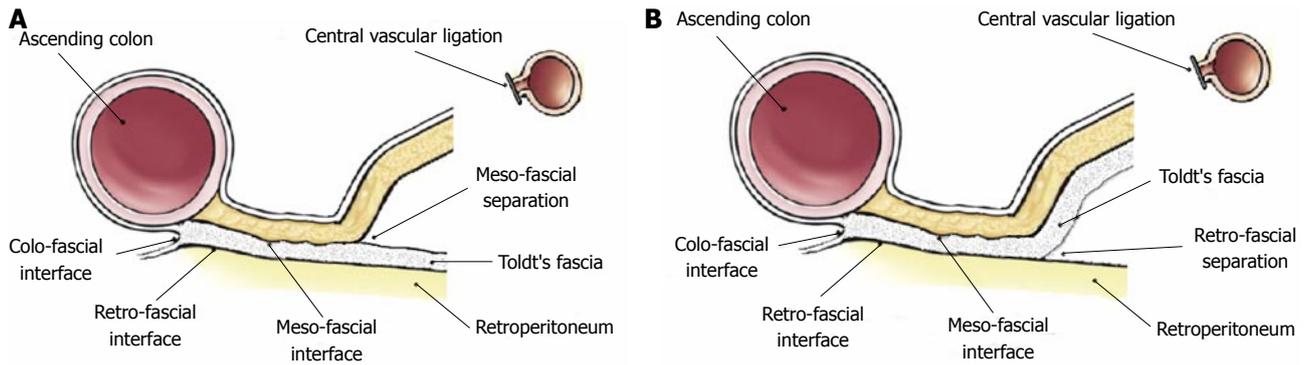


Figure 2 Depiction illustrating the meso-fascial (A) and retro-fascial (B) separation performed in the medial to lateral approach for laparoscopic right meso-colectomy. In Meso-fascial separation (A), the plane of dissection lies between the inferior leaf of the mesocolon and the underlying Toldt's fascia (schematically exaggerated for descriptive purpose), separating both components of the meso-fascial interface. In Retro-fascial separation (B), the plane of dissection lies between the Toldt's fascia and the posterior parietal peritoneum covering the retroperitoneum, separating both components of the retro-fascial interface. Both dissections end with colo-fascial separation.

early stages colorectal cancers and D3 dissection for more advanced disease: Impressive results in terms of local recurrence and patients survival have been reported^[33,34], also by Western authors who claim CME with CVL for right colonic cancer as oncologically effective as D3 right hemi-colectomy performed in Eastern Countries^[8,35,36]. CVL could be crucial in micro-metastatic clearance of central nodes, which are frequently missed by routine histological examination^[37], and thus responsible for loco-regional recurrence and systemic dissemination^[34]. For cancers located in the hepatic flexure and proximal transverse colon, possibly because of an embryological coalescence of mesenteric fascia, metastatic nodes incidence of about 5% for subpyloric station and about 4% for right gastroepiploic arcade has been reported^[38]: Central transection of middle colic vessels, ligation of right gastroepiploic vessels at the origin, 10 to 15 cm of greater omentectomy off the tumor and removal of subpyloric nodes could be beneficial, especially in advanced stages (clinically T3c-d and T4)^[8,39], as shown in Figure 3.

Blending CME with CVL is thus the logical step to ensure the best loco-regional control: CME maximizes the local clearance of the surgical field both increasing the chance for an uninvolved CRM and limiting any neoplastic spillage; CVL enhances regional control, removing apical nodes along the surgical trunk of the superior mesenteric vein (SMV), preventing regional recurrence and systemic dissemination: This is probably plausible for cancer without spread beyond the primitive *meso-structure*, as macroscopic involvement of apical nodes carries a poor outcome, independently from the extension of the surgical resection^[40].

SURGICAL TECHNIQUE OF LAPAROSCOPIC COMPLETE RIGHT MESO-COLECTOMY

Patient is administered general anesthesia and placed in

the supine or lithotomy position; a pneumoperitoneum is maintained at 10-12 mmHg using CO₂. The first step is always a thorough exploration of the abdominal cavity and peritoneal washing for cytology.

Once created the working space, a medial to lateral technique is generally adopted: The ileocolic vessels are stretched so to delineate the Treves arcade, and peritoneal incision is commenced at the base of the created peritoneal fold; dissection of the anterior peritoneal leaf is performed along the left margin of the SMA, with transection of the ileocolic and of the inconstant right colic vessels at their roots. An *en-bloc* lymphadenectomy of the anterior aspect of the SMV from the ileocolic vessels to the gastro-colic trunk of Henle is preformed (D3 lymph node dissection).

The anatomico-embryological plane along the Toldt's fascia is sharply divided from medial to lateral and from bottom to top along the meso-fascial or retro-fascial plane, sometime mobilizing the duodenum, as suggested by Hohenberger *et al*^[8], but usually dissecting along the plane between the intact dorsal mesocolon of the hepatic flexure and the Fredet's pre-duodenopancreatic fascia; the meso-fascial or retro-fascial interface must be carefully identified and components separated without breaching of either, respecting the integrity of the right mesocolon and of the retroperitoneal structures such as right ureter and gonadal vessels. The dissection stops at the lateral aspect of the right colon (right lateral peritoneal fold) exposing the colo-fascial interface, which will be separated later.

In case of caecum or ascending colon cancer, the stretched transverse mesocolon is progressively transected with central ligation of the right branch of the middle colic vessels and the colon is stapled 10 cm off the tumor (Total Right Meso-colectomy; Figure 3, blue lines); for hepatic flexure or proximal colon transversum cancers, middle colic and right gastroepiploic vessels are ligated at their roots, subpyloric lymph nodes are removed, 10 to 15 cm of greater omentum off the tumor is excised and colon stapling is carried out just

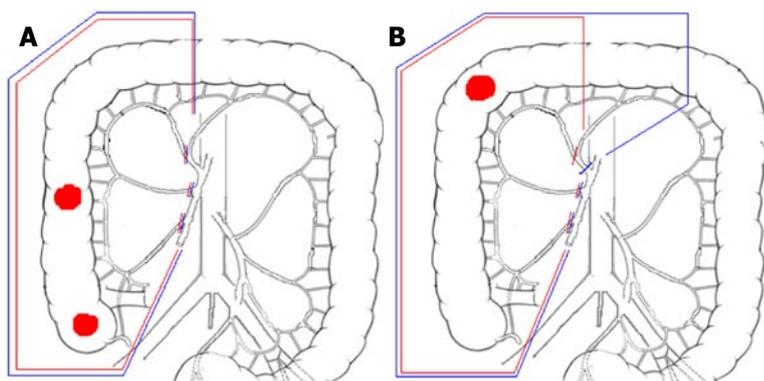


Figure 3 Schematic drawing illustrating the difference between extent of colon resection and lymph node harvesting between D3 right hemicolectomy according to 2010 JSCCR guidelines (red lines) and complete mesocolic excision with central vascular ligation according to Hohenberger's rules (blue lines). A: Cancer located in the caecum or ascending colon; B: Cancer located in the right (hepatic) flexure.

proximal to the splenic flexure (Total Extended Right Meso-colectomy; Figure 3, blue lines).

The hepatic flexure is mobilized by severing the lateral hepatocolic peritoneal fold, with the double components of the superior attachment (right phrenocolic ligament) and the medial attachment (cholecystoduodeno-colic ligament); division of these peritoneal folds demonstrate the colo-fascial interface at this level, which can be easily mobilized.

The right lateral peritoneal fold and the ileocecal peritoneal folds (caecal ligaments) are progressively severed to obtain complete mobilization of the specimen.

The ileum is stapled at 10-15 cm from the ileocaecal valve and the specimen is extracted within a plastic bag through a protected mini-Pfannestiel incision; side-to-side mechanical intracorporeal or extracorporeal anastomosis is fashioned.

Variants to laparoscopic classic CME with CVL

Some authors proposed their experience with modification of the classical approach in CME and CVL: Cho *et al*^[41], adopted a modified CME in respect to 3 major aspects: (1) non performance of Kocherization as described in the original paper of Hohenberger *et al*^[8]; (2) clearance of the pre-renal soft tissue behind Gerota's fascia for T3/4 cancer; and (3) tailored resection of the mesentery and mesocolon according to tumor location.

Feng *et al*^[42] proposed a hybrid medial approach prospectively compared to a completely medial approach: The hybrid approach is based on a first up-to-bottom dissection (section of the gastrocolic ligament and dissection of the middle colic vessels and Henle's trunk) blending with a subsequent classical medial-to lateral bottom-to-top approach; the study demonstrated less time for CVL and fewer vessel-related complications, especially for the pancreatico-duodenal vessels.

Matsuda *et al*^[43] also stressed a cranio-to-caudal approach for total right meso-colectomy, noting that lymph node dissection around the middle colic vessels is technically demanding and potentially exposed to severe intra-operative bleeding: The author suggests a caudal traction of the mesocolon to detect the origin of the middle colic vessels, maneuver suitable for detecting easily various types of middle colic vein

branching and thus reducing the risk of Henle's trunk and/or pancreatico-duodenal vessels injury.

QUALITY OF THE SURGICAL SPECIMEN

Laparoscopic CME with CVL, when performed in the right mesocolic plane, produces high quality surgical specimens. A grading system was developed in the CLASICC trial^[44], with the aim to compare laparoscopically assisted surgery with open resection for colorectal cancer; it was based on translation of the grading system used in the MRC CR07 trial for rectal cancer^[45]: (1) mesocolic plane of resection (“good” plane of surgery; intact, inviolate mesocolon with a smooth peritoneal-lined surface); (2) intramesocolic plane of resection (“moderate” plane of surgery; irregular breaches in the mesocolon, none reaching down to the muscularis propria of the viscus); and (3) Muscularis propria plane (“poor” surgical plane; disruption of the mesocolon down to the muscularis propria).

In the initial study of West *et al*^[46], the *mesocolic plane* translated into a higher quality of the surgical specimen: Wider cross-sectional tissue around the muscularis propria (mean 2181 ± 895 mm² compared to muscularis propria plane with a mean of 1447 ± 913 mm²; *P* = 0.0003), longer distance between the tumor and the mesocolic/retroperitoneal resection margin (44 ± 21 mm vs 21 ± 12 mm for muscularis propria plane, *P* < 0.0001), longer distance between the tumor and the high vascular tie and greater lymph node yield. The same group, in 2010 compared the quality of specimen between the Erlangen and Leeds experience, by precise tissue morphometry and grading of the surgical plane, concluding that CME with CVL routinely performed in Erlangen yields wider mesocolic area (19657 mm² vs 11829 mm²; *P* < 0.0001), longer large bowel (median, 314 mm vs 206 mm; *P* < 0.0001) and ileal (median, 83 mm vs 63 mm; *P* = 0.003) segment, higher distance between the tumor and the high vascular ties (131 mm vs 90 mm; *P* < 0.0001) and more lymph nodes harvested (median, 30 vs 18; *P* < 0.0001), reflecting in higher quality of the surgical specimens and better oncologic outcome^[9]. In 2012, CME with CVL was compared to Japanese D3 resection,

Table 1 Pathological data and oncologic outcome of the principal studies in literature

Ref.	Plane of surgery	High tie	LN harvested	RO	5y LR	5y OS	5y DFS
West <i>et al</i> ^[9]	Ms	90%	CVL 13 cm	CVL 30	Ms 94%	Ms 4.90%	Ms 85%
	NMs	40%	Ctl 9 cm	Ctl 18	NMs 85%	NMs NR	NMs 70%
Hohenberger <i>et al</i> ^[8]	Ms	100%	CVL 13 cm	CVL 32	Ms 97.40%	Ms 4.90%	Ms 85%
	NMs	0%					Ms NR
Siani <i>et al</i> ^[40]	Ms	65%	CVL 13 cm	CVL 30	Ms 97%	Ms NR	Ms 82.60%
	NMs	35%	Ctl 9 cm	Ctl 18	NMs 85%	NMs NR	NMs 60%
Kanemitsu <i>et al</i> ^[34]	Ms	100%	CVL NR	CVL 31	Ms NR	Ms 6%	Ms 84.50%
	NMs	0%					Ms 91.60%
Liang <i>et al</i> ^[48]	Ms	100%	CVL NR	CVL 34 ± 8	Ms NR	Ms 2%	Ms NR
	NMs	0%					Ms NR
Feng <i>et al</i> ^[53]	Ms	94%	CVL NR	CVL 19	Ms NR	Ms NR	Ms NR
	NMs	6%	Ctl NR	Ctl 14	NMs NR	NMs NR	NMs NR
Gouvas <i>et al</i> ^[55]	Ms	68.70%	CVL 8.7 cm	CVL 33	Ms 85.70%	Ms NR	Ms NR
	NMs	31.20%	Ctl NR	Ctl NR	NMs NR	NMs NR	NMs NR
Adamina <i>et al</i> ^[54]	Ms	100%	CVL NR	CVL 22	Ms 100%	Ms NR	Ms NR
	NMs	0%					Ms NR
Bertelsen <i>et al</i> ^[57]	Ms	82%	CVL NR	CVL 36	Ms 97%	Ms 11.30%	Ms 74.90%
	NMs	18%	Ctl NR	Ctl 20	NMs 95%	NMs 16.20%	NMs 69.80%
Shin <i>et al</i> ^[51]	Ms	100%	CVL NR	CVL 27.8 ± 13.6	Ms NR	Ms 3.60%	Ms NR
	NMs	0%					Ms 88%
Bae <i>et al</i> ^[52]	Ms	100%	CVL NR	CVL 28	Ms NR	Ms NR	Ms 90.30%
	NMs	0%					Ms 83.30%

Ms: Mesocolic plane; NMs: Non-mesocolic planes; CVL: Central vascular ligation; Ctl: Control; NR: Not reported.

benchmark for highest survival reported in worldwide literature: Even in this case, CME with CVL showed wider mesocolic area (17957 mm² vs 8309 mm², $P < 0.001$), longer bowel segment (324 mm vs 162 mm, $P < 0.001$) and greater nodal yield (32 vs 18, $P < 0.001$), but equivalent distance between the tumor and the high vascular tie not statistically different (100 mm vs 99 mm; $P = 0.605$), translating in similar impressive long term survival^[10].

RESULTS

The higher quality of surgical specimen translates in better long term oncologic outcome, with significant impact on local recurrence rate, disease free and overall survival: In the pioneering studies of West^[46,9,10], Mesocolic plane of surgery and high tie ligation showed a non-stratified 15% survival advantage at 5 years when compared to *non-mesocolic planes* of resection; interestingly, the survival boost was even more remarkable in the subset analysis for stage III patients, with an increased survival by 27% at 5 years.

These results were confirmed in subsequent studies comparing the different planes of resection, both in open^[8-10,35,36,47] and laparoscopic surgery^[40,48-55], reflecting a significant interest for the brilliant results of CME with CVL. Recently, two important studies further substantiated the effect of the correct plane of resection in colonic cancer: A systematic review on 5246 patients revealed a local recurrence rate, 5 years overall and disease free survival of 4.5%, 58.1% and 77.4% respectively^[56]; and in 2015, a well structured population-based study by the Danish Colorectal Cancer Group^[57] demonstrated a better disease-free survival

for patients with stage I-III colonic cancer, suggesting that both laparoscopic and open CME with CVL may significantly improve outcome.

Unfortunately, these numerous studies (the most relevant reported in Table 1) have significant statistical power limitations, being predominately retrospective and non-homogeneous, so that at the moment a definitive high level of evidence cannot be drawn and thus no strong grade of recommendation may be assigned. This highlights the need for sufficiently powered randomized trials, to definitively address the issue and affirm with conclusive evidence that CME with CVL represents the gold standard in the surgical management of (right) colonic cancer.

CONCLUSION

The current evidence shows the equivalence in terms of tissue morphometry, quality of the surgical specimen and long term oncologic results between laparoscopic and open techniques^[39,43,46,52,55-57], but with laparoscopic approach offering all the advantages of minimally invasive surgery, both in faster recovery and in less immunological stress response which could affect long term outcome^[58-62].

In the multimodal management of right sided colonic cancer, laparoscopic CME with CVL is progressively gaining a pivotal role on the base of high quality surgical specimen, better local recurrence rate, better 5 years overall and disease-free survival when compared to less radical planes of surgery.

Laparoscopic CME with CVL should be regarded as the new frontier of a modern, *meso-resectional* oriented surgery, with all the advantages of minimally

invasive techniques, which allow for faster recovery and better immunological stress response: Higher quality of yielded surgical specimen, less complications when the laparoscopic procedure is *embedded* in an Enhanced Recovery After Surgery program^[63-72] and better immuno-competence due to less surgical stress^[58-62], may thus collectively contribute to better long term oncologic outcome.

Yet, in the absence of high level of evidence which precludes strong grade of recommendation, laparoscopic CME with CVL should be intensely investigated with highly powered, well structured prospective studies, so to define its role in the modern, multimodal management of right colonic cancer.

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Intestinal inflammation and the diet: Is food friend or foe?

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Abstract

Inflammatory bowel disease (IBD) is a chronic intestinal illness of autoimmune origin affecting millions across the globe. The most common subtypes include ulcerative colitis (UC) and Crohn's disease. While many medical

treatments for IBD exist, none come without the risk of significant immunosuppression and in general do not have benign side effect profiles. Surgical intervention exists only as radical resection for medically refractory UC. There exists a dire need for novel treatments that target the inherent pathophysiologic disturbances of IBD, rather than global immune suppression. One avenue of investigation that could provide such an agent is the interaction between certain dietary elements and the aryl hydrocarbon receptor (AHR). The AHR is a cytosolic transcription factor with a rich history in environmental toxicant handling, however, recently a role has emerged for the AHR as a modulator of the gastrointestinal immune system. Studies have come to elucidate these effects to include the enhancement of T_H cell subset differentiation, interactions between enteric flora and the luminal wall, and modulation of inflammatory interleukin and cytokine signaling. This review highlights advancements in our understanding of AHR activity in the digestive tract and how this stimulation may be wrought by certain dietary "micro-nutriceuticals", namely indole-3-carbinol (I3C) and its derivatives. Greater clarity surrounding these dynamics could lead to a novel diet-derived agonist of the AHR which is not only non-toxic, but also efficacious in the amelioration of clinical IBD.

Key words: Inflammatory bowel diseases; Aryl hydrocarbon receptor; Mucosal immunity; Dietary phytochemicals; Autoimmune diseases

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Core tip: Inflammatory bowel disease (IBD) is a chronic illness with a paucity of safe and effective treatments, either medically or surgically. The aryl hydrocarbon receptor represents a novel target for future treatments of IBD using dietary ligands of the receptor. Many studies have examined the interplay between the aryl hydrocarbon receptor and gastrointestinal mucosal immunity, though there remains a gap in the understanding of how dietary ligands can modulate

this activity. Our objective was to highlight elements of current literature focusing on aryl hydrocarbon receptor biology, IBD, and how their interplay can be activated with dietary “micronutriceuticals”.

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INTRODUCTION

The incidence of inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and Crohn’s disease (CD) has been increasing worldwide; it is now estimated that between 1 and 1.3 million Americans are currently diagnosed with IBD^[1,2]. This increased incidence is possibly due to currently unidentified environmental factors, which interact with an inherent genetic predisposition^[3]. IBD is a family of chronic inflammatory conditions primarily involving the digestive tract, and often having additional extra-intestinal manifestations. The unique chronic inflammatory milieu maintained by IBD predisposes patients to non-adenomatous colorectal cancer as well as small bowel adenocarcinoma^[4]. To date there is no accepted etiology or preventive measures for these conditions. Even more, there exists no cure aside from radical surgery for refractory ulcerative colitis^[5].

The medical management of IBD currently stands at topical intestinal anti-inflammatories, systemic immunosuppression/immunomodulation, and novel biologic agents. The response rates, or rather the percentage of IBD patients experiencing true and deep remission using currently available treatment, is notoriously low. Only just recently have gut-specific monoclonal antibody inhibitors such as vedolizumab, which targets the integrin $\alpha 4\beta 7$ receptor, been approved for the treatment of IBD, possibly ushering in an age of targeted therapies^[6]. However, many if not all of the current treatment modalities for IBD have significant side effect profiles, exorbitant cost, or both^[7,8]. A prospective avenue of treatment for IBD that avoids many of the pitfalls of current therapy involves modulating mucosal inflammation using bioactive phytochemicals delivered by the diet. In fact, it has been reported that diets rich in fruits and vegetables are protective of IBD, which may indicate a role for future diet-derived treatments^[9,10]. The ideal treatment would have influences on gut barrier permeability, innate GI inflammation, and mucosal immunity, all pathophysiological hallmarks of IBD.

One potential mediator of anti-inflammatory dietary compounds is the aryl hydrocarbon receptor (AHR). The AHR is a chaperoned cytosolic protein that has been found to influence transcription after binding to an

exogenous ligand^[11]. It is a member of the basic helix-loop-helix transcription factor family as well as the Per-Arnt-Sim protein homology that regulates environmental adaptation to ligand exposure^[12,13]. Once bound, the AHR can shed its cytosolic chaperones, heterodimerize with the aryl hydrocarbon receptor nuclear translocator, bind to specific xenobiotic response elements within the genome, and induce downstream genes *via* transcriptional activation (Figure 1)^[14,15]. The canonical function of the AHR exists as an environmentally responsive “sensor” which acts to detoxify its own ligands *via* upregulation of phase I and phase II enzymes, most notably the cytochrome P450 superfamily^[16]. Its biology has been most famously attributed to the metabolism of dioxin, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)^[17]. In addition to its roles in toxin handling, recently the AHR has been implicated in inflammatory pathways, tumorigenesis, and immune regulation within the intestines^[18-20]. These downstream effects of AHR activity have been linked to manipulations of T-cell response, interleukin (IL) production, as well as altered cytokine function^[21]. All of these phenomena have been found to contribute in some way to regulation of intestinal immunity, mucosal integrity, and alterations to the microvasculature of the intestine, which are all pathological disturbances inherent to IBD^[22]. While it is known that AHR biology is linked to the development and progression of IBD, it is yet to be determined if the AHR can be manipulated in such a way to exert a preventative, protective, or even therapeutic role in IBD *via* dietary ligands^[23].

The well-studied dietary component indole-3-carbinol (I3C) has been recognized as a precursor to a host of AHR ligands that are active in the gut. The compound glucobrassicin (precursor to I3C) is found in high concentrations in the Brassica family of vegetables which includes broccoli, cabbage, and Brussels sprouts (Figure 2)^[24]. Mastication-induced enzymatic hydrolysis of glucobrassicin produces I3C in the mouth. I3C then dimerizes to 3,3'-diindolylmethane (DIM) in the presence of gastric HCl as well as indole [3,2-b] carbazole (ICZ) among others further down in the GI tract^[25]. It is known that DIM is the molecule which exerts more robust effects on the AHR, not its parent I3C^[24]. AHR activation has been found to modulate activity of intraepithelial lymphocytes, preserve lymphoid organs in the gut, and maintain mucosal homeostasis^[26,27]. Moreover, DIM-supplemented diets have been shown to attenuate colonic inflammation as well as suppress colitis-associated tumorigenesis in mice^[28]. This effect may be due to the ability of DIM to modulate various inflammatory cell actions in the gut lining^[29]. What is known for certain is that dietary AHR ligands are able to induce the receptor within the gut epithelium as well as globally^[30]. These recent advances in the understanding of the effects of AHR stimulation *via* dietary ligands may lead to diet-derived novel anti-inflammatory agents which combat the inherent disturbances of IBD.

This review highlights current knowledge on AHR

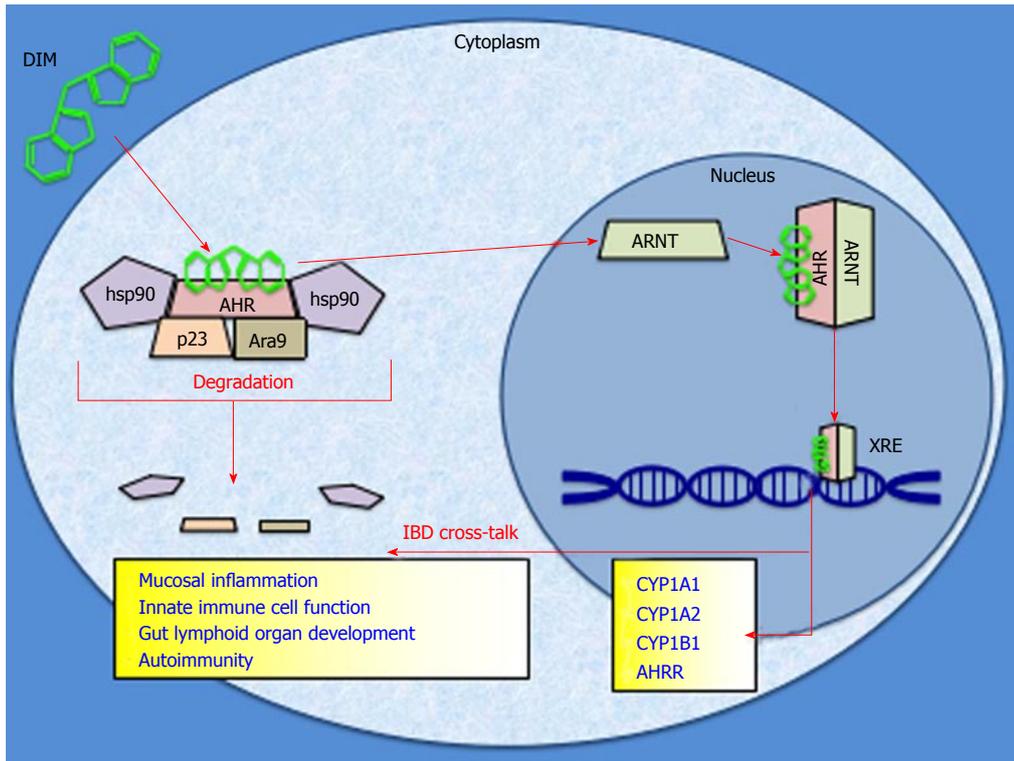


Figure 1 The aryl hydrocarbon receptor signaling pathway is depicted with 3,3'-diindolylmethane as a model agonist. Upon binding to a ligand, aryl hydrocarbon receptor (AHR) sheds its cytosolic chaperones and translocates to the nucleus to heterodimerize with aryl hydrocarbon receptor nuclear translocator (ARNT). This complex binds to the xenobiotic response element (XRE) within the genome and drives transcription of cytochrome P450 detoxifying enzymes. Proposed avenues of cross-talk with inflammatory bowel disease pathology are listed. IBD : Inflammatory bowel disease.

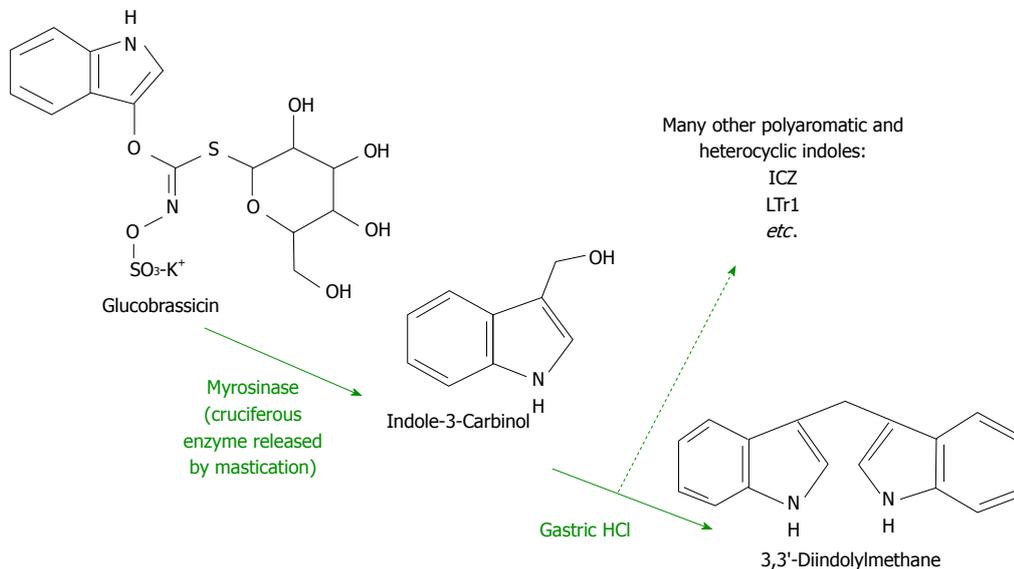


Figure 2 Presented is a simplified model for glucobrassicin digestion. I3C is freed from glucobrassicin by the mastication-released enzyme myrosinase. Gastric HCl drives dimerization of I3C to 3,3'-diindolylmethane, as well as other indole complexes that are released to the duodenum and distal digestive tract. I3C: Indole-3-Carbinol.

stimulation in the context of IBD, especially as it relates to dietary stimulation of the receptor. Continued study of the manipulation of the unique gastrointestinal inflammatory milieu associated with IBD could eventually lead to both novel therapeutics as well as

diet-modifying strategies. Due to the apparent benign side effect profile of dietary AHR ligands, clinical application of this knowledge could reduce iatrogenic immunosuppressive morbidities associated with current IBD treatment as well as improve overall disease

control.

LITERATURE SEARCH

A systematic literature search was conducted using PubMed and Google Scholar for "aryl hydrocarbon receptor", "AHR", "IBD", "ulcerative colitis", "3,3'-diindolylmethane", "indole-3-carbinol", and "mucosal immunity". Searches containing relevant synonyms and combinations of the above terms were also utilized. Eighty-nine relevant references were identified and cited within this review. Included studies ranged from basic science investigations to clinical trials.

IN VITRO INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

The biology of the AHR is well studied in numerous *in vitro* models, however, recently the common understanding of the AHR solely acting as a toxicological sensor that upregulates detoxification enzymes has been challenged^[31]. Interactions between the receptor and dioxin (TCDD) have always been the cornerstone of mechanistic and physiologic AHR studies, however it is now known that there is a wide compendium of exogenous chemicals that operate *via* the AHR^[32-34]. In fact, it is micronutritional chemicals such as the indole family including I3C and DIM that have recently been identified as the bridge between AHR signaling and anti-inflammatory as well as chemoprotective effects in the gastrointestinal system^[35]. These chemicals have been found to enhance mucosal integrity, maintain intraepithelial lymphocyte populations, as well as sensitize the GI tract to certain populations of enteric flora^[36,37]. In contrast, TCDD treatment has been found to weaken mucosal immunity in the gut^[38]. This would present a possible bifunctional role for the AHR and IBD. Further investigation of these actions is warranted to elucidate their role within the inherent disturbances of IBD. An important step in understanding the role of both the AHR and its dietary ligands is to examine their roles modulating inflammation *in vitro*.

Research surrounding the aryl hydrocarbon receptor and various aspects of immunity has recently exploded, especially concerning the effects of dietary ligands. First, it is important to note that not only has DIM been found to activate the AHR *in vitro*, but has also been found to elicit multiple chemoprotective responses in various intestinal cell lines^[39-42]. In addition to its ability to upregulate the AHR in cells of the digestive tract, DIM treatment also modulates immune cell activity. For instance, DIM treatment suppresses the inflammatory response of murine macrophages *in vitro* *via* downregulation of TNF- α , IL-6, and IL-1 β ^[43]. These effects and more were also found when murine dendritic cells were treated with I3C. This protocol prompted a downregulation of TNF- α , IL-6, and IL-1 β as well as an upregulation of IL-10^[44]. These are important

findings as activated macrophages as well as these inflammatory cytokines, especially TNF- α , play key roles in the pathogenesis of IBD^[45-49]. In fact, many of the most widely used biologic agents for the treatment of IBD are anti-TNF- α antibodies^[50].

In addition to various cytokine and interleukin abnormalities, IBD has also been linked to various T-cell populations and their relative size and function in the GI tract^[51]. Two distinct populations that have been linked to IBD disease activity are T-regulatory cells (T_{reg}) and T_H17 T-cells^[52-54]. The action of T_{reg} cells has been found to be protective, while T_H17 cell activity has propagated inflammatory damage in IBD. It is well established that the aryl hydrocarbon receptor modulates various populations of immune cells, which has implications for the future treatment of IBD^[55]. In fact, AHR stimulation *via* natural ligands has been linked specifically to upregulated T_{reg} cell activity and inhibition of T_H17 cell activity^[27,55-57]. These effects have been further proven to be AHR-dependent^[58]. Another immunomodulatory effect of *in vitro* AHR stimulation comes as a consequence of T_{reg} cell biology. AHR activity enhances T_{reg} differentiation and thus increases the population of immunoregulatory/anti-inflammatory cell populations that are responsive to IL-10^[59]. This is not only important because, as mentioned earlier, DIM treatment of murine immune cells leads to the induction of IL-10, but also because IL-10 has a firmly seated role in the pathophysiology of IBD. Mice null for IL-10 have been found to be deficient in various immunoregulatory functions in the GI tract^[59]. Even more, in a small trial, patients with CD responded favorably to treatment with recombinant IL-10 producing microbes^[60]. Further study of the interaction between dietary AHR ligands and immune cell function could lead to a better and more targeted understanding of their interplay.

There exists a large battery of cellular cascades and signaling pathways enhanced, inhibited, or modulated by the actions of dietary indoles such as I3C and DIM, though there remains a gap concerning a full understanding of their anti-inflammatory effects^[61]. Further *in vitro* protocols focusing solely on the interaction between the AHR and certain "micronutriceuticals" like I3C and DIM could one day lead to a better understanding of their cellular effects in the context of IBD.

IN VIVO INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

The AHR has been extensively studied *in vivo*, mainly through the use of murine models null for the AHR to better understand its unique role in toxicology. Previous research has suggested the need to better understand the potential immunological function of AHR across various disciplines^[62]. The AHR has been previously implicated as an important autoimmune target *in vivo* as it alters expression of the T_H17 cell subset and

associated cytokines in response to environmental toxins in the intestine^[56,63]. Perhaps one of the most interesting avenues of research linking environmental exposures to altered immune response *via* the AHR can be found in the pathogenesis of IBD^[21]. To best study the complex interaction of environmental factors and AHR expression in the context of immune function in the gut, many *in vivo* models have been developed to pick apart this inflammatory environment.

Due to the historical classification of AHR as the dioxin receptor, many models have been developed using TCDD treatment after induction of IBD. Dextran sulfate sodium (DSS) is a commonly employed agent to induce colitis in murine models, and multiple studies have shown that pre-treatment with low dose TCDD can prevent inflammation associated with colitis and/or reduce inflammation when administered after the onset of colitis in mice^[57,64]. A similar study using trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice as a model for CD, showed that animals treated with TCDD recover quicker and experience less colonic damage than those that are untreated^[43]. While these studies show promise for the role of AHR in IBD, dioxin is a carcinogen that is highly persistent in tissue, leading to efforts to identify novel AHR ligands with low toxicity for use *in vivo*.

As a non-toxic agonist of the AHR, β -naphthoflavone (β NF) has shown great potential in attenuating colitis through reducing the histological score in both wild-type and AHR null mice with varying severities of DSS-induced colitis^[65]. Perhaps even more interesting is the use of an endogenous mammalian AHR ligand such as the non-toxic tryptophan byproduct 6-formylindolo(3,2-b)carbazole (FICZ), which has been shown to protect mice from DSS-, TNBS-, and T-cell transfer-induced colitis through reduced inflammatory cytokine levels and lack of IL-22 induction^[18]. While these compounds attenuate colitis without the potential toxic side effects of TCDD, research into the use of dietary phytochemicals as AHR ligands is of even greater interest for the treatment of IBD^[66]. One study showed that the AHR is induced by phytochemicals derived from plants of the Brassicaceae family, which includes broccoli, cabbage, kale, and others. It was found that this AHR activation is required for development of ROR γ ^t-expressing innate lymphoid cells (ILCs), as shown by increasing pools of these cells when mice are fed a diet supplemented with I3C, a product of glucobrassicin breakdown^[6]. Another study established a role for I3C in controlling bacterial colonization of the gut, sustaining immune function, and protecting epithelial barrier organization as it pertains to colitis severity^[27]. I3C remains a compound of great interest for the treatment of IBD, but the activity of I3C in the diet is most likely dependent on the activity of DIM, the dimer product of I3C hydrolysis by gastric acid. DIM would make up the majority of the indole load that reaches portions of the intestinal tract distal to the duodenum.

DIM has previously been shown to alleviate hepatic

inflammation through shifting of diet-induced T_H17 dominance to T_{reg} dominance^[67]. These data were further supported in studies where DIM was shown to attenuate experimental colitis as determined by pathological findings in mouse models, including evidence that DIM works through the AHR to decrease the T_H17 cell population while increasing the number of T_{reg} cells^[29,68]. In DSS-induced colitis experiments, DIM has been shown to attenuate the disease by reducing the clinical severity of colitis, including prevention of colonic shortening and weight loss in addition to dramatically decreasing the number of tumors in AOM/DSS treated mice, which provide a common model of colitis-associated colorectal cancer^[28].

In vivo models to study the AHR and IBD remain warranted, as there are numerous unidentified factors that affect progression of the disease. In particular, the interaction between immune cells and the gut microbiome is of growing interest to the research community. For example, AHR null mice succumb to infection by *Citrobacter Rodentium* because the absence of AHR signaling leads to a lack of ROR γ ^t+ ILCs that consequently do not produce enough IL-22^[69]. Furthermore, the balance between ILCs and T_H17 cells regulated by AHR has been shown to control the composition of commensal flora^[69]. In fact, the menaquinone precursor 1,4-dihydroxy-2-naphthoic acid, an AHR ligand produced by *Propionibacterium freudenreichii* has been shown to inhibit DSS-induced colitis in mice and is even commercially available in Japan as a dietary supplement that holds promise as an IBD treatment agent^[70]. These findings are critical to the continued study of IBD, as interactions between dietary factors and various states of colonic dysbiosis have been shown to contribute to disease progression^[71,72].

HUMAN AND CLINICAL INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

While there is a wealth of data and analysis surrounding the aryl hydrocarbon receptor and DIM in both tissue culture and murine models, there are few studies in humans related to IBD, clinical or otherwise. Some correlations have been made however, and these have prepared the way for many potential future studies. Arsenescu *et al.*^[23] found that AHR activity is upregulated in colonic biopsy tissue in IBD patients when compared to healthy controls. Even more, this increased activity mirrored that of IL-8, a neutrophil chemotactic that is elevated in IBD patient tissues^[23,73]. Conversely, it has also been reported that biopsies from patients with CD exhibit downregulated levels of AHR, which is thought to be due to T_H17 cell infiltration of inflamed tissue in CD^[18]. This underscores the inherent bifunctionality of the AHR. Even though there are few studies which investigate human tissue, they do provide some exciting

evidence to a role for the AHR in human IBD.

There are not currently any clinical trials using DIM for any form of IBD. However, there are multiple chemopreventive and chemotherapeutic trials using both DIM and its parent I3C in the context of a variety of neoplasms. These trials aimed to treat, prevent, or modulate hormone response in breast cancer, vulvar epithelial neoplasia, cervical intraepithelial neoplasia, and recurrent respiratory papillomatosis^[74-77]. Again, while these examples are outside the realm of IBD, they do serve to prove that a clinical trial using I3C and/or DIM is biologically feasible in humans. In addition, there have been multiple studies which have analyzed the pharmacodynamics of these compounds in humans, which provide groundwork to one day optimize dosing protocols for trials aimed at IBD^[78-80]. One pharmacokinetic and safety investigation established that not only are I3C and DIM non-toxic at doses ranging from 200-800 mg daily, but also that in most of the participants tissue concentrations over 1 mmol/L were observed^[81].

What all of this work has done is prove that both I3C and DIM have some form of biologic and therapeutic activity in humans. Whether or not this activity is the result of AHR stimulation remains to be seen. Moving forward, a clinical trial utilizing these phytochemicals to combat IBD is warranted. The concept of using natural chemicals to treat intestinal inflammation is not new. Curcumin, the biologically active derivative of the spice turmeric, has been found to modulate numerous inflammatory, oxidative, and tumorigenic pathways in various tissues, including the colorectum^[82-85]. Numerous *in vitro* and *in vivo* studies have propelled curcumin into multiple IBD-related clinical trials. The first of these investigations was a very small pilot study which discovered that in IBD patients curcumin treatment lowered both erythrocyte sedimentation rates and CD Activity Index scores vs placebo^[86]. More recently, Hanai *et al*^[87] found in their RCT that curcumin performed well vs placebo for maintenance therapy of mild-moderate ulcerative colitis. While oral delivery proved to have therapeutic activity, curcumin enemas have also been employed in the treatment of distal colitis with similarly efficacious results^[88]. In relevance to the paradigm of I3C/DIM acting *via* the aryl hydrocarbon receptor, curcumin as well as other dietary phytochemicals have been found to modulate AHR activity^[89]. These trials of curcumin provide relevance to investigating the therapeutic potential of natural dietary chemicals such as I3C and DIM in the context of IBD.

CONCLUSION AND FUTURE DIRECTIONS

The complex and often dangerous treatment of IBD is a dilemma faced by gastroenterologists and colorectal surgeons alike. The intricate inflammatory milieu of IBD presents many avenues for potential targets to attenuate the inherent autoimmunity of the condition. In order to better understand the role that dietary

ligands of the AHR play in attenuating IBD, potential avenues of study should focus on the aryl hydrocarbon receptor as it pertains to intestinal barrier function, immune regulation, and inflammation. To achieve this, portions of the IBD phenotype would be isolated and measured under AHR stimulation by a dietary agonist such as I3C or DIM. Also, the binding affinities of these compounds to the AHR in an array of gastrointestinal tissues must be established in order to localize the cell and tissue types where these agents will achieve the most robust response. Another important line of inquiry is to delineate the molecular cross-talk between AHR stimulation and the numerous other pathways previously identified as those that drive IBD. More globally, tissue-specific AHR activity should be investigated in order to ascertain off-target effects of treatment with a dietary AHR agonist. Finally, the most rigorous examination of these agents would be a randomized controlled trial of I3C or DIM for the treatment of IBD within the Phases set by the FDA. However, incorporation of dietary AHR ligands into human clinical studies demands a crystal clear picture put forth by exhaustive *in vitro* and *in vivo* murine models as to how these compounds exert their effects. Throughout these various investigations, it would remain important to delineate additional molecular pathways engaged by these dietary ligands in addition to the AHR in order to better understand their complete mechanisms of action.

Further investigation of how IBD-related cascades can be manipulated exogenously, perhaps *via* the AHR, could one day lead to diet-derived and well-tolerated regimens for those with ulcerative colitis and CD. That being said, it must be appreciated that the AHR is only one of many potential signaling cascades that may influence the IBD phenotype in humans. The characterization of a diet-derived agent, AHR agonist or not, that targets the hallmark imbalances in IBD without compromising host immune function would revolutionize current medical treatment modalities and save many from radical surgical intervention.

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Associating liver partition and portal vein ligation for staged hepatectomy: From technical evolution to oncological benefit

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Abstract

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a novel approach in liver surgery that allows for extensive resection of liver parenchyma by inducing a rapid hypertrophy of the future remnant liver. However, recent reports indicate that not all patients eligible for ALPPS will benefit from this procedure. Therefore, careful patient selection will be necessary to fully exploit possible benefits of ALPPS. Here, we provide a comprehensive overview of the technical evolution of ALPPS with a special emphasis on safety and oncologic efficacy. Furthermore, we review the contemporary literature regarding indication and benefits, but also limitations of ALPPS.

Key words: Liver tumor; Resection; Hepatectomy; Staged; Portal vein embolization; Future liver remnant; Liver hypertrophy; Liver failure; Morbidity; Mortality

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Core tip: We provide a comprehensive overview of the technical evolution of Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) with a special emphasis on safety and oncologic efficacy. Furthermore, we review the contemporary literature regarding indication and benefits, but also limitations of ALPPS.

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INTRODUCTION

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), initially known as “*in situ* split”, was first performed in September 2007, and until today, more than 600 procedures have been performed worldwide^[1-4]. ALPPS has shown to have a promising efficacy regarding the induction of a rapid liver hypertrophy, thereby increasing the resectability of previously unresectable liver malignancy^[5]. Furthermore, a sufficient volume increase can also be achieved by liver partition after unsuccessful portal vein embolization (PVE)^[6,7].

Since the pioneering publication of Schnitzbauer *et al.*^[1] in 2012 with the first 25 cases in a multicentric study, considerable experiences have been obtained. A technical evolution of this novel procedure has been observed during the last four years. This was accompanied by a better understanding of the importance of patient selection, not only to minimize morbidity and mortality, but also to achieve the most oncological benefit^[8].

This review was performed to report a current overview on the development of the ALPPS procedure. The review is based on personal experience from our institute as well as a detailed analysis of the international literature of the last four years.

LANDMARKS

The pioneer case and the first multicenter study

The pioneer case of ALPPS was performed in September 2007 by Dr. Schlitt at the University Hospital Regensburg, Germany in a young patient with hilar cholangiocarcinoma (CCA)^[2]. During the exploration, the surgeon decided to perform a left hepaticojejunostomy to relieve the cholestasis of the future liver remnant (FLR), which was considered too small for a one stage right trisectionectomy. To provide an access to the left bile duct, the liver was transected along the falciform ligament. The right portal vein was ligated to enhance the hypertrophy of the remnant liver. The patient recovered so well that a computer tomography (CT) was performed at the postoperative day (POD) 8, showing a 94% gain of the future remnant liver volume. Thus the second stage operation was successfully performed on POD 9.

This method was found to be reproducible and was soon adopted by many other surgeons around the world. In 2012, Dr. Schnitzbauer reviewed the first 25 cases of this novel concept of 2-staged hepatectomy in five German university hospitals between September 2007 and January 2011^[1]. The indications were patients with either primary or secondary liver malignancy, who underwent a right trisectionectomy with a preoperative left lateral lobe to body weight ratio of less than 0.5%. After a median interval of 9 d (range, 5 to 28 d) from *in situ* splitting and right portal vein ligation (PVL), a CT volumetry was performed, indicating a median

increase in volume of 74% (range: 21% to 192%). The procedure was then completed on the same or following day without drop-out. None of the patients developed irreversible liver failure after surgery. Sixteen patients (68%) experienced perioperative complications^[1]. In-hospital mortality was 12%, the six-month median overall survival was 86%.

The above procedure was considered as a novel concept representing one of the most promising advances in oncological liver surgery by the editors of the *Annals of Surgery*^[3]. The new strategy was found to elegantly address the most feared complication following major hepatectomy, postoperative liver failure (PHLF). The amount of hypertrophy induced by this procedure is unparalleled by any other techniques. Moreover, the rapid regenerative response offers additional significant advantages. For example, tumor progression is unlikely during this short period, and there are less adhesions during the second stage operation. Furthermore, this procedure thereby allows a faster recovery for the patient, with the possibility to resume chemotherapy earlier. The acronym “ALPPS” was proposed to describe this novel approach: “Associating Liver Partition and Portal vein ligation for Staged hepatectomy”^[3].

ALPPS registry

The ALPPS registry was initiated by Dr. De Santibanes, Dr. Lang and Dr. Clavien in 2012 to achieve a more systematic exploration of this new surgical procedure^[9]. It is an internet-based international registry for cases performed using the above method. The headquarter is located at the Department of Surgery, University Hospital Zurich, Switzerland. To establish the registry, an electronic case report form using the clinical trials software SECUTRIAL (Interactive System, Berlin, Germany) was presented to selected experts worldwide for approval (Scientific Committee of the ALPPS Registry). Any center willing to report patients in the registry is given access through the internet. The aim of the registry is to systematically and uniformly collect information from multiple centers worldwide^[10]. Despite of a possible reporting bias, the registry enables surgeons to study a larger population to overcome shortcomings inherent to small case series reports. In 2014, the first report by the registry consisted of a total of 202 patients from 41 centers, provided complete data sets of procedures and 90 d survival status^[10]. Till July 8th, 2015, 583 cases performed worldwide were enrolled into the registry.

The first consensus meeting on ALPPS

In February 2015, the first ALPPS consensus meeting was held by Dr. Oldhafer and Dr. van Gulik in Hamburg, Germany. Nearly all groups with vast experience in the ALPPS approach were invited to participate as faculty. The key points consisted of indications, preparations, techniques and outcomes. The two-day meeting provided the community a scientific base for future decision-making. The video and slides are available at the

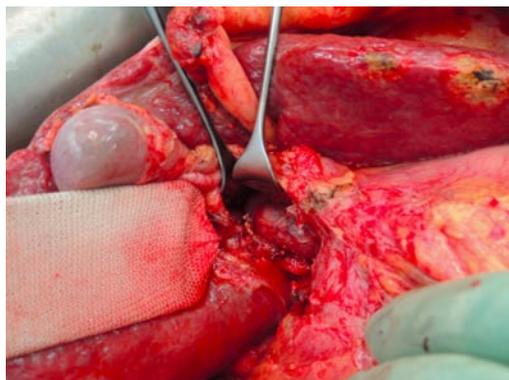


Figure 1 Exposure of the portal vein by lifting the common bile duct and right hepatic artery using a lid retractor. Here the right portal vein branches were transected.

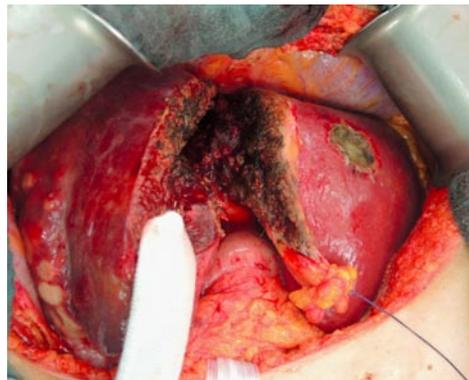


Figure 2 Liver parenchyma transection along the falciform ligament.

official website (www.alpps.com). The meeting not only summarized the development and the limitations of ALPPS, but also inspired the ideas and promoted the cooperation between international centers. The summary of the consensus meeting is yet waiting for publication.

EVOLUTION OF THE SURGICAL TECHNIQUE

Classical ALPPS

The first operation (right portal vein transection and in situ liver splitting): During the first operation, an exploration is carried out to exclude extrahepatic tumour dissemination. Resectability is determined if the remnant segments 2 and 3 have adequate inflow as well as outflow. Tumour involvement of segments 2 and 3 is no contraindication as long as it could be safely resected without tumour residual. The next step is the dissection of the hepatoduodenal ligament. A cholecystectomy is optional. In patients without tumour infiltration of the gall bladder, a cholecystectomy is usually carried out. After lifting the common bile duct and right hepatic artery by a lid retractor, the right portal vein and main portal vein is exposed (Figure 1). At this stage, the main right portal vein branch could be transected after suture ligation at the distal end and continuous suture, *e.g.*, with 5/0 Prolene at the proximal end. In patients with trifurcation of the portal vein with separate entry of the right anterior and posterior sectional branches, the anterior and posterior portal veins should be divided separately.

The umbilical portion of the left portal vein is exposed by dissecting the umbilical fissure. The portal branches of segment 4 are ligated and divided at its origin. The hepatic artery, the bile duct and the right hepatic vein are dissected and identified with rubber bands. Subsequently, transection of the liver parenchyma along the falciform ligament is performed (Figure 2). The falciform ligament could also be kept in the future remnant side for re-fixation of the left lateral lobe at the diaphragmatic dome if technically

possible. Intraoperative ultrasound should be performed to confirm the absence of right portal flow at the end of the operation. Silicone sheeting or drainage could be applied to separate the two parts of the liver and the surrounding organs in order to prevent strong adhesion among the above mentioned structures. Closed drainage is placed in the liver hilum. An intraabdominal swab should be taken for microbiological analysis at the end of the operation.

Postoperative management after the first operation:

The patient is usually transferred to the intermediate care unit and discharged to the normal ward according to the postoperative course. Prophylactic antibiotics are given as single shot intraoperatively. If any bacteria are isolated from the intraoperative swab, the antibiotics should be given until the second operation. In patients with stented bile duct, antibiotics and antimycotics are administered during the whole postoperative phase.

One week after the first operation, depending on the logistics, an abdominal CT scan (native phase) is performed for re-evaluation of the liver volume (Figure 3). When the future liver remnant/total liver volume ratio (FLR/TLV) is more than 30%, the second operation, *i.e.*, right trisectionectomy, could be carried out on the next available operation day. If the FLR/TLV is less than 30%, a repeat CT scan would be carried out in an interval of seven days, and the second operation being postponed accordingly.

The second operation (right trisectionectomy):

After relaparotomy, the silicone sheeting or drainage is removed. An intraabdominal swab is taken for microbiological analysis for orientated antibiotic therapy if indicated. The hilar structures are easily identified by the rubber bands, and the right hepatic artery, right hepatic ducts (or the left hepatic duct when extrahepatic bile duct should be resected) and the right and middle hepatic veins are transected (Figure 4). Liver segment 1 could be preserved in patients with non-perihilar CCA without tumour involvement.

After removal of the transected liver, a lymphadenectomy could be conducted at this stage. Biliodi-



Figure 3 Computed tomography scan before associating liver partition and portal vein ligation for staged hepatectomy in a patient with intrahepatic cholangiocarcinoma and on day 10 after liver partition. A: The future liver remnant consisted of segment 2 and 3 with volume of 347 mL (23% of the standardized total liver volume); B: Showing the hypertrophy of the segment 2 and 3 with volume of 610 mL (41% of the standardized total liver volume).

gestive anastomosis is followed when resection of the extrahepatic bile duct is indicated in patients with perihilar CCA. The postoperative treatment after the second operation is the same as for the patients undergoing any major hepatectomy.

ALPPS variations

Improvement of patient safety by different approaches of *in situ* liver splitting: One of the major differences between traditional PVE and ALPPS in liver partition is that the latter, has a liver splitting along the transection line of the FLR. To simplify the first operation, three methods were developed to achieve liver partition without physically splitting the liver: Tourniquet compression, radiofrequency ablation (RFA) or microwave ablation.

The use of a tourniquet to ensure parenchymal compression and intrahepatic collateral occlusion along the future transection line was first described by Robles *et al.*^[11]. He used a 1 cm deep groove to place and tighten a 3 mm Vicryl tourniquet, after which ultrasound confirmed occlusion of the vessels between the two parts. This technique was termed Associating Liver Tourniquet and Portal Ligation for Stage Hepatectomy (ALTPS)^[11]. In 22 patients undergoing ALTPS procedure, FLR at 7 d increased by a median of 61% (range: 33% to 189%).

Jiao *et al.*^[12] used in-line radio frequency (Habib Sealer, LH4X, Rita) to create a virtual liver partition in combination with portal vein ligation. The RFA produce a precise avascular area up to 1 cm wide. In the initial report of five patients, Radiofrequency-Assisted Liver Partition with Portal Vein Ligation could significantly increase the FLR by a median of 62.3% (range: 53.1% to 95.4%) after 21.8 ± 9.4 d.

Similar to RFA, Cillo *et al.*^[13] used microwave ablation on segment 4 in the first stage operation to complete the liver partition. The authors reported that this technique could minimize the risk of neoplastic left lobe invasion and limit portoportal shunts. They observed a 78% FLR growth, performing the second stage after 10 d.

All three techniques could be performed laparoscopically^[13,14]. However, superiority of these procedures

to the classic ALPPS approach regarding safety has not been confirmed apart from case reports.

Improvement of patient safety by partial ALPPS:

To avoid bile leak from incidental transection of the segment 4 bile duct and to avoid segment 4 ischemia due to transection of the segment 4 artery or middle hepatic vein occlusion, non-total parenchymal transection was carried out systematically in the author's institute (Figure 5) and selectively in other institutes^[15-17].

The group of De Santibanes identified total parenchymal transection as an independent predictor of postoperative complications during ALPPS. They found that most complications in patients with total parenchymal transection were surgical complications following the first stage. Avoiding total parenchymal transection might be related to the better outcomes in terms of liver-related complication in these patients^[15]. The Zurich group observed in an experimental model that partial (75%-80%) transection of the liver triggered a similar degree of hypertrophy of the FLR compared to complete transection. On the basis of experimental observation and clinical implications, they switched from a complete to a well-defined partial transection (> 50% of the transection surface) in 2013^[16]. In partial-ALPPS, a median hypertrophy of 60% was observed, compared to 61% after classic ALPPS approach, within a median time of 7 d. To facilitate communication among clinicians, Petrowsky *et al.*^[16] proposed to standardize the name of ALPPS with non-total parenchymal transection at stage 1 operation as "partial-ALPPS".

Improvement of patient safety by selecting different planes of liver splitting:

Various modifications of ALPPS that alter the specific segments comprising the FLR have been described, including right hepatectomy ALPPS (segment 2-4 as FLR), left hepatectomy ALPPS (segment 5-8 as FLR), central hepatectomy ALPPS (segment 4, 5 and 8 as FLR)^[18]. Liver partition in different extent of hepatectomy is aimed to increase the FLR, thereby avoiding post-hepatectomy liver failure.

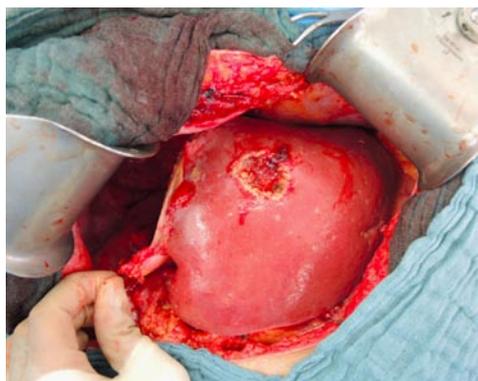


Figure 4 Completion of right trisectionectomy.

Recently, the concept of a monosegmental ALPPS has been addressed^[19,20]. The authors proposed to name such procedures, leaving only a one-segmental FLR in the context of ALPPS, according to the remnant liver segment using third-order segment terms, for example "Segment 2 ALPPS", "Segment 3 ALPPS", "Segment 4 ALPPS" and "Segment 6 ALPPS". Among 333 patients, 12 underwent monosegment ALPPS hepatectomies in six centers, all for extensive bilobar colorectal liver metastases (CRLM). Four patients experienced liver failure, but all recovered. There was no mortality. Complications higher than Dindo-Clavien IIIa occurred in four patients with no long-term sequelae. The authors concluded that extreme liver resections for CRLM based on a single segment liver remnant are feasible and safe using the novel monosegmental ALPPS technique, a new surgical tool in the management of extensive CRLM^[20].

Improvement of patient safety by imaging study and liver function test: The estimation of the postoperative liver function is mainly based on the remaining liver volume and liver function blood tests. Volumetric measurement of the intended FLR by CT or MRT is routinely carried out prior to the second stage operation. A FLR/TLV ratio exceeding 30% in patients with normal liver or higher than 40% in patients with parenchymal disease is preferred^[8]. In the author's institute, a FLR to body weight ratio over 0.6% in patients with normal liver, or more than 0.8% in patients with preexisting parenchymal damage is used as a threshold, additionally to FLR/TLV ratio for performing the second stage operation. Otherwise, the operation is postponed for another week or even cancelled.

Tanaka *et al.*^[21] performed technetium-99 m galactosyl human serum albumin (99mTc-GSA) scintigraphy single-photon emission computed tomography (SPECT)/CT with 3-dimensional volume-rendering fused images preoperatively and at 7 d after the first surgical procedure. They found that the increase in functional FLR calculated at 7 d after the liver partition by ALPPS was similar to functional FLR at 3 wk after the liver partition by PVE alone (52.1% vs 59.2%). In the group of De Santibanes, hepatobiliary scintigraphy was performed in patients with borderline sufficient FLR



Figure 5 Partial associating liver partition and portal vein ligation for staged hepatectomy. The non-total liver parenchymal transection is indicated by the clips, left along the liver split area in a computed tomography scan performed on day 10 after the liver partition.

volume after first stage operation, or when there were doubts regarding functional sufficiency. The regional FLR function was determined by quantifying 99mTc-dimethyl iminodiacetic acid uptake during 10 min (liver uptake phase) after intravenous injection^[15]. They found this method to be helpful to decide the best timing of the second stage operation in four patients of this series. In those four patients with delayed hypertrophy, an increase of the FLR function over time was observed, although there was no significant volume increase. These findings suggested that in some patients, the recommended waiting time until second stage operation may be shorter than indicated by volumetric parameters alone.

Lau *et al.*^[22] described an intraoperative indocyanine green (ICG) clearance assessment to estimate the function of the future liver remnant. After complete parenchymal transection, Bulldog vascular clamps were applied to occlude the right hepatic artery and the portal vein, and ICG clearance was carried out. They found the plasma disappearance rate was 7.9%/min and with a 15 min residual (R15) amount of 30.6% during the first stage operation. During the second stage operation 14 d later, the plasma disappearance rate increased to 12.1%/min and an R15 of 16.3% was observed. They concluded that intraoperative ICG clearance allows for the direct assessment of the actual future liver remnant function. However, since no safe cut-off levels were suggested, future validation studies would be necessary.

Improvement of patient safety by other modifications: In the International ALPPS Registry, 35% of centers did not use any coverage on the raw surface after liver transection, 26% used a plastic sheet, 26% TachoSil, and 16% of centers still used a plastic bag (of a total 192 patients). The use of a plastic bag or plastic sheeting to cover the cut area and prevent adhesions is not an essential component of ALPPS^[10,23]. In the author's institute, Penrose drainages are routinely used to separate the raw surface after liver transection as well as to avoid collections in case of a bile leak (Figure

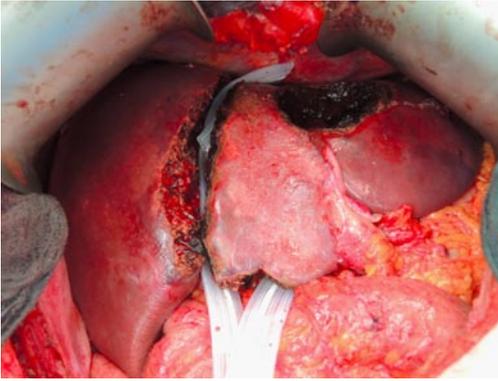


Figure 6 The future liver remnant was separated by two Penrose drains from the right liver lobe in a patient with bilobar colorectal liver metastases during the first stage operation. Three lesions at the left hemi-liver were resected.

6). However, the most important aspect to avoid bile leak and consecutive infection is not to perform *in situ* splitting in patients with dilated bile duct or cholangitis^[24].

Improvement of surgical approach under oncological aspects: The classic approach of ALPPS includes full mobilization of the liver and dissection of the liver hilum^[1]. Aloia *et al*^[25] criticized that ALPPS was supposed to be an “all-touch” technique that would reduce the oncological efficacy to treat liver malignancy. This comment was addressed by two technique refinements: “anterior approach” and “hybrid ALPPS”, to improve the efficacy of surgical oncology as well as to reduce the adhesion at the second stage of the operation^[26,27]. An analysis of the registry data found that in 37% (66/175) of patients that underwent transection during the first stage of ALPPS, an anterior approach was applied. However, caution has to be taken while applying the anterior approach due to the inability to achieve optimal vascular control during this technically complex procedure^[23]. “Hybrid ALPPS” was developed in authors’ institute to treat advanced gall bladder carcinoma in two patients^[27]. *In situ* split of the left lateral liver lobe was combined with postoperative right-PVE as a hybrid procedure. The authors concluded that hybrid ALPPS provided rapid hypertrophy of the FLR for a right trisectionectomy in case of tumor infiltration of the RPV or biliary bifurcation, while allowing to adhere to the non-touch principles. A similar procedure was performed by Robles *et al*^[28] by using a tourniquet-technique and sequential PVE to achieve liver partition in a patient with perihilar tumor burden.

Despite lacking sufficient data for a statistical analysis of disease-free or overall survival, non-touch technique is possible, and should therefore be applied for the resection of hepatic malignancy in ALPPS. Furthermore, hybrid ALPPS combining non-physical liver split and sequential PVE could be employed to reduce the rate of bile leak in patients with dilated bile duct.

Summary: Current results on safety and efficacy

Among the preliminary reports, ALPPS showed a high morbidity (59% to 68%) and mortality (12% to 12.8%)^[1,29]. In the first report of the international ALPPS registry, 90 d mortality was 19/202 (9%). Severe complications including mortalities (Clavien-Dindo \geq IIIb) occurred in 27% of patients^[10]. In experienced centers, including the authors’ institute, a much lower rate of major morbidity (13.6% to 14%) and mortality (0% to 6.6%) have been reported^[15,17]. As is the case with many new techniques, there will be an inherent learning curve, and lower rates of morbidity and mortality will be observed, along with further technical improvements and standardization of the ALPPS procedure.

ALPPS has been found to result in faster FLR growth in comparison with PVE alone^[30]. In a recent systemic review with a total of 295 patients, the FLR hypertrophy was 84%, with a confidence interval (CI) of 78%-91%^[31]. This high efficacy in inducing FLR hypertrophy was confirmed universally by the published case series and the international ALPPS registry. Moreover, in contrast to a failure rate of 20%-30% after PVE due to inadequate hypertrophy or disease progression^[32] (97%CI: 94%-99%) of all patients underwent stage one operation of ALPPS completed the procedure. Furthermore, histological complete resection (R0) was achieved in (91%CI: 87%-94%) of these patients^[31].

BENEFITS OF ALPPS

To decrease the risk of grade C PHLF

Similar to PVE and 2-stage hepatectomy, the aim of ALPPS is to decrease the risk of grade C PHLF after major liver resection in otherwise too small FLR. Beside a more rapid FLR hypertrophy induced by ALPPS, this approach can also be used in cases of failed portal vein occlusion (PVO) or an anticipated extremely small FLR^[33]. For an early prediction whether a patient will obtain a sufficient FLR, the concept of kinetic growth rate (KGR) or degree of hypertrophy has been introduced^[34]. Growth rate was shown to be a predictor of PHLF. Patients with low KGRs are unlikely to benefit from PVO only and could thus be candidates for ALPPS. Another group of patients who might be especially suitable for ALPPS are those with “extremely low” FLRs, who, given the boundaries of growth achieved with PVO, are unlikely to reach a FLR volume deemed necessary for resection.

In the first report of the international ALPPS registry, a median KGR of 2% FLR or 30 mL FLR per day have been observed^[10]. The second stage operations were performed at 10 d (interquartile ranges, 8 to 15) after the liver partition. Only 9% (16/202) of patients experienced liver failure according to the 50-50 criteria^[35]. Within them PHLF was regarded as the main cause of mortality in 8 patients^[10].

To provide more chance of R0 resection

Resection of a large tumor load in the liver may result in an excessive removal of hepatic parenchyma leading to PHLF and associated complications^[36]. ALPPS not only allows for resection in patients with very small anticipated FLR that would not be possible with conventional techniques, but also enables surgeons to proceed with multi-staged resections in a short interval before a substantial tumor progression^[17]. PVO is burdened with a considerable failure rate, and only about two thirds of patients will eventually be eligible for a subsequent curative resection due to tumor progression during the waiting interval between the two stages, or failure of the FLR to grow^[37-39]. A retrospective multicenter study was carried out to compare the rate of complete tumor resection after ALPPS vs conventional two-stage approaches^[5]. Eighty-three percent (40/48) of ALPPS patients achieved complete resection compared with 66% (55/83) in the PVO group. Seventeen percent (8/48) of ALPPS patients failed to achieve the primary endpoint due to mortality ($n = 7$) or incomplete resection (R1, $n = 1$). The author concluded that ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumours^[5].

Evidences of oncological benefits compared to other two-stage liver resection when R0 achieved

Colorectal liver metastasis: Colorectal liver metastasis (CRLM) is the most common indication for ALPPS as indicated in the first report of the international ALPPS registry^[10]. To compare the benefits of ALPPS to conventional 2-stage hepatectomy by PVO, evaluation of resection rate, postoperative mortality, as well as disease-free survival (DFS) or/and overall survival (OS) are necessary.

Resection rate, the resection rate for CRLM by traditional two-stage liver resection, either PVE or PVL, was reported to be 52%-80%^[40-42]. Non-resectability was mainly due to progression of metastasis^[40,41]. ALPPS avoided this type of drop-out by effectively inducing a sufficient liver hypertrophy within 6 to 15 d^[33]. A retrospective study carried out by Tanaka *et al*^[21] found that at first hepatectomy, Ki67 expression was evident in 28.2% \pm 42.7% of tumor cells in the ALPPS group and 51.7% \pm 35.6% in the conventional 2-stage group ($P = 0.09$). However, at second hepatectomy, expression of Ki67 was detected in 20.5% \pm 24.7% and 54.5% \pm 26.9% of patients in the ALPPS and in the conventional 2-stage group respectively ($P = 0.01$)^[21]. Therefore, the reduced expression of Ki67 in tumors resected during the second stage in the ALPPS group may indicate an oncologic benefit from ALPPS, as the short period between the two interventions helps to avoid the risk of tumor progression. Of note, in a recent review on the treatment of CRLM, the resection rate by ALPPS was reported to be about 97.1%^[33].

Postoperative mortality, PVO is a well-established, state of art procedure for patients with insufficient FLR

whereas ALPPS is still among the phase of exploration. Therefore, a comparison of these two procedures should be done when the learning curve of ALPPS is overcome. According to the first report of the international registry data, mortality of ALPPS for CRLM is 8%, and 5.1% in CRLM- patients younger than 60 years of age^[10]. In experienced centers, including the authors' institute, nil mortality after ALPPS for CRLM has been reported^[17].

DFS/OS, the 1 and 2-year DFS for patients undergoing ALPPS for CRLM from the ALPPS registry is 59% and 41% respectively^[10]. Overall survival is 86% at six months postoperatively, dropping to 59% at 2 years^[10]. Similar to the high recurrence rate despite a survival advantage observed in patients with advanced CRLM (> 4 metastases) undergoing traditional resection^[43-45], high recurrence rates have also been reported in patients undergoing ALPPS^[5,33,46]. In some case series, the recurrence of CRLM after ALPPS was quite early. For example, in the 7 patients reported by Oldhafer *et al*^[41] recurrence was observed after 3, 6, 7, 8, 11, 13 and 13 months respectively following ALPPS procedure^[46]. However, to date there is no direct comparison of DFS in patients undergoing PVE or ALPPS. Of note, two RCTs investigating ALPPS vs conventional two-stage hepatectomies for CRLM were recently launched (clinicaltrials.gov-identifier NCT01775267 and NCT01842971).

To get the best benefit of ALPPS, Hernandez-Alejandro *et al*^[17] proposed selecting the group of patients with biologically favorable CRLM. The inclusion criteria for ALPPS in their group were (1) no evidence of extrahepatic disease; (2) good functional capacity Eastern Cooperative Oncology Group performance status grade 0 or 1 and (3) complete or partial response to systemic chemotherapy after 6 cycles. In the 14 patients reported in this series, recurrence developed in 2 patients after a median follow-up of 9.4 mo. Overall survival at the time of follow-up was 100%^[17].

Hepatocellular carcinoma: An aggressive surgical approach in patients with locally advanced hepatocellular carcinoma (HCC) has been reported to yield an acceptable long term outcome that is significantly better than that of patients with unresectable HCC treated with Sorafenib^[47-49]. In this view, the ALPPS procedure could yield a better outcome and further expand the number of patients undergoing radical major liver resection for HCC in liver cirrhosis that were previously considered non-resectable, compared to non-surgical treatment^[49].

Chan *et al*^[50] reported the largest case series with 17 patients having HCC on the basis of chronic hepatitis B infection. Selection criteria included Child-Pugh A liver cirrhosis, indocyanine green retention rate < 20% at 15 min, FLR/sTLV (standardized total liver volume) < 40%, and platelet count $\geq 100 \times 10^9/L$. After a median of 6 d, a hypertrophy of the left FLR by 48.7% with a FLR/sTLV ratio of 38.5% (preoperative FLR/sTLV 24.2%) was noted. All patients proceeded to second-stage hepatectomy. Major surgical complications

Table 1 Recent published studies on associating liver partition and portal vein ligation for staged hepatectomy (only case series with more than 10 patients are listed)

Ref.	Date (yr)	Total cases (center involved)	Interval ¹ (d)	FLR hypertrophy (median)	Completion stage 2	R0 resection	PHLF	Morbidity ²	In-hospital mortality	Follow-up (median, months)	Recurrence	Overall survival
Schnitzbauer <i>et al</i> ^[11]	2012	25 (5)	9	74%	88%	96%	-	Overall: 64% ≥ III: 40%	12%	6	20%	86% at 6 m
Torres <i>et al</i> ^[29]	2013	39 (9)	14	83%	94.80%	100%	-	Overall: 59%	12.80%	-	-	-
Schadde <i>et al</i> ^[10]	2014	202 (56)	7	80%	98%	91%	-	≥ III: 40%	9%	9	40% at 12 m	73% at 12 m
Truant <i>et al</i> ^[4]	2015	62 (9)	8	48.60%	95.20%	-	25.8%	≥ III: 40.3%	12.90%	-	-	-
Robles <i>et al</i> ^[11]	2014	22 (1)	7	61%	100%	100%	22.7%	Overall: 64%	9%	6	5%	91% at 6 m
Nadalin <i>et al</i> ^[53]	2014	15 (1)	10	87.20%	100%	87%	-	Overall: 67%	28.70%	17	29%	67% at 17 m
Alvarez <i>et al</i> ^[15]	2015	30 (1)	6	89.70%	93%	93%	14%	Overall: 53% ≥ III: 43%	6.60%	17	22% at 12 m	67% at 12 m
Petrowsky <i>et al</i> ^[16]	2015	24 (1)	7	61%	100%	-	-	≥ IIIb: 33%	16.70%	-	-	-
Hernandez-Alejandro <i>et al</i> ^[17]	2015	14 (1)	7	93%	100%	86%	29%	Overall: 36% ≥ IIIb: 14%	0%	9	14%	100% at 9 m
Tanaka <i>et al</i> ^[21]	2015	11 (1)	7	54%	100%	100%	18%	Overall: 46% ≥ III: 27%	9%	-	-	-
Chan <i>et al</i> ^[50]	2015	17 (1)	6	48.70%	100%	-	-	≥ III: 11.8%	5.90%	-	-	-

¹Interval: Median days from the stage 1 to CT scan; ²Morbidity: Clavien-Dindo classification was applied; FLR: Future liver remnant; PHLF: Post-hepatectomy liver failure according to 50-50 criteria (35).

(Clavien–Dindo grade III or above) occurred in 11.8% of patients ($n = 2$), and in-hospital mortality rate was 5.9% ($n = 1$). No follow-up data were reported. Chan *et al*^[50] concluded that ALPPS could also promote liver hypertrophy in patients with chronic liver diseases, with a similar safety profile compared to other established series. Another case series by Vennarecci *et al*^[51] suggested that the ALPPS procedure could be very useful in a subgroup of patients with HCC and venous thrombosis. In their series, portal hypertension or liver cirrhosis more than Child-Pugh A was considered as a contraindication^[49,52]. However, data regarding the long term outcome of ALPPS in patients with HCC are still very limited, and further reports on the use of the ALPPS in this setting are expected^[49].

Perihilar cholangiocarcinoma: Although the first case of ALPPS was successfully performed in a patient with hilar CCA, high rates of major postoperative complication and mortality were found in this population after ALPPS^[10]. Li *et al*^[24] first questioned the benefit of ALPPS in treatment of perihilar CCA. The authors found that patients undergoing ALPPS for perihilar CCA were at a high risk of intraabdominal infection and bacteraemia as the diseased liver and stented biliary system were not removed between the two operations. Two of three patients with hilar CCA received ERCP and a stent before referral. Both of them had postoperative intraabdominal bacterial infections, and eradication of bacteria failed. The deaths of those two patients account for the 22% mortality observed in the cohort of 9 ALPPS patients from this series. Thus, the authors considered the combination of a stented biliary system and cholestatic liver with low potential of regeneration as a contraindication for ALPPS. This opinion has been

shared with the HPB community, in which caution has aroused against the use of ALPPS for hilar tumors^[8,53].

Other indications: The other indications of ALPPS comprised of intrahepatic cholangiocarcinoma, gallbladder cancer, neuroendocrine tumors and other liver metastases. Because of the limited number of cases, no high quality evidence on the oncological benefit other than increased resectability is available^[5,8,10].

Summary - current status of oncological benefit by patient selection

The ALPPS procedure was developed to decrease the morbidity and mortality related to PHLF, to avoid drop-out in patients undergoing conventional two-stage liver resection and to achieve histopathological complete tumor resections (R0) in otherwise non-resectable patients. Although contemporary reports have highlighted the importance of patient selection in avoiding perioperative morbidity and mortality, suitable indications for the ALPPS approach remain to be determined^[17]. Till date, there is no clear evidence for the oncological benefit of ALPPS in treatment of CRLM over other procedures as long as R0 resection is achieved. For patients with hilar CCA, ALPPS should be considered with extreme caution due to the aforementioned safety issue. For other indications, there are no ongoing studies comparing ALPPS with non-surgical treatment in term of overall survival.

CONCLUSION

ALPPS is a pertinent alternative approach to the conventional two-stage liver resection after PVE or PVL. In selected cases, it could even increase the resectability of

previously unresectable liver malignancy by promising rapid hypertrophy of the FLR (Table 1). With the evolution of surgical technique, proper patient selection for ALPPS has been found to be the key element to achieve the best oncological results.

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Laparoscopic treatment of complicated colonic diverticular disease: A review

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Abstract

Up to 10% of acute colonic diverticulitis may necessitate

a surgical intervention. Although associated with high morbidity and mortality rates, Hartmann's procedure (HP) has been considered for many years to be the gold standard for the treatment of generalized peritonitis. To reduce the burden of surgery in these situations and as driven by the accumulated experience in colorectal and minimally-invasive surgery, laparoscopy has been increasingly adopted in the management of abdominal emergencies. Multiple case series and retrospective comparative studies confirmed that with experienced hands, the laparoscopic approach provided better outcomes than the open surgery. This technique applies to all interventions related to complicated diverticular disease, such as HP, sigmoid resection with primary anastomosis (RPA) and reversal of HP. The laparoscopic approach also provided new therapeutic possibilities with the emergence of the laparoscopic lavage drainage (LLD), particularly interesting in the context of purulent peritonitis of diverticular origin. At this stage, however, most of our knowledge in these fields relies on studies of low-level evidence. More than ever, well-built large randomized controlled trials are necessary to answer present interrogations such as the exact place of LLD or the most appropriate sigmoid resection procedure (laparoscopic HP or RPA), as well as to confirm the advantages of laparoscopy in chronic complications of diverticulitis or HP reversal.

Key words: Diverticulitis; Laparoscopy; Emergent; Lavage; Drainage; Peritonitis; Purulent; Stercoral; Complicated; Perforation

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Core tip: With the aim to improve surgery outcomes, laparoscopy has been increasingly performed in complicated diverticulitis. Despite the absence of solid proofs and under the condition of large expertise, it is an appropriate approach for the surgical management of both elective and emergent situations related to complicated diverticulitis. Moreover, the laparoscopic

lavage drainage represents a previously unknown modality of treatment of purulent peritonitis. Validation of these data by large-scale randomized controlled trials is mandatory to build future therapeutic algorithms on which general surgeons can rely in their daily practice.

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INTRODUCTION

Colonic diverticulosis is mainly an acquired disease with an age-dependent prevalence, ranging from 5% at 30 years to 60% at 80 years^[1]. Acute diverticulitis occurs in 4%-25% of cases^[2,3] of which 8%-35% present with perforated disease^[4]. Generalized peritonitis from colonic diverticulitis (graded as Hinchey 3 and 4^[5]) is a life-threatening situation requiring immediate surgical intervention^[2,6,7]. Designated by Hartmann's procedure (HP), resection of the affected diverticular colon segment, closure of the rectal stump and formation of an end colostomy has been considered the treatment of choice for many years^[8-13]. However, morbidity and mortality rates of 24% and 19% as well as high risk of permanent stoma^[14-18] have pushed general surgeons to look for surgical alternatives with better outcomes.

In colorectal surgery, large-scale prospective studies have confirmed the superiority of laparoscopy over the open approach in terms of lowered postoperative morbidities, reduced postoperative pain, improved respiratory function and shortened hospital stay^[19-22]. Based on that, laparoscopy has been considered as the preferred approach for the elective treatment of diverticular disease^[1,23,24]. In 2006, however, the European Association of Endoscopic Surgeons^[25] and the American Society of Colon and Rectal Surgeons^[23] expressed their opposition to the routine usage of laparoscopy in the acute setting. Due to insufficient data confirming validity of the presumed advantages in emergent surgery, the laparoscopic approach was estimated not to be appropriate for the management of complicated perforated diverticulitis.

Since then, worldwide increasing experience in colorectal and minimally invasive surgery has broadened applicability of laparoscopy to abdominal emergencies, hypothesizing that the advantages observed in the elective setting can be translatable to acute situations^[26]. Several recent studies claim the benefits of laparoscopy over the open approach when performed by experienced surgeons in selected patients with perforated diverticulitis^[25,27-31].

Virtually all procedures for complicated diverticular disease have been achieved under laparoscopy. Since its first description almost twenty years ago^[32], the

laparoscopic reversal of HP has been progressively performed promising reduced morbidity and mortality^[33,34]. Similarly, sigmoid resection and primary anastomosis (RPA) with or without derivating loop ileostomy (DI) has been repeatedly performed in diverticular peritonitis^[35]. Furthermore, during the last ten years, we have been observing the emergence of the laparoscopic lavage drainage (LLD), a previously unknown technique for the management of purulent peritonitis^[36,37].

In parallel, laparoscopy is being increasingly performed for elective surgeries related to complicated diverticulitis. The most common examples are the reversal of HP and the sigmoidectomy for chronic complications (such as fistula, inflammatory stenosis and phlegmon).

Nonetheless, despite worldwide application, laparoscopic surgery for complicated diverticulitis mostly relies on empirical experience. A precise consensus based on level 1 evidenced data has not yet been established to determine the exact status of laparoscopic techniques in this field.

This review aims to provide a critical appraisal of currently available data concerning the laparoscopic approach in both emergent and elective settings of complicated diverticulitis. We will focus on ongoing randomized controlled studies (RCTs) that are expected to provide clear practical recommendations for emerging techniques. Perspectives for future research will also be suggested to assist tomorrow's surgeons in their decision making when addressing these situations.

LITERATURE RESEARCH

A bibliographic search was performed in PubMed and Cochrane library for case series and comparative studies published from January 1995 to July 2015. RCTs were recorded from the official web site www.clinicaltrials.gov. The following medical subject heading (MeSH) terms were searched for titles and abstracts in the English or French languages: Diverticulitis; acute; emergent; laparoscopy; lavage; drainage; peritonitis; purulent; stercoral; fecal; complicated; perforation; Hinchey; Hartmann. The "related articles" function was used to enlarge the search. A manual search of the reference lists was also performed to identify additional relevant studies. The first two authors separately classified the selected articles into elective, emergent and future situations. Subsequently, relevant articles were discussed and discrepancies of findings were resolved with agreement of both authors. Overlapping publications were identified and only the most recent paper was selected for the review.

DISCUSSION

Emergent surgery

Laparoscopic surgery for failed medical treatment: Diverticulitis complicated by pericolic and/or

pelvis abscess (Hinchey 1 and 2) are most often managed conservatively with intravenous antibiotics more or less combined to percutaneous drainage^[1,38,39]. In case of failure, an emergent surgery may be indicated for sepsis control and resection of the diseased colon. Available data are, however, limited to a single-institutional retrospective series^[40] which has been recently updated^[41]. When comparing outcomes of the laparoscopic approach (24 patients) to those of laparotomy (18 patients), laparoscopy was associated with a 4-fold decrease in overall complication rate, faster bowel movement, shorter hospital stay and comparable rate of RPA despite a longer operative time. In the laparoscopy group, RPA could be achieved in all but one patient and conversion to open surgery occurred in 2 patients. In regard to these encouraging results and motivated by the scarcity of data on this specific aspect of colonic diverticular surgery, RCTs are needed to confirm the suggested benefits of laparoscopy in this group of patients.

LLD: First described in 1996^[42,43], the procedure consists of a laparoscopic exploration of the abdominal cavity followed by lavage with heated saline serum and drainage of the diseased colon for the next several days. The need for extensive adhesiolysis in search of the colonic perforation remains controversial^[44]. In a prospective multi-institutional study^[45], 92 patients underwent laparoscopic peritoneal lavage for Hinchey 2 or 3 diverticulitis. All patients but two had complete clinical resolution. One patient required subsequent colonic resection whereas the other required percutaneous drainage for pelvic abscess. Mortality and morbidity rates were 3% and 4%, respectively. After a median follow-up period of 36 mo, only two patients were readmitted with acute diverticulitis successfully treated with antibiotics. The authors concluded that LLD can be a reasonable alternative to HP for Hinchey 3 perforated diverticulitis. Another prospective study^[46] found that LLD offers the advantages of shorter operative time and hospital stay, reduced estimated blood loss and better postoperative outcomes compared with laparoscopic HP. Including all stages of complicated diverticulitis (mainly Hinchey 3), only 2.1% of patients undergoing LLD were converted to open HP, and 6.4% were reoperated for uncontrolled sepsis. Almost half of the patients who received LLD underwent subsequent sigmoid resection, but the reasons were not mentioned. Such favorable results (low morbidity and mortality rates, high chance of sepsis control, avoidance of stoma and bowel salvage) have been constantly reported in case series and systematic reviews^[37,44,47-53]. Soon after and despite robust evidence, LLD was cited in national and international scientific committees' reports as a potential therapeutic option for purulent peritonitis of diverticular origin^[1,54,55].

Preliminary results of the DILALA prospective randomized trial have been recently published after complete accrual^[56]. Although the primary endpoint

(the number of reinterventions) could not be assessed because of incomplete follow-up, this trial showed a higher than usual mortality rate of 7.7% after LLD. This result was comparable to that found in the open HP group. Both procedures provided comparable complication profiles, but LLD resulted in shorter operative time, shorter time in the recovery unit and shorter hospital stay. Recently, the enthusiasm toward LLD has been hindered by the results of the LOLA group within the Ladies trial confronting LLD to sigmoidectomy in Hinchey 3 diverticulitis^[57]. This multicenter RCT has been prematurely terminated because of significantly increased in-hospital major morbidity or mortality in the lavage group compared with sigmoidectomy. Surgical reinterventions accounted for most of these adverse events. However, mortality rate was unaltered (9% in the LLD group vs 14% in the sigmoidectomy group), and sepsis was successfully controlled in 76% of cases (vs 90% in the sigmoidectomy group). In the long-term, there was no difference in the incidence of major morbidity or death between the two groups (37% vs 40% in the LLD and sigmoidectomy groups, respectively). LLD allowed salvage of the sigmoid in almost half of the cases and avoided stoma formation in three-quarters of the patients. In contrast to the resection procedure, LLD allows bowel salvage and avoids stoma but requires a multi-step careful surveillance and timely management. The authors conclude that peritoneal lavage cannot be favored over sigmoid resection as a routine intervention for purulent peritonitis of diverticular origin. Instead, it may be an alternative approach to sigmoidectomy with similar length of stay and long-term outcome in select patients. From this standpoint, in the Dutch Collaborative study group^[58] as well as in another study^[59], age older than 80 years, American Society of Anesthesiologists grade 3 or above, multiple comorbidities, immunosuppression, high C reactive protein and/or high Mannheim peritonitis index were associated with increased risk of failure after LLD. Currently, there are two ongoing RCTs comparing LLD to sigmoidectomy^[60,61]. The results are eagerly awaited to provide further evidence about expected outcomes after LLD and to identify criteria for patients who would preferably benefit from each technique.

In contrast to the enthusiasm for LLD in purulent peritonitis, this approach is not commonly admitted for Hinchey 4 diverticulitis. The presence of a visible perforation in the colon has always represented the limit of application of the technique^[42,62]. In his prospective study, Myers *et al.*^[45] stated that stercoral peritonitis constitutes an indication for conversion to open HP. Conversely, Liang *et al.*^[46] reported very encouraging results despite the inclusion of more than 10% of Hinchey 4 peritonitis in his prospective study. Many authors agree that LLD cannot be accepted unless perforation of the colon is formally ruled out^[45,53]. Conversely, others propose suturing the colonic hole if stercoral peritonitis is not evident^[59]. The diagnosis of stercoral peritonitis on explorative laparoscopy

excluded patients from both of the available randomized controlled trials^[56,57]. This condition is presumed to significantly modify the results observed with purulent peritonitis. In fact, the high reintervention rate found in the Ladies trial is mostly attributed to the misdiagnosis of stercoral peritonitis. To optimize outcomes after peritoneal lavage, the authors pushed toward a meticulous search for colon perforation. In all cases, the adoption of LLD in emergency settings, abdominal exploration for generalized peritonitis, pelvic dissection in inflammatory conditions and possible suture of a diseased colon require that the surgeon have a minimum of colorectal and minimally invasive skills before he can propose this conservative approach^[51,58].

Sigmoidectomy: Primary anastomosis and

HP: Supported by considerable improvement in the perioperative care, RPA (without or without DI) has been proposed as an alternative to HP in emergent situations. A comparison of these two techniques has mostly enrolled patients undergoing open procedures before the widespread application of laparoscopy in emergent colorectal surgery. In fact, several comparative studies, systematic reviews and meta-analyses favored RPA over HP in respect to reduced mortality and morbidity rates, shorter cumulative operative time and hospital stay, more frequent stoma reversal and reduced cost^[63-76]. Even without DI, RPA was shown to be preferable than HP for purulent peritonitis^[70,72,77]. These studies, however, suffer from marked heterogeneity and selection bias with low-risk patients mainly undergoing RPA, whereas HP is offered to high-risk elderly patients^[63,74]. A recent RCT showed that for Hinchey 3 and 4 diverticular disease, the main differences between RPA with DI and HP occur during the stage of stoma reversal^[78]. When both stages (colonic resection and stoma reversal) were combined, the rates of overall complications, severe complications and mortality (13% in HP vs 9% in PA) were similar in both groups. In contrast, when the reversal procedure was considered alone, HP was associated with lower stoma reversal rate (58% vs 90%), more frequent severe complications (20% vs 0%), and longer operative time and hospital stay. The main flaw of this RCT would be the lack of information about the adopted approach (laparoscopic or open) for the reversal of the stoma. This issue is of paramount importance because laparoscopy has been proved to decrease the morbidity of HP reversal in several case series and systematic reviews^[79-86]. The elevated rate of severe complications during stoma closure in the HP group may have been overemphasized by the open approach *per se*.

This evidence raises the question whether the laparoscopic HP may offer advantages over the open approach in terms of reduced morbidity and mortality in the acute setting of perforated diverticulitis. To improve the outcome after open HP, we have been among the first to show the feasibility of a laparoscopic two-staged strategy for complicated diverticular disease.

Despite conversion in 19% of cases, this approach offered adequate control of sepsis with low rates of mortality (3%) and morbidity (23%)^[33]. Similarly, in a small case series, Agaba *et al.*^[34] described favorable outcomes after laparoscopic HP for Hinchey 3 and 4 diverticulitis. Recently, a propensity-matched analysis of the ACS NSQIP database failed to show a decrease in postoperative morbidity and mortality when HP was performed under laparoscopy compared with the open approach. This study, however, suffers from substantial imperfections in methodology such as retrospective data acquisition and lack of analysis of pertinent variables that might substantially interfere with the results^[26].

To clarify the role of laparoscopy in emergent sigmoidectomy, Mbadiwe *et al.*^[87] retrospectively analyzed the ACS NSQIP database. In a total of 11981 patients, a bivariate analysis showed that patients undergoing laparoscopy experienced lower rates of complications with both RPA (14% vs 26%, $P < 0.001$) and HP (30% vs 37%, $P = 0.02$). The laparoscopic approach was associated with decreased mortality rate for patients undergoing RPA (0.24% vs 0.79%, $P < 0.001$). The reduced complication rate after laparoscopic RPA was confirmed in the multivariate analysis^[87].

To provide a high level of evidence in the present era of widespread use of laparoscopy for colorectal disease, a well-built RCT is highly desirable comparing laparoscopic RPA (with or without DI) with a two-step laparoscopic HP (sigmoid resection and stoma closure) in perforated complicated diverticulitis. Not only outcomes of both procedures will be clarified but also identification of precise criteria would define the subgroups of patients who will benefit more from each technique. Based on this perspective, the results of the ongoing DIVA section of the Ladies trial are keenly awaited to provide us with level 1 evidence about the preferable laparoscopic attitude in Hinchey 4 complicated diverticulitis^[57].

Elective surgery

Based on solid proofs from a large-scale meta-analysis^[88] and RCTs^[89,90], international committees have adopted laparoscopy as the preferred approach for elective sigmoidectomy after acute diverticulitis^[1,23,24]. Compared with an open procedure, the laparoscopic modality offers a significant decrease in major complications and morbidity, less blood loss, fewer analgesic requirements, shorter hospital stay and improved quality of life.

Conversely, in early experience, laparoscopy was contraindicated for the treatment of diverticular chronic complications (stricture, fistula and persistent phlegmon) because severe inflammation and distorted anatomy exposes the patient to high risks of bleeding and adjacent organ trauma (bladder, left ureter, female genital organs)^[11,91]. With increasing experience, the laparoscopic approach has been progressively accepted as an alternative to open surgery but its routine usage in chronic complications remains controversial^[92].

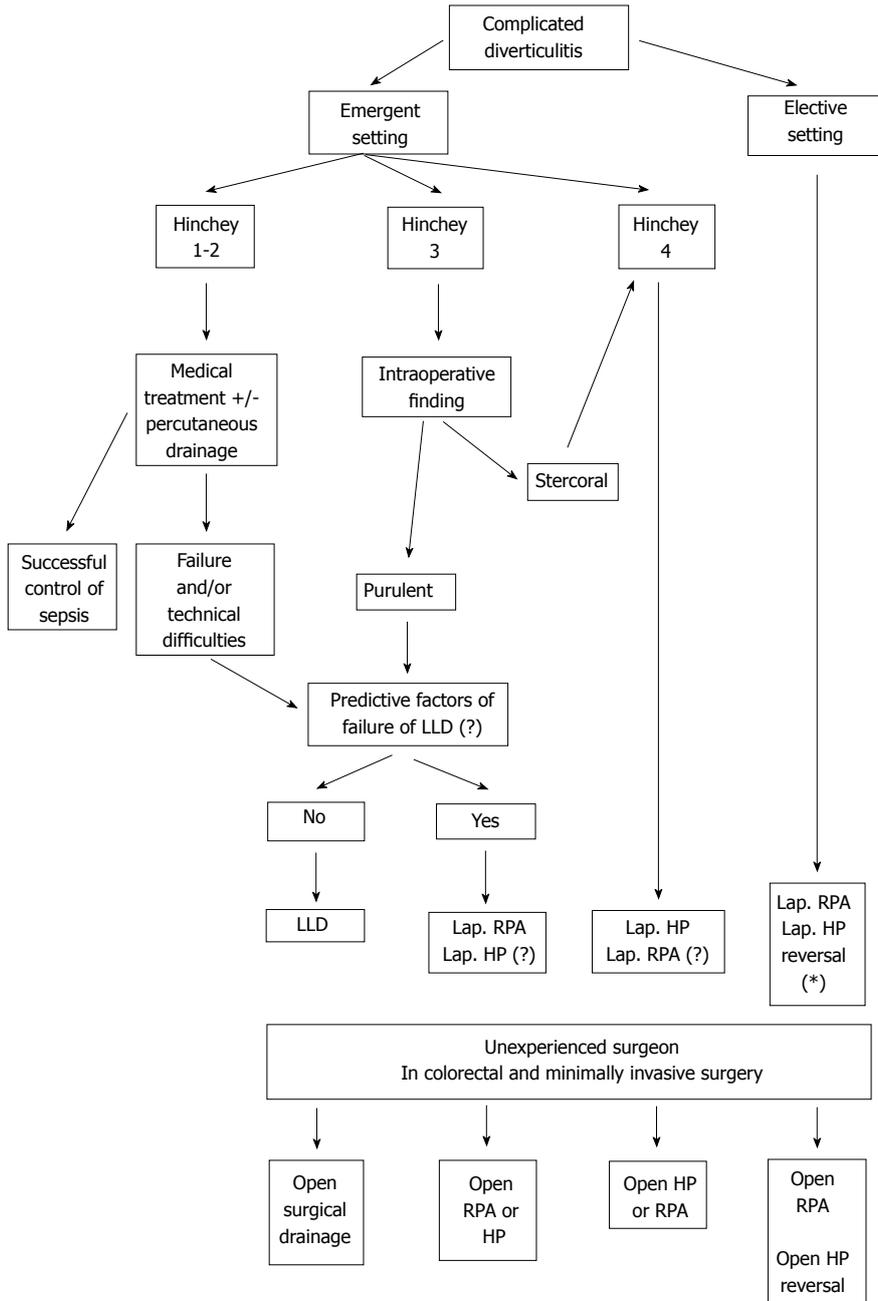


Figure 1 Algorithm for the laparoscopic management of complicated colonic diverticulitis. Lap: Laparoscopic; LLD: Laparoscopic lavage drainage; RPA: Resection with primary anastomosis; HP: Hartmann's procedure; (?): Data that need to be elucidated in RCTs, (*): Data that need confirmation in RCTs.

Because presently available data mostly rely on small retrospective series and case reports, several controversies cannot be fully elucidated. In a descriptive case series, Le Moine *et al*^[93] suggested that chronic complicated diverticulitis increases the risk of conversion to laparotomy in elective laparoscopic sigmoidectomy. This effect has been recently disproved by two comparative studies^[94,95] which stated that surgeons' expertise in minimally invasive and colorectal surgery is the principal determinant of morbidity and conversion rates in complicated cases. This evidence outlines that accumulating experience during the last ten years has inevitably challenged previously accepted knowledge.

Colonic fistula is the most reported late compli-

cations of diverticular disease, although available data is scarce and confined to retrospective case series. In recent systematic reviews^[96,97], the laparoscopic approach was judged to be feasible and safe for the treatment of colovesical fistulae. However, due to a lack in methodology and/or a limited number of patients, the studies failed to show superiority of laparoscopy over the open approach. Furthermore, the conversion rate could not be determined and the predictive factors of its occurrence were not discussed^[96]. This issue has been addressed in a previous case series including 31 patients conducted over 10 years. The overall conversion rate was approximately 30% but declined to 10% during the second half of the study period^[98].

This finding is consistent with the statement of Abbas *et al*^[99] that similar rates of conversion, morbidity and mortality can be expected with laparoscopy regardless of the presence of colonic fistula. Therefore, the current surgical management of colonic fistula relies on poor data derived from empirical experiences in open surgery. The most salient example is the adoption of a single-stage procedure as the preferred surgical option despite the absence of solid proofs confirming its superiority^[98].

During this study, we noticed a striking lack of high quality papers dedicated to the issues of inflammatory phlegmon and stricture. Information on the most appropriate treatment in these situations is thus absent. If low incidence of such cases is the cause of this shortage, prospective enrollment of patients in large multi-institutional databases might be the solution to build precise therapeutic algorithms on which tomorrow's general surgeons can use for the treatment of their patients.

Finally, with the emergence of LLD as a conservative modality for complicated perforated diverticulitis, controversies have arisen about the need for systematic elective sigmoidectomy after the diseased organ has been saved. In a recent systematic review^[44], rehospitalization was observed in 7% of patients who underwent LLD. More than half of them presented with a new episode of diverticulitis, 21% with generalized peritonitis, 10% with colovesical fistula and 7% with undetected colon cancer. At this stage of experience, the present data lack sufficient proof to know whether LLD can be regarded as a definitive treatment or a bridge to elective laparoscopic sigmoidectomy^[100]. If LLD becomes widely admitted, well-built RCTs will be necessary to answer these questions and to determine the best candidates for bowel sparing.

CONCLUSION

In conclusion, accumulated empirical experience during the last two decades shows that laparoscopy is undeniably a promising adjunct in the management of complicated colonic diverticulitis. Analysis of presently available data also highlights the urge to build large-scale prospective RCTs in order to elucidate the exact benefits of laparoscopy and to define patients who are the best candidates for each approach. Like the ongoing trials NCT01019239 and NCT01047462, solid data are particularly awaited in order to clarify the exact place of LLD and to determine the most appropriate sigmoid resection procedure (laparoscopic HP or RPA) in Hinchey 3 and 4 peritonitis. The advantages provided by laparoscopy in chronic complications of diverticulitis and HP reversal also need to be confirmed. In the absence of precise recommendations, we suggest the following algorithm that may assist general surgeons in their decision-making when dealing with complicated colonic diverticulitis (Figure 1).

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Overview of robotic colorectal surgery: Current and future practical developments

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Abstract

Minimal access surgery has revolutionised colorectal surgery by offering reduced morbidity and mortality over open surgery, while maintaining oncological and

functional outcomes with the disadvantage of additional practical challenges. Robotic surgery aids the surgeon in overcoming these challenges. Uptake of robotic assistance has been relatively slow, mainly because of the high initial and ongoing costs of equipment but also because of limited evidence of improved patient outcomes. Advances in robotic colorectal surgery will aim to widen the scope of minimal access surgery to allow larger and more complex surgery through smaller access and natural orifices and also to make the technology more economical, allowing wider dispersal and uptake of robotic technology. Advances in robotic endoscopy will yield self-advancing endoscopes and a widening role for capsule endoscopy including the development of motile and steerable capsules able to deliver localised drug therapy and insufflation as well as being recharged from an extracorporeal power source to allow great longevity. Ultimately robotic technology may advance to the point where many conventional surgical interventions are no longer required. With respect to nanotechnology, surgery may eventually become obsolete.

Key words: Colorectal surgery; Robotic surgery; Endoscopy; Robotics; Nanotechnology; Microtechnology; Rectal neoplasms; Colonic neoplasms

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Core tip: Robotic assistance has the potential to revolutionise the way colorectal surgery is delivered. This overview summarises the current status of robotic colorectal surgery and considers the direction of developments in robotic and endoscopic surgery and future developments in micro- and nanotechnology.

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BACKGROUND

The objective of robotic surgery is allowing us to operate in challenging environments or to achieve levels of performance we would otherwise not be capable of. Surgeons interact with their environment by using their senses to gather information (perception), combining these inputs with their pre-existing knowledge and experience (processing) to change the environment (action). A robot may augment any or all of these aspects in order to improve the final outcome.

Over the last two decades colorectal surgery has dramatically changed due to the widespread implementation of laparoscopic surgery. Laparoscopic surgery offers comparable oncological outcomes^[1], but with improved post-operative recovery^[2]. The move towards minimal access surgery has, however, put challenges upon the surgeon's perceptive and action abilities with a resultant increased reliance on processing abilities required to make up for these deficits. Robotic assistance in minimal access surgery aims to make up for some of the practical shortcomings of laparoscopic surgery, providing assistance to the surgeon with improvements to perception, processing and action.

This aim of this review is to summarise the current benefits and shortcomings of robotics in colorectal surgery and endoscopy and to identify how the implementation of developing robotic technology may shape the future of colorectal surgery.

ESTABLISHED ROBOTIC COLORECTAL SURGERY

At present the Da Vinci Robot (DVR) (Intuitive Surgical) is the most widely used platform for robot assisted laparoscopic colorectal surgery. It consists of a high definition three-dimensional camera system allied to a patient "sidcart" that allows instruments to be delivered and controlled. The surgeon sits at a separate control module (Figure 1) that delivers three-dimensional images and allows remote control of the sidcart-mounted effectors.

The DVR addresses some of the limitations of conventional laparoscopic surgery by allowing dexterity in 7 planes of movement within a limited space, static ports, filtering of physiological tremor and variable motion scaling. The potential drawbacks of the system include lack of tactile feedback, prolonged operative time and financial cost, including initial outlay, consumables and servicing of equipment.

The attributes of the DVR make it suitable for assisting in precision surgery within confined spaces such as the pelvis and use of the DVR for radical prostatectomy is now widespread in the United Kingdom



Figure 1 Surgeon interaction with the Da Vinci robot control module.

for this reason. Robotic prostatectomy is now seen as the primary treatment for localised prostate cancer, delivering equivalent oncological outcomes with decreased morbidity^[3,4], but equivocal improvement in sexual function^[5].

The practical challenges of pelvic surgery for prostate cancer are similar to those encountered in rectal surgery, particularly when performing total mesorectal excision (TME). It has been demonstrated that laparoscopic TME offers equivalent oncological outcome with faster recovery and less morbidity than open surgery^[2,6]. However, it is technically demanding with higher conversion rates seen in the obese and during low rectal surgery^[7].

Comparative studies have suggested an improved TME grade following robotic TME^[8,9] and it is hypothesised that the improved precision of surgery enables the TME plane to be more accurately preserved, offering greater preservation of the pelvic autonomic nerves resulting in improved urinary and sexual function with some evidence of short-term benefit^[10]. Rates of conversion are often used as a surrogate marker of operative difficulty and a systematic review of case-controlled studies identified that conversion rates may be lower in robotic assisted cases, although this was not statistically significant^[11].

The Robotic vs Laparoscopic Resection for Rectal cancer trial is the first international, multi-centre randomised controlled trial to compare laparoscopic with robotic TME. The results of 471 participants have been presented at the European Society of Coloproctology, September 2015 and demonstrated no statistically significant difference in oncological clearance, patient outcome or conversion to open surgery between the two groups. These findings may impact the usage of the DVR in TME as it seems that the increased financial cost of robotic usage is not offset by improved surgical outcomes.

There are several centers performing robotic ventral mesh rectopexy. It has been argued that the increased dexterity of the instruments of the DVR facilitates dissection and more precise suturing of the mesh^[12]. There are few studies that compare outcomes between laparoscopic and robotic ventral mesh rectopexy, however functional improvements with respect to obstructive defaecation symptoms have been noted in patients having robotic surgery^[13].

The COST and COLOR trials demonstrated that laparoscopic surgery offers oncological and survival outcomes commensurate with open surgery in colonic tumors^[14,15]. Decreased morbidity and length of hospital stay have also been shown^[1,16,17]. The improved dexterity the robot offers has demonstrable benefit when performing intracorporeal anastomosis^[18], but the benefits of robotic over laparoscopic colonic surgery however are less well established and no benefit of has been demonstrated when comparing laparoscopic to robotic right hemicolectomy^[19]. Robotic left hemicolectomy can be used as training platform to practice mobilization of the left colon and splenic flexure as part of robotic anterior resection.

Currently there appears to be little evidence to support the use of DVR type robots in conventional multiport trans-abdominal surgery. The development of transanal endoscopic microsurgery (TEM) and single port laparoscopic surgery (SPLS) limits a surgeons dexterity still further and these fields may be particularly suited to robotic augmentation.

COLORECTAL ROBOTIC SURGERY UNDER DEVELOPMENT

Robotic surgical technology is expensive- initial outlay, maintenance and purchasing disposable equipment contributes to the financial expense that must be justified by reproducible cost effectiveness. This currently restricts robotic surgery to larger institutions that are able to absorb these costs and provide high utilisation in circumstances where financial gains can offset expenditure. Therefore developments in colorectal robotics over the next decade will concentrate on the widening application of robotics to other colorectal disciplines, such as endoscopy, single port surgery and transanal surgery and minimisation of cost.

Single port robotic laparoscopic surgery

SPLS offers improved cosmesis and less post-operative discomfort compared to that seen in multiport laparoscopic surgery^[20]. SPLS restricts the triangulation and retraction easily achieved in multiport surgery. This can be managed utilising conventional straight instruments that are crossed intracorporeally or by using curved or articulating instruments such as the Autonomy Lapro-angle^[20]. The technique is associated with equivalent oncological outcomes^[21], but a systematic review of colorectal SPLS found conflicting evidence regarding



Figure 2 Robotic single port laparoscopic surgery module designed by Intuitive Surgical. ©[2015] Intuitive Surgical, Inc.

demonstrable improvements in patient recovery and length of stay^[22].

Robotic assisted SPLS systems offer superior triangulation, without the need for crossing instruments, while incorporating other robotic technology. The Da Vinci Si Surgical Robot (Intuitive Surgical) has obtained FDA approval. It incorporates remote centre technology that reduces interference between instruments in addition to a three dimensional camera, motion scaling and removal of tremor (Figure 2). Evidence has been published demonstrating the feasibility of robot assisted SPLS in right hemicolectomy^[23] but to date no advantage of robot assisted over conventional SPLS has been demonstrated. Alternative robotic SPLS platforms are in the prototype stage, including the Single Port Orifice Robotic Technology robotic SPLS module (Titan Medical) which is predicted to cost a third of the Da Vinci system, although data on efficacy is awaited^[24].

Robotic transanal surgery

TEM offers similar practical challenges to SPLS and has become established as an effective method of removing non-advanced distal rectal lesions and may be oncologically superior to conventional transanal excision^[25]. Initially described in 2011, a SILS (Covidien) port was placed in the anus and the Da Vinci machine deployed as for SPLS^[26]. The first cohort study of sixteen patients managed with robotic TEM reported that the procedure was technically feasible but did not offer comparative data with conventional TEM. Use of the robot added an additional €1000 per procedure in disposables alone^[27].

Robotic transanal total mesorectal excision (RT-TME) is an alternative method of TME where the standard abdominal component of an anterior resection is completed laparoscopically before the DVR is introduced transanally to complete the TME in a retrograde fashion. This method facilitates distal rectal dissection in patients who are obese or who have narrow pelvises^[28]. A study of twenty patients did not compare RT-TME to conventional TME but demonstrated the feasibility of the approach in distal rectal cancers^[29].

Improving current laparoscopic technology

Modifying and augmenting existing laparoscopic surgical instrumentation to offer additional degrees of movement, tactile or haptic feedback may narrow the gulf between laparoscopic and robotic surgery with potentially significant cost savings. Movement of conventional laparoscopic instruments is restricted by the fulcrum of movement existing at the point of entry into the abdomen. The Radius Surgical System (RSS, Tuebingen Scientific) has been in circulation for over ten years and offers an additional fulcrum at the tip of the instrument to allow a greater degree of movement. As with the DVR, it offers 7 degrees of freedom for a significantly lower financial outlay although the extent of its distal joint articulation is reduced^[30].

The RSS generally offers tools for suturing and manipulation, rather than dissection and there is no mechanism for removing surgeon tremor or changing the ratio of hand to instrument movement. Results suggest a shorter learning curve compared to the DVR^[31] and it has been demonstrated that they can be used in sutured intracorporeal colorectal anastomosis with encouraging results^[32]. The parallel development of reliable laparoscopic stapling devices has, however, generally obviated the need for an advanced suturing instrument, which may account for the lack of take up of the RSS system. The Autonomy Laparo-angle (CambridgeEndo) is a simpler system offering a range of graspers, scissors and needle holders that can articulate at a distal joint allowing a greater degree of movement not offered by conventional laparoscopic instruments. However, to date there is no published evidence of its use in colorectal surgery.

Robotic endoscopy

Developments in robotic endoscopy have focused on automatic endoscope propulsion and improved endoscopic instrumentation. Balloon endoscopy mimics the movement of an earthworm, using coordinated inflation and deflation of a series of balloon to advance the camera and it has been successful in small bowel enteroscopy^[33]. Current research focuses on providing propulsion at the endoscopic tip to pull the scope through the colon, reducing discomfort and procedure duration. Development of legged locomotion allows efficient propulsion and a steering capability, but risks iatrogenic injury from the traction of the legs on the colonic surface. New generations of microscopic leg effectors aim to minimise injury while offering sufficient propulsive force for effective motion^[34].

Capsule endoscopy utilises passive propulsion to traverse the GI tract and has proved successful in endoscopic practice, particularly in visualisation of the small bowel. The purely passive locomotion is also a drawback and does not allow retrograde motion to recheck areas of incomplete examination. Capsules with active control could be steered to closely examine certain areas, release medications and

perform diagnostic or therapeutic interventions but they are limited by size as they must be swallowed. Size constraints currently preclude independently self-propelled capsules.

Vectoring using external magnets allows the capsule to remain as small as possible and was originally described using a hand-controlled external magnet^[35]. To offer accurate and reproducible magnetic control requires a generated magnetic field utilising a series of magnets under computer control and offering very high positional accuracy at the cost of extensive magnetic equipment^[36]. Early trials demonstrate that the technique is feasible but movement is restricted by collapsed bowel with no method of insufflation available and there are no reports from trials in human subjects^[37].

Endoscopic mucosal resection is an established method of endoscopic piecemeal removal of sessile polyps or superficial cancers less than 20 mm in diameter that would otherwise require surgical excision^[38]. Endoscopic submucosal resection (ESR) can be applied to larger lesions and aims to remove a greater depth of tissue in a single specimen. This allows more accurate histological examination and reduces the risk of recurrent disease^[39]. Although initially developed for the management of upper gastrointestinal lesions, the procedure has shown great promise with respect to colonic lesions greater than two centimeters in diameter^[40]. The procedure is technically challenging and relies on the application of tension to the target lesion to allow careful dissection, which is challenging with conventional endoscopic instruments.

A number of flexible multi-tasking platforms are available that consist of conventional endoscope video technology with an enhanced multichannel intervention system allowing two working instruments operated mechanically or robotically. The Master and Slave Transluminal Endoscopic Tool (MASTER) is a robotic endoscopic surgical system that introduces a two-channel endoscope with two slave robotic effectors possessing nine degrees of freedom. The system allows separation of the endoscopic control and instrument control to allow two operators to work together in tandem^[41]. The MASTER was originally developed for Natural Orifice Transluminal Endoscopic Surgery (NOTES) but has been tested in ESR in animal models with success^[42]. A trial of the MASTER system in ESR in human subjects was planned but results have not been published yet.

POTENTIAL FUTURE OF ROBOTIC COLORECTAL SURGERY

The ultimate aim of minimal access surgery is for surgery to be completed *via* natural orifices without any disruption to the normal functioning of the patient. Ultimately the development of nanotechnology may make this a reality but in the meantime the direction

of minimal access surgery is to further minimise access without compromising surgical outcome and to improve patient safety.

Advanced instrumentation

The Image-Sensing Navigated and Kinematically Enhanced (i-SNAKE) is an instrument delivered *via* a standard laparoscopic port. The distal end of the instrument possesses an articulated section carrying a camera, driven by a hybrid motor design, allowing a greater degree of flexion compared to cable actuators used in a conventional flexible endoscope^[43]. In addition, there are two flexible surgical arms driven by cables that can carry a range of instruments and there is an additional channel that allows an instrument to be passed through the articulated section. The three arms are delivered *via* a 15 mm trocar and the arms are extended once safely within the peritoneal cavity.

Flexible robots such as this are required to operate in highly angulated positions while maintained sufficient control to allow careful dissection and to produce enough force to manipulate tissue. The i-SNAKE can retroflex completely, allowing tubal ligation from a vaginal NOTES approach^[44]. The suitability of the platform for conducting intraluminal interventions such as ESR and Per-Oral Endoscopic Myotomy have been assessed^[45] and it is would be anticipated that this technology could be used to augment SPLS and intraluminal colorectal interventions.

Haptic feedback

Haptic feedback describes the conveying of information from the robotic effector, now also functioning as a receptor, back to the surgeon. The aim is to provide "transparency", where the surgeon feels that they are contacting the patient directly, rather than *via* a robotic mechanism^[46]. To achieve this level of feedback requires transmission of information regarding temperature, texture, force and vibration, and may not be technically feasible. Other industries make use of limited forms of haptic feedback, but surgery offers the unique challenges of size limitation, sterilisability and cost implications over existing technology. An economical approach would be to modify existing technology with feedback sensors and effectors^[47], but this may make integration with complex technology such as the DVR challenging.

Colorectal surgery demands soft tissue differentiation, the careful manipulation of tissues and suturing, all of which benefit from haptic feedback. The TELELAP ALF-X (SOFAR) is a surgical robot that offers haptic feedback in a smaller package compared to the DVR^[48]. The TELELAP ALF-X provides haptic feedback by exerting forces on the surgeon's hands- this requires a complex system of processors and actuators to achieve adequate fidelity and is therefore inherently complex. An alternative approach would be to relay haptic information to the surgeon by an auditory or visual representation of force feedback. Lab studies

have demonstrated that color-coded visual display of stitch tension improves consistency in tension applied to ligatures^[49,50].

To provide haptic feedback in the seven degrees of freedom that the DVR offers would be even more challenging. Given the wide uptake of the DVR it may be unlikely that institutions will invest in another robot simply to take advantage of haptic feedback when the surgeon feels it may be helpful. Therefore a successful haptic feedback system would most likely have to be integrated with the DVR, or operate in parallel with it.

A force-sensing adaptor for the Da Vinci Robot has been developed with some success in lab testing but there are no data from *in vivo* tests^[51]. A wireless palpation probe is an alternative that could be used both in robotics and conventional laparoscopic surgery. This battery operated unit can be introduced *via* a port and used to measure indentation pressure and depth in order to characterise tissues. Initial porcine studies used the probe to serially palpate a porcine liver to produce a "stiffness map" that could be used to guide subsequent resection^[52].

Tactility

Open surgery offers a uniquely tactile experience that is significantly dampened by minimally invasive surgery. Haptic feedback may offer some gross information on tissue resistance, but not the degree that the surgeon requires for accurate tissue differentiation. The technology to provide tactile transparency does not currently exist and may not do so for some time due to the technical complexity of detecting, processing and displaying such information.

Instruments for the detection of gross tactile information in minimal access surgery have been developed and tested in order to locate arteries and detect blood flow, in identifying the inferior mesenteric artery for example. The tools, such as TactArray (Pressure Profile Systems) carry multiple pressure sensitive receptors that may be applied to the tissues producing graphic representations of the tactile feedback detected^[53]. An alternate approach would be to use intracorporeal Doppler ultrasonography as a proxy to assess the tissue instead or relying on tactile feedback. This has already been demonstrated in laparoscopic nephrectomy^[54] but has not been utilised in colorectal surgery.

Capsule endoscopy

Diagnostic capsule endoscopy has proven itself as a diagnostic modality and is already in widespread use. Further development of this technology in the future will look to expand its diagnostic and therapeutic possibilities. Wireless capsule endoscopy is limited by the lack of a conventional insufflation system and the resultant lack of bowel distension limits diagnostic capability. Preliminary studies have demonstrated the feasibility of a wireless insufflation capsule utilising liquids or powders to produce gaseous insufflation^[55]. There have been no published results from animal

studies but this demonstrates the widening functionality of capsule intervention.

As capsule endoscopes become more complex they will become limited by their power storage capacity. Complex luminal processes such as delivery of topical chemotherapy, brachytherapy or treatments for inflammatory bowel disease may require capsules to remain inside the body for a prolonged period of time. Therefore an alternate source of power may be necessary. Magnetic induction offers a method of transmitting power to a device within the body from an external charger over a prolonged period of time without causing deleterious effects^[56].

Micro- and nanotechnology

Nanotechnology offers opportunities to investigate and intervene at the cellular level and may ultimately lead to a step change in the conduct of colorectal surgery over the next fifty to one hundred years. Currently machine actuators limit the minimum size of machines to a few millimetres- too large to be injected into the circulation for example, but alternative avenues for micro-interventions have been investigated.

Minimally invasive biopsy retrieval has been demonstrated using "micro-grippers". These tools possess minuscule biopsy tools that close in response to a change in temperature and are also composed of a ferromagnetic alloy. These tools were injected into the common bile duct during an endoscopic retrograde cholangiopancreatography in a live porcine model, allowed to sit for ten minutes to allow the grippers to close in response to change in temperature before being retrieved by a catheter with a magnetic tip^[57]. The retrieved tissue was assessed and deemed suitable for cytological analysis. Potentially this technology could be adapted for use as a non-invasive diagnostic aid in colonic conditions such as inflammatory bowel disease.

Nanobot technology in medicine aims to deliver therapy at the cellular level and may have particular importance in the treatment of cancers. Mechanical actuators and processors are not viable at this scale and therefore the robots are genetically engineered bacteria that allow cellular-level interactions, containing ferromagnetic granules that allow steering and propulsion using magnetic fields. Microbot technology and its application in medicine are likely to radically change how we view therapeutics. The ranges of possible applications include targeted therapy, material removal, deployment of structures, such as stents and telemetry^[56]. Although currently in its infancy, this aspect of robotic technology has the greatest potential to revolutionise how we manage colorectal pathology in the future.

CONCLUSION

The development of minimal access surgery has spurred the creation of robotic assistance in order to aid surgeons to overcome the shortcomings of this surgical technique. The breadth of robotic advancement

considered in this review demonstrates that robotic colorectal surgery has advanced far beyond its original brief of surgeon assistance. The potential advancements within this field will allow utilisation of minimal access surgery in a wider range of increasingly technically challenging environments and could fundamentally change the way surgeons manage their patients.

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Chronic radiation proctopathy: A practical review of endoscopic treatment

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Abstract

Chronic radiation proctopathy (CRP) is a troublesome

complication of pelvic radiotherapy. The most common presentation is rectal bleeding. CRP symptoms interfere with daily activities and decrease quality of life. Rectal bleeding management in patients with CRP represents a conundrum for practitioners. Medical therapy is ineffective in general and surgical approach has a high morbidity-mortality. Endoscopy has a role in the diagnosis, staging and treatment of this disease. Currently available endoscopic modalities are formalin, potassium titanyl phosphate laser, neodymium:yttrium-aluminum-garnet laser, argon laser, bipolar electrocoagulation (BiCAP), heater probe, band ligation, cryotherapy, radiofrequency ablation and argon plasma coagulation (APC). Among these options, APC is the most promising.

Key words: Endoscopic treatment; Radiation proctopathy; Proctitis; Argon plasma coagulation; Cryotherapy; Radiofrequency ablation; Formalin; Laser; Bipolar probe; Pelvic radiotherapy

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Core tip: The objective of this review is to critically analyze the available data and our experience with this disease, with suggestions for daily practice and further research. In our view, laser treatment is an obsolete technology and can be abandoned. The bipolar probe (BiCAP) is very well indicated for patients with implantable electronic devices. The best way to use formalin is still unknown. More studies with band ligation, cryotherapy and radiofrequency ablation are still needed. Argon plasma coagulation has emerged as the front-runner, due to its ease of use, affordability, better-defined settings, effectiveness and low risk of complications.

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INTRODUCTION

Chronic radiation proctopathy (CRP) is recognized as injury to the rectum and/or colon due to radiotherapy for the treatment of pelvic malignancies; it occurs when clinical symptoms persist or appear months to years after therapy (median 6-12 mo). The sigmoid colon may also be affected^[1,2]. The term radiation proctitis is a misleading term since epithelial damage to the rectum due to radiation is associated with minimal or no inflammation^[1,3]. Cancers of the cervix, prostate, rectum, bladder, testicles and uterus are commonly treated with pelvic irradiation. Among these, prostate malignance is the most frequent^[1].

The incidence of CRP has yet to be ascertained due to the lack of prospective studies and variability in the definition and classification systems used for the condition^[1,2]. However, it is estimated to range from 2% to 20%^[3,4]. The method of radiation delivery is an important predictor of the risk for radiation proctopathy^[2,5]. The rate of colorectal complications with brachytherapy is lower compared to external beam radiation^[6]. The use of newer conformal radiation therapy techniques maximizes the dosage directed to the tumor while minimizing the dosage of radiation to the rectum^[6,7]. CRP may be more frequent in patients with inflammatory bowel disease, diabetes, hypertension or peripheral vascular disease and in those who develop severe acute proctopathy^[2].

CRP should be suspected in patients who develop symptoms such as diarrhea, urgency, tenesmus or bleeding, usually 6 mo or more after pelvic radiation exposure. Hematochezia occurs due to oozing from a friable, ischemic mucosa, and the rupture of radiation-induced telangiectasias and can lead to anemia and the need for blood transfusions^[1-3,8]. Symptoms are non-specific and the diagnosis requires exclusion of other etiologies of colitis^[3,4]. Diagnosis can be confirmed by colonoscopy or sigmoidoscopy^[7]. Endoscopic findings of CRP are mucosal pallor, telangiectasias, spontaneous hemorrhage, edema and friability. Less frequent findings are ulcers, strictures and fistulas^[9]. A scoring system has been developed for the endoscopic evaluation of radiation proctopathy severity, based on three factors: The presence of fresh blood, the telangiectasia distribution and the surface area involved^[10]. Although biopsies are not diagnostic, they can rule out other causes of proctopathy such as inflammatory bowel disease or infection and can grade the mucosal damage^[11,12].

TREATMENTS FOR CRP

In patients with CRP, the management should be based upon the severity and pattern of symptoms and experience within the treatment center^[13].

Therapy for CRP includes medical, endoscopic and

surgical therapies. Medical therapy includes: Use of non-steroidal anti-inflammatory drugs, sucralfate, short chain fatty acids, metronidazole, pentoxifylline, vitamins (A, C and E), and hyperbaric chamber treatment; all have been described with limited success. In a small study, vitamin A also showed some benefits on functional symptoms^[14], although the effect of retinol on rectal bleeding was not evaluated^[15]. Enemas of sucralfate are safe and well tolerated and have become the best medical therapeutic option^[7,15,16].

The management of patients with symptomatic CRP remains essentially empirical because there are only a few randomized trials, in addition to the difficulty of grading symptoms, endoscopic severity and response to therapy. However, some concepts regarding the management of these patients have been suggested: Treatment for hematochezia is in general better if it involves a sclerosing agent or a topical cautery to obliterate telangiectatic mucosal vessels; non-steroidal anti-inflammatory drugs have a limited role in treatment; large rectal ulcers, strictures, fistulas, abscesses and intractable bleeding generally require surgical management^[1,15]. However, surgical therapy has high morbidity and mortality rates^[16].

ENDOSCOPIC TREATMENTS FOR CRP

The main objective of endoscopic therapies of CRP is to achieve control of blood loss, leading to improvements in quality of life by reducing the requirement for blood transfusions, iron replacement and hospital admissions, resolving anemia and hematochezia^[10,16]. Endoscopic therapy using potassium titanyl phosphate (KTP) laser, argon laser, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, BiCAP, heater probe, endoscopic band ligation (EBL), cryotherapy, radiofrequency ablation (RFA) and argon plasma coagulation (APC) have been reported^[15,16]. Formalin is a miscellaneous technique with aspects of medical and endoscopic approaches. However, Cullen *et al*^[17] described instilling formalin into the rectum during flexible sigmoidoscopy, and it shall be included in the endoscopic treatment group. Endoscopic treatment can also be used for radiation-related strictures^[7].

Formalin therapy

Formalin therapy for CRP is based on its use in patients with hemorrhagic cystitis^[18]. Since Rubinstein's work, in 1986, reported the first successful CRP treatment using a rectal wash with formalin, many authors have published on the treatment of hemorrhagic CRP using this therapy^[19]. Formalin functions as a local sclerosant and causes chemical cauterization of telangiectasias.

According to an email survey with members of the American Society of Colon Rectal Surgeons, formalin is the most popular method to treat CRP. Of the 327 respondents, 85% favored to formalin, while 42% used APC. Only 25% of practitioners reported using sucralfate (more than one modality could be chosen)^[20].

Success rates vary from 27% up to 100%^[16-23]. This

difference can be explained by the wide variability in application technique and concentration^[21]. Formalin can be administered as an enema, irrigation in small aliquots, or soaked pledgets of cotton wool applied under rigid sigmoidoscopic, proctoscopic or flexible endoscope guidance^[17,22]. Sedation may be needed, but because of pain due to the procedure, most authors reported the use of general anesthesia for this procedure. Formalin therapy can be repeated for two or three more applications until symptomatic improvement, especially with the cessation of rectal bleeding. Ulcers due to formalin application preclude repeating the procedure^[18].

Patel *et al.*^[19], in a retrospective study, evaluated the combination of oral vitamin A with formalin application. The addition of vitamin A led to a significant decrease in the number of formalin sessions and a significantly shorter time for resolution. Supplementation with vitamin A also has a better success rate in controlling rectal bleeding than formalin alone (94% vs 64%).

There are also two small studies comparing formalin with APC. Yeoh *et al.*^[21] suggested that formalin and APC had similar success in managing hemorrhagic CRP. Nevertheless, Alfadhli *et al.*^[22] concluded that APC was significantly more effective (78.5% vs 27.2%, $P = 0.017$) and safer ($P = 0.001$) than formalin.

The advantages of formalin application include low cost, wide availability and good efficacy in general^[23]. Despite this, high rates of complications have been reported, including chemical colitis, anorectal pain, anal and rectal strictures, rectal perforation, fissures, incontinence and diarrhea^[16,18]. Further studies are needed to determine the optimal method of delivery.

Laser therapy

Lasers cause thermal destruction by tissue absorption of laser light and have been used to coagulate radiation proctopathy related vascular lesions in small retrospective series. The KTP laser, the Nd:YAG laser and the argon laser have been effectively used for CRP. A laser fiber is advanced into the working channel of a regular endoscope and is activated by the endoscopist, generating several laser pulses. The depth of thermal effect is dependent on the duration of pulses, power setting and light wavelength. Multiple sessions are generally required. Laser therapy usually decreases rectal bleeding, transfusion dependence and the frequency of hospitalization^[24,25].

Complications secondary to deeper thermal injury, which include strictures, transmural necrosis, perforations and fistulas, occur in up to 15% of patients. Intervals between sessions of at least a few weeks and using the least amount of energy for ablation are recommended to avoid complications^[26].

Chapuis *et al.*^[24] described the combination of formalin and Nd:YAG laser in 34 patients with CRP. The patients underwent an endoscopic Nd:YAG laser session and then were treated with formalin application. The authors reported that bleeding ceased in 25 patients

(74%) with no major complications.

Compared with other ablative devices, lasers are unwieldy and far more expensive. Other considerations include availability, safety issues and limited portability^[25]. The use of lasers in the treatment of CRP has declined^[27].

Heater probe and BiCAP - contact therapy

BiCAP and heater probe are contact methods for CRP treatment. The heater probes have Teflon-coated heating components at the extremity of a plastic catheters that deliver standardized energy over set times. The BiCAP probes have pair of electrodes (negative and positive) at its end through which current is passed using the tissue as a conduction surface^[3,16]. No current is passed through the tissues to either a distant or local electrode; for this reason, the induced electromagnetic field is insignificant^[28]. Both devices are directed in the setting of active bleeding^[16]. In contrast to BiCAP, heater probe mucosal injury is based on direct heat application rather than electrical current. Both probes have an irrigation port^[25].

The heater probe and BiCAP have advantages. They cause less tissue injury (in comparison to laser therapy), permit tangential application of cautery, and are both relatively inexpensive and widely accessible^[11]. They are also considered the best methods to use in patients with electronic devices, such as pacemakers and defibrillators^[28]. The disadvantage of both methods is char formation on the tip of the probe, requiring catheter retrieval and repeated cleaning^[7,11,16].

In a randomized prospective trial by Jensen *et al.*^[29], 21 patients with chronic recurrent hematochezia and anemia due to CRP were followed for 12 mo. Nine patients were treated with heater probe and 12 with BiCAP (power of 10-15 W). A median of four sessions was required. Severe bleeding episodes were significantly reduced after BiCAP (75% vs 33%) and heater probe (67% vs 11%) treatment without a statistically significant difference between the methods. The decreased rate of bleeding was accompanied by hematocrit improvement in both groups. There were no major complications.

A retrospective study evaluated 55 patients treated with three sessions of BiCAP (power of 30 W) and sucralfate enemas. The authors concluded that BiCAP was effective in stopping bleeding from telangiectasias, decreasing recurrence, hospital stay and blood requirements (especially in the group of more severe patients). Unfortunately, there were no comments about complications and follow-up in this study^[30].

We recently published a prospective randomized trial comparing APC and BiCAP for rectal bleeding due to CRP. Fifteen patients were enrolled in each group. BiCAP was performed using a 7Fr Gold probe (Wilson-Cook, Winston-Salem, United States) and a high frequency generator (ERBE ICC 200; Electromedizin, Tübingen, Germany). The power setting was 50 W. Coagulation was achieved by applying light pressure with the

probe directly into each telangiectasia. Success was considered as the eradication of all abnormal vessel, and failure as the requirement for more than seven sessions or the need for other therapeutic modality. The complete eradication success rate was 93.3% for BiCAP after a mean of 2.9 sessions, vs 80% at 3.7 sessions for APC ($P > 0.05$). Ten of 15 (66.7%) patients had minor complications, mainly transitory anal and abdominal pain. One developed symptomatic stenosis (successfully managed with a fecal emollient). Five patients presented major or hemorrhagic complications (two patients had both minor and major complications). There were no statistical differences between the groups regarding complications when categorized as major ($P = 0.169$) or minor ($P = 0.068$). Nevertheless, the total rate of complications was significantly higher in the BiCAP group ($P = 0.003$, with power 97.4%). No other more severe adverse events, such as fistulas, extensive necrosis, bowel explosion or perforations were noticed in this study. The frequency of complications was evidently superior than those reported so far. Many potential factors can account for such a difference: Most prior studies have been retrospective and underestimated the real incidence of complications; in our study, BiCAP was used at a higher power setting; our patients had a meticulous follow-up; most of the complications were minor and all of them were managed on an outpatient basis. We concluded that APC and BiCAP are both effective for hemorrhagic CRP. There are probably no significant differences between the two methods. Even though, APC seemed to be safer than BiCAP in our study, further research with a larger sample size is necessary to assess complication rates and determines the best therapeutic choice^[31].

Endoscopic band ligation

Endoscopic band ligation (EBL) was introduced in 1986 and is currently considered the endoscopic method of choice for the prevention of esophageal varices bleeding^[32]. As far as we know, there is only one paper published on the use of EBL as a treatment for CRP^[33]. The authors reported one patient who had been treated with APC sessions with no success. EBL was performed with a gastroscope and a standard multiband ligation kit. Three bands were placed in the first session and two during the second session (interval of 20 d between the first and second sessions). The procedure was well tolerated. A lower gastrointestinal endoscopy 45 d after the completion of treatment showed no evidence of ongoing CRP^[33]. This was the first experience using this technique, and more data are needed to make further conclusions.

Cryotherapy

Cryospray ablation, similar to APC, is a non-contact therapeutic method by the application of liquid nitrogen or carbon dioxide gas at extremely cold temperatures^[8,16]. Cryoablation has been used to treat esophageal early cancer and high-grade dysplasia^[8].

Limited data exist on the efficacy of this technique for treating vascular lesions^[25]. In a few studies, endoscopic cryoablation was performed in patients with CRP^[34-38].

Cryotherapy is performed with a catheter passed through the working channel and its tip is positioned around 0.5 to 1.0 cm from the end of the scope. The spray is applied for 5 s directly onto the mucosa. The freeze/thaw cycle is repeated for a total of three series (total of 15 s) per involved area. A decompression tube with ports spanning the distal 35-40 cm is inserted over a Savary-like guide wire. Suction *via* the decompression tube is applied for the period of cryospray application to protect against over-insufflation^[8,35]. Despite this care, one patient was reported with a cecal perforation caused by malfunction of the decompression tube. For this reason, the procedure was adapted to reduce treatment time and carry out full colonoscopy after the cryotherapy for bowel decompression^[35]. Difficulties include the field of view with frosting of the lens, and management around the decompression tube. Using a friction-fit mucosectomy cap reduces the chance that the catheter will adhere to the surface and improves access to difficult areas^[39].

The required number of sessions ranges from one to four. In one study, the endoscopic score considerably improved, as well as hematochezia and rectal pain. Symptomatic improvement was observed in 80% of patients^[35].

The cryospray generators currently on the market are more cumbersome and less mobile than most APC and the radiofrequency units, and need maintaining a supply of liquid nitrogen, which lasts around 2 wk in the holding tank. Therefore, therapies for rare findings, mainly in a lower volume service, may be more difficult. One possible advantage of cryospray over the heat-generating ablative techniques is that colonic lavage is not required to reduce the probability of gas ignition. However, studies in animals showed that the depth of tissue destruction may be deeper with cryospray than that achieved by RFA, and it is unknown whether this could lead to fistulas, abscesses and strictures or whether cryospray is inherently less prone to such complications. Furthermore, the quickly expanding gas requires adequate venting, which may be difficult for proximal lesions in the sigmoid^[16].

Studies using cryospray for CRP remain experimental and anecdotal. These initial case reports support the use of cryotherapy for the treatment of CRP. In spite of this, there has been no prospective study comparing cryotherapy with other methods such as APC, regarding the durability of results, safety and efficacy. Supplementary research is required to confirm the superiority or even utility of cryospray^[16].

RFA

RFA is a newer endoscopic technique. The Halo RFA system uses two different types of probes with a closely spaced arrangement of electrodes, which thermally ablate tissue. The depth of injury (0.5-1 mm)

is dependent on the power, density and duration of contact. A generator connects to either a 360° Halo catheter or a 90° Halo catheter to provide circumferential or more focused ablation^[40]. The FDA (United States Food and Drug Administration) approved the RFA for the treatment of Barrett's esophagus and for gastric hemostatic applications. RFA reaches large areas in a superficial way, suggesting that analogous benefits could be applied in the rectum and colon^[41].

Recently, a number of studies have evaluated the safety and efficacy of RFA for CRP treatment^[40-45]. RFA is generally performed on outpatients using a single use Halo90 electrode catheter (BARRx/Covidien, Sunnyvale, United States) that is passed through a standard gastroscope. A gastroscope is used instead of a colonoscope because Halo devices are designed for a gastroscope, and because retroflexion is easier using a gastroscope, especially with the RFA catheter attached. During the ablation procedure, the Halo90 catheter is mounted in the 6 o'clock position (as opposed to the 12 o'clock location usually used for the ablation of Barrett's esophagus). To promote hemostasis, the coagulum in treated areas is not scraped off. The endoscope and device are removed for cleaning every eight applications in order to preserve electrode surface effectiveness for subsequent areas treatment. Ablations are performed about 1 mm proximal to the dentate line (to prevent sensory injury to the anal mucosa) and restricted to a short length (less than 6 cm to the dentate line). The procedure is repeated as needed until complete rectal mucosa ablation is achieved. Based on prior studies, an energy density of 12-15 J/cm² at a power density of 40 W/cm² was selected, which showed no transmural damage at these settings^[8,41,43].

Generally, the procedure is well tolerated with mild anorectal pain was reported in 12% of sessions. One of 39 patients presented with significant anorectal bleeding (endoscopic exam demonstrated arterial-like hemorrhage from a vessel in a shallow erosion at a place of excessive ablation) and was treated with a single hemostatic clip^[41]. After one or two RFA sessions, hemostasis was achieved with a significant decrease in clinical symptoms and an increase in the hemoglobin concentration^[8,41,43]. Thus, RFA seems to be safe and effective to treat CRP. The benefits of RFA include re-epithelialization with the prevention of rebleeding without stenosis and ulceration that may be more frequently observed in other thermal methods. The narrowly spaced bipolar array of the RFA catheter confines the radiofrequency energy penetration, restricting the RFA lesion to the superficial mucosa, in this manner avoiding deep tissue injury. In conclusion, RFA permits much broader areas of tissue to be treated at the same time compared to the point-by-point approach required with the bipolar or heater probes, or even with APC. Similar to APC, the equipment is transportable and can be utilized in different places. The BARRx units also deliver a consistent energy to the surface by using a well defined and a reproducible

ramp-up of energy. This diminishes the likelihood of over-treatment and operator-dependence that may lead to ulcerations or perforations^[16]. However, despite these theoretical advantages, some statements should be made before RFA is considered the treatment of choice for CRP. First of all, these studies were retrospective and conclusions are limited by the lack of a control group. They were also non-powered and even considering all published works, only a few dozen patients with CRP have been treated with RFA. Another important limitation is that no sigmoid or proximal rectal lesions were ablated, thus safety in those areas (with a thinner wall) remains uncertain. The cost of the RFA energy generator (applicable in only a few indications) and the price of the Halo catheter can be another drawback. Therefore, additional controlled studies are required to compare RFA to other therapeutic modalities for CRP.

APC

APC is a non-contact thermal method using ionized argon gas to deliver a monopolar high-frequency current, which efficiently coagulates tissue. APC is applied to tissue until a white coagulum appears, and then the endoscope and catheter are maneuvered in a vertical or circumferential linear pattern to coagulate additional tissue. The depth of tissue destruction is limited due to increased resistance and decreased current flow through coagulated tissue^[39]. Once the tip makes contact with the target tissue, it works as a monopolar probe and it can cause deeper damage. And contact between the tissue and tip may also result in the infusion of extraluminal or submucosal gas. Due to repeated contact with the mucosa, a coagulum may also develop on the extremity of the catheter, which needs intermittent removal of the probe for manual cleaning^[25].

The second-generation equipment (VIO/APC2) integrates numerous improvements over the first-generation device. The total effectiveness of the method was improved by 30% ± 50%, so lower power settings can be utilized to create the same thermal effects and, conversely, the same power settings may produce deeper and more extensive tissue injury than expected. Three different modes are now available on the apparatus: Forced, pulsed and precise. Forced mode provides continuous output and corresponds to the settings on the earlier system. Pulsed mode delivers an intermittent current with two alternative effects: Effect 1 pulses nearly every second with a higher energy output following each pulse, while effect 2 pulses around 16 times per second with a lower energy output *per pulse*. The latter may be preferred when superficial treatment of large surface areas is desired. Precise mode uses an integrated regulation system to control the flow. This results in a more superficial depth of damage compared to the other settings^[39].

APC has been used to treat a wide spectrum of bleeding lesions in the gastrointestinal tract^[25]. However, CRP is really a niche for APC^[46]. An impressive

number of studies evaluated APC efficacy and safety for the treatment of CRP, with more than 500 patients enrolled^[15,21,31,47-52]. Thus, APC is certainly the best-studied technique in the management of this disease. Nevertheless, until now, there has been no consensus regarding the best APC settings (gas flow rate and power). Power settings reported in the literature range from 25-80 W and flow from 0.6-2.5 L/min^[8,15]. Gheorghie *et al.*^[53] compared two different power settings: 23 patients were treated with 60 W and 19 patients with 50 W. They concluded that there was no statistical significance concerning the efficacy and safety of APC application between the 60 W and 50 W power setting, although rectal stenosis was described only in patients treated with the higher power setting. Sato *et al.*^[52] using a porcine rectal wall *ex vivo*, found that the optimal setting was 40 W with 1.2 L/min gas flow and a two-s application, which was enough to treat submucosal vessels but did not affect the muscle layer.

More spread lesions commonly need repeated applications per session and several treatments. The mean number of sessions varies from 1 to 3.7 with a calculated overall cumulative mean of 2.13 sessions per patient (median: 2)^[16,31]. APC session intervals range from every 2 d to every 8 wk^[15,16]. APC improves rectal bleeding in 80%-90% of cases as well as symptoms of tenesmus, diarrhea and urgency in 60%-75% of cases^[16]. Follow-up ranged from 2 to 60 mo^[15]. Recurrences have been reported, which responded to additional rounds of APC therapy^[16,31].

Ulcers after APC can be considered an effect of thermal injury to already damaged, compromised more fragile and tissue, with poorer healing. Ulcer incidence may be affected by the flow rate and power settings of the argon gas, way of application, interval between sessions, and number of sessions subsequent to ulcer development, which may delay ulcer healing due to repeated thermal damage. The fact that rectal ulcers are not clinically problematic denotes they should not be considered a complication or an absolute contraindication to APC, nor do they necessarily need any further endoscopic follow-up^[16,54]. However, it is advisable that in the presence of a large ulcer (> 1.0 cm), treatment should be delayed.

The overall reported complication rate with APC has been variable^[16], probably due to the lack of a standard technique, variation in the criteria for defining complications and different follow-up periods. The most common procedure-related complication is rectal or anal pain with or without tenesmus, which is most probable to occur following treatment near the dentate line, and habitually resolves spontaneously within a few days, with or without regular analgesics^[16,31]. A method described by Coriat *et al.*^[55], using a transparent cap attached to colonoscope tip, improved visualization of the upper part of the anal canal and of low rectal lesions without retroflexion and a proper distance for safe and effective APC use. Vagal symptoms, cramping and

abdominal bloating related to luminal distension have also been reported. One potential drawback of using APC is the risk of excessive bowel distention from the quick instillation of argon gas. It is recommended that, whenever available, a two-channel endoscope should be utilized so that the insufflated argon gas can be removed periodically, associated with a low flow rate^[16].

Overall, the frequency of asymptomatic rectal strictures is 4.3%^[16]. Although some eschew treating in a circumferential manner to avoid stricture formation, the results of Villavicencio *et al.*^[56] seem to indicate otherwise. It is likely that the long trawl back technique is more associated with rectal strictures than single-shot procedures with separated spots^[57-59]. Ben-Soussan *et al.*^[59] reported three cases of colonic explosion in two poorly prepared patients. The pathophysiology of the explosion remains unclear but an accumulation of bowel gas (methane and hydrogen) at potentially explosive concentrations due to poor preparation could be the cause. Theoretically, intestinal gas production could also be influenced by the presence of fermentable products in the administered enema. In the Ben-Soussan study^[59], the enema used (disodium phosphate and monosodium phosphate) did not contain any fermentable agent likely to increase gas production and facilitate colonic explosion. Thus, these authors concluded that rather than the type of preparation, the presence of stools above the telangiectasias constituted the main risk. In our previous study, we also used enema preparation before the APC session and did not encounter any colonic explosions^[31]. As far as we know, no other explosions have been recently reported in the literature.

Bacterial translocation of endogenous microbial flora into the bloodstream may occur during any endoscopic procedure. We prospectively evaluated the frequency of bacteremia following APC during CRP treatment. A total of 21 patients were included and 30 APC sessions were performed. Bacteremia was found in two patients (6.67%). In one case, the isolated bacterium was *Staphylococcus hominis*, and regarded as a contaminant. Another patient had two different microorganisms (*Rhodotorula sp.* and *Streptococcus bovis*). None had infectious symptoms^[50].

There are few comparative studies using APC. One of them compared two different power settings^[53] and the other compared oral sucralfate with placebo following APC; the authors stated that additional sucralfate treatment did not influence clinical or endoscopic outcomes^[49]. Only four studies have compared APC with other therapy for CRP. Two compared APC with formalin (vide formalin section)^[21,22], one with hyperbaric oxygen^[48] and our study assessed APC vs BiCAP (see contact method)^[31]. The results of these preliminary studies show that APC is at least as effective and safer than other treatments. However, more comparative studies with larger series, especially between APC and the newest techniques (RFA and cryotherapy) are needed for definite conclusions.

DISCUSSION

CRP is a troublesome complication with an adverse effect on quality of life. The most common complaint is rectal bleeding. Most available data come from uncontrolled, undersized studies with short-term follow-up. Satisfactorily powered, randomized trials comparing different modalities are lacking, and an optimal management strategy has yet to be determined.

Vitamin A had some benefits on functional symptoms, but has not been studied regarding blood loss. Sucralfate enema seems to be the best medical therapy and is well tolerated and secure^[15,16]. There is not enough data to support the use of other medical options in daily practice^[1-3,8]. Surgical management is associated with high morbidity and mortality and should be considered a last resort. Fewer than 10% of patients eventually require surgery, which is usually for intractable bleeding, perforations, strictures and fistulas^[6,7]. In this scenario, endoscopic treatment is becoming increasingly popular^[31].

Besides the therapeutic aspects, endoscopy plays a role in diagnosis and grading and in ruling out another sources of bleeding, especially malignancy^[3,4,11]. Full colonoscopy is recommendable for all patients with rectal bleeding. Due to the risk of fistula formation, rectal biopsies should be performed judiciously. If necessary, they should be directed to the lateral and posterior walls to avoid irradiated areas^[11].

Patients considered to be ideal candidates for endoscopic treatment are those with transfusion dependency, chronic hematochezia, refractory to medical management, no tumor recurrence, no other bleeding source, and no fistulas, ulcerations or strictures^[18]. It is still controversial that patients with occasional hemorrhage without anemia should be treated endoscopically. We think that at least one endoscopic session during the first diagnostic colonoscopy is a reasonable approach. Presumably, it will resolve once and for all these milder cases^[60]. Of course, this and subsequent treatments (if necessary) should be tailored to the patient's preferences.

Nowadays, we agree with other authors in advocating a four to 6 wk interval between sessions^[46,59,61]. It is likely that the ischemic rectal mucosa needs this minimal amount of time to recover from thermal or chemical injury^[1-3,8]. We agree with John Lee^[46] that repeating endoscopy is not necessary in the absence of symptoms.

Good bowel preparation is crucial for endoscopic therapy. We currently recommend complete anterograde bowel preparation for all treatment sessions. Because enemas can cause trauma to a friable mucosa, and many patients with CRP have fecal incontinence^[21], retrograde preparation may be more difficult and provide worse results. Because feces above the lesions are the main risk for bowel explosion^[59], in cases of poor preparation, the procedure should be postponed or vigorous washing must be done. In the presence of

significant oozing, adrenaline solution (1:10000) should be sprayed over the mucosal surface^[31].

Like other invasive procedures, there is a debate about antibiotic, antiplatelet and anticoagulant prophylaxis with endoscopic therapy for CRP. The current American Society for Gastrointestinal Endoscopy guidelines do not mention the use of antibiotics in this patient condition (CRP) nor in this procedure (endoscopic ablation)^[62]. Tam *et al.*^[57] suggested the use of antibiotics for immunocompromised patients before APC for CRP. Postgate *et al.*^[63] made this recommendation for all patients. However, in our study, the incidence of bacteremia after APC for CRP was low (6.67%), similar to the mean frequency of bacteremia associated with colonoscopy in the literature (4.4%). Therefore, APC for CRP may be considered a low-risk method regarding infectious complications, and does not demand the prophylactic administration of antibiotics^[50]. Unfortunately, until now, no other study like ours has been done with other endoscopic techniques for CRP. Chrusciewska-Kiliszek *et al.*^[47] suggested that antiplatelet drugs can play a protective role against ulcer formation after APC. In our study, we found a negative impact of antiplatelet medication, with a statistically significant higher number of APC sessions being required to eradicate telangiectasias in patients using aspirin ($P = 0.047$) (unpublished data). Kaassis *et al.*^[61] also reported a higher number of treatments in patients using anticoagulants. In the Karamanolis *et al.*^[64]'s study recurrence was higher in those using an anticoagulant or aspirin ($P = 0.02$). The present European Society of Gastrointestinal Endoscopy guidelines recommend that clopidogrel or aspirin can be continued in patients undergoing APC for vascular lesions (recommendation grade C). In the lack of appropriate studies, no recommendation can be made for patients taking a combination of thienopyridines and aspirin^[65].

Another issue is whether concomitant medical treatment improves the results of endoscopic treatment. Patel *et al.*^[19] demonstrated that adding vitamin A enhances the effectiveness of formalin application (see the section on formalin treatment). On the other hand, combined oral sucralfate for 4 wk with APC was not better than APC alone in improving the overall disease severity score (see APC section)^[49]. Two possible reasons for the absence of an effect of sucralfate are the short-term period of use and the oral route. Kochhar *et al.*^[66] identified a good response with enemas with a 77% response in 4 wk and 92% response in 16 wk. Studies using oral vitamin A and sucralfate enemas (or both) for longer periods in association with different endoscopic modalities are welcome, especially in patients with intractable bleeding.

Intractable bleeding is traditionally managed surgically. Nonetheless, when surgery is needed, most studies have demonstrated poor outcomes (because a diversion rarely controls the bleeding completely), as well as high complication (15%-80%) and mortality (3%-9%) rates^[6]. Therefore non-surgical strategies

are desirable. Some authors described the success of a second endoscopic modality when the first one had failed^[22,33,56,67]. So a cross-over (two endoscopic methods) or a combined (medical plus endoscopic treatments - see above) schemes may avoid surgery in some patients.

A variety of endoscopic techniques for treating CRP were evaluated and discussed in this review. The choice of treatment should be based on the availability and experience of each center^[13]. If there is more than one method at hand, some considerations can be made. Laser therapy is an obsolete technology and should be abandoned. Contact methods, especially BiCAP, are very well indicated for patients with pacemakers and other implantable devices. The best way to use formalin is still unknown. More studies with EBL, cryoablation and RFA are still needed. APC has emerged as the front-runner due to its ease of use, affordability, better-defined settings, efficacy and safety. Perhaps in the future, the results of the second generation APC device will improve further.

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Retrospective Cohort Study

Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence?

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Abstract

AIM: To analyze outcomes in patients who underwent liver transplantation (LT) for hepatocellular carcinoma (HCC) and received autologous intraoperative blood salvage (IBS).

METHODS: Consecutive HCC patients who underwent LT were studied retrospectively and analyzed according to the use of IBS or not. Demographic and surgical data were collected from a departmental prospective main-

tained database. Statistical analyses were performed using the Fisher's exact test and the Wilcoxon rank sum test to examine covariate differences between patients who underwent IBS and those who did not. Univariate and multivariate Cox regression models were developed to evaluate recurrence and death, and survival probabilities were estimated using the Kaplan-Meier method and compared by the log-rank test.

RESULTS: Between 2002 and 2012, 158 consecutive patients who underwent LT in the same medical center and by the same surgical team were identified. Among these patients, 122 (77.2%) were in the IBS group and 36 (22.8%) in the non-IBS group. The overall survival (OS) and recurrence free survival (RFS) at 5 years were 59.7% and 83.3%, respectively. No differences in OS ($P = 0.51$) or RFS ($P = 0.953$) were detected between the IBS and non-IBS groups. On multivariate analysis for OS, degree of tumor differentiation remained as the only independent predictor. Regarding patients who received IBS, no differences were detected in OS or RFS ($P = 0.055$ and $P = 0.512$, respectively) according to the volume infused, even when outcomes at 90 d or longer were analyzed separately ($P = 0.518$ for both outcomes).

CONCLUSION: No differences in RFS or OS were detected according to IBS use. Trials addressing this question are justified and should be designed to detect small differences in long-term outcomes.

Key words: Cell saver; Cancer; Hepatocellular carcinoma; Liver transplantation; Recurrence

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Core tip: This study addresses an alternative option for allogeneic blood transfusion during liver transplantation (LT) for hepatocellular carcinoma (HCC). The autologous blood salvage in LT, in our series, did not impact recurrence or death. This suggests that autologous blood transfusion should be considered an option avoiding the deleterious effects of allogeneic blood transfusion. Overall, we do believe that our data claim for trials looking for non-inferiority comparing the two modalities of blood transfusion in patients who underwent LT for HCC. We do believe that further studies are justified and should be designed to detect small differences in long-term outcomes.

Araujo RLC, Pantanali CA, Haddad L, Rocha Filho JA, D'Albuquerque LAC, Andraus W. Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence? *World J Gastrointest Surg* 2016; 8(2): 161-168 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i2/161.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i2.161>

INTRODUCTION

Autologous intraoperative blood salvage (IBS) is used routinely in many surgical specialties to minimize the effects of intraoperative bleeding, avoiding the risks of allogeneic red blood cell (RBC) transfusion. A recent cochrane review showed a 40% reduction in the requirements for allogeneic blood transfusion with cell salvage^[1]. IBS has been generally used in liver transplantation (LT), although it is not usually recommended in patients with hepatocellular carcinoma (HCC) since there is a putative risk of reinfusion of neoplastic cells. The IBS is an alternative to allogeneic blood transfusion but it remains a controversial technique in oncologic procedures since it could represent an uncertain risk of malignant cell reinfusion^[2-5].

The circulation of viable neoplastic cells in the IBS device and their detection in the leukocyte depletion filter (LDF) have been proved, and LDF has been used as an effective method to clean the RBC component before infusing it back^[5-9]. Although the rationale to use LDF to block neoplastic cells back by the IBS device has been investigated on experimental studies, the clinical relevance analysis over patients who underwent LT for HCC has been restricted to a single study^[5]. In the latter case, no differences were observed in recurrence between patients who received IBS and those who did not. However, it was not possible to rule out the possibility that this result was a consequence of a small sample size.

The aim of this study was to evaluate if the use of IBS for HCC patients who underwent LT increases the risk of tumor recurrence. To our knowledge, this is the largest series addressing this question in this population.

MATERIALS AND METHODS

Subjects and data collection

Patients submitted to LT for HCC at Hospital das Clínicas of University of São Paulo Medical School (HCFMUSP) were analyzed from a prospectively maintained database containing demographic, clinical, operative, pathological, and follow-up data and studied retrospectively. Permission was obtained from the informed consent statement and institutional review board according to the institutional policy for protected health information.

All patients presented in this analysis were initially considered to meet the Milan criteria or UCSF criteria^[10,11]. Patients who had detectable extra-hepatic disease during the pre- or intraoperative course and patients with a concurrent second neoplasm were not included. Patients who did not present HCC in the specimen were excluded with the exception of those previously treated with radiofrequency or chemoembolization. Pre-operative imaging modalities to evaluate the extent of intrahepatic disease and to exclude extra-hepatic metastatic sites included

computed tomography and/or magnetic resonance imaging of the chest, abdomen, and pelvis. Model of end-stage liver disease (MELD) scores were calculated using laboratory results collected prior to the LT. The MELD score was calculated using the standard UNOS formula: $MELD = 3.78 \times \ln(\text{bilirubin}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine}) + 6.43$, where bilirubin and creatinine are in mg/dL units and INR is the international normalized ratio. The MELD score was analyzed separately as both continuous and categorical variables (*i.e.*, ≥ 20 vs <20).

The estimated blood loss was not fully available and thus it was not described and analyzed. The intraoperative decision to transfuse either allogeneic or autologous blood was consensual between the surgeon and the anesthesiologist. It was based on hemodynamic status, blood loss, hemoglobin concentration and patient's comorbidities.

Follow-up time was calculated from the date of LT to the date of last clinical encounter captured by the HCFMUSP medical record system or the date of death. Recurrence-free survival (RFS) was calculated from the LT to the first detected recurrence or last follow-up without recurrence. Overall survival (OS) was calculated based on the survivorship status (deceased or alive) at last follow-up.

Blood salvage processing

The blood from the surgical field was collected using a Cell Saver auto-transfusion device (Fresenius C.A.T.S, Terumo Cardiovascular Systems, Germany) and anticoagulated with heparinized saline and stored. The RBC component of aspirated blood was centrifuged and washed with heparinized saline. The RBC concentrates were filtered through an LDF (FTS-RC202, Shuangweibio Corp., Nanjing, China). Processed RBCs were transfused back to the patient when appropriate.

Statistical analysis

Statistical analyses were performed using the Fisher's exact test and the Wilcoxon rank sum test to examine covariate differences between patients who underwent IBS and those who did not. Values are expressed as median (interquartile) or percentage, as appropriate. Survival probabilities were estimated using the Kaplan-Meier method and compared using the Log-Rank test. A Cox regression model was developed to determine factors independently associated with death. The use of IBS was included in the multivariate analysis regardless of its univariate significance. Other factors that were significantly associated with outcomes by univariate analysis (inclusion criterion, $P \leq 0.1$) were entered into a multivariate analysis to test for significance of IBS adjusting for possible confounders. For recurrence assessment, no Cox regression was used since the number of events per variable was not appropriated^[12,13]. A P value < 0.05 was considered significant for univariate and multivariate analyses. All statistical analyses were conducted using STATA v 9.0

Table 1 Clinicopathological distribution according to the use of autologous intraoperative blood salvage for patients with hepatocellular carcinoma who underwent liver transplantation

	Total (%) <i>n</i> = 158	Intraoperative blood salvage		<i>P</i>
		Yes (%) <i>n</i> = 122 (77.2)	No (%) <i>n</i> = 36 (22.8)	
Age ¹	58 (51-62)	58 (51-62)	58 (51-62)	0.958
Male gender	122 (77.2)	95 (77.9)	27 (75)	0.821
BMI ^{1,2}	25.7 (23.6-27.8)	25.7 (23.6-27.8)	25.5 (23.5-2.3)	0.712
Pre-op AFP ³	9.2 (3.7-35.4)	8.9 (3.5-3.6)	10.9 (6.7-33.7)	0.175
Cirrhosis ⁴	135 (88.3)	100 (84.8)	35 (100)	0.014
Alcohol ⁴	22 (14.4)	18 (15.3)	4 (11.4)	0.785
Hepatitis ⁴				
B	20 (13.1)	12 (10.2)	8 (22.9)	0.082
C	97 (63.4)	73 (61.9)	24 (68.6)	0.551
Others ⁴	8 (5.2)	8 (6.8)	0	0.199
Blood type				0.420
A	60 (37)	42 (34.4)	18 (50)	
B	21 (13.3)	17 (13.9)	4 (11.1)	
AB	14 (8.9)	11 (9)	3 (8.3)	
O	63 (39.9)	52 (42.6)	11 (30.6)	
Rhesus ⁵	123 (86.6)	93 (86.1)	30 (88.3)	1.000
MELD ¹	10 (8-15)	10.5 (9-17)	9 (8-13.5)	0.058
Radiofrequency ⁴	4 (2.6)	3 (2.6)	1 (2.8)	1.000
Chemoembolization ⁴	69 (45.1)	53 (45.3)	16 (44.5)	1.000
Alcoholization ⁴	7 (4.6)	5 (4.3)	2 (5.6)	0.668
Graft/body proportion ^{1,2}	1.75 (1.5-2.2)	1.8 (1.5-2.2)	1.7 (1.4- 2.2)	0.454
Number of lesions ¹	2 (1-3)	2 (1-3)	2 (1-3)	0.715
Largest lesion, mm ¹	25 (19-31)	25 (19-30)	25 (18-35)	0.384
Edmond-steiner degree (III and IV) ⁶	88 (59.9)	67 (58.8)	21 (63.5)	0.689
Vascular invasion	53 (33.6)	44 (36.1)	9 (25)	0.236
Microsatellite lesions	26 (16.5)	19 (15.6)	7 (19.4)	0.612
Cholangiocarcinoma	6 (3.8)	6 (4.9)	0	0.338
Recurrence	14 (8.9)	10 (8.2)	4 (11.1)	0.525
Death	52 (32.9)	41 (33.6)	11 (30.6)	0.841

¹Expressed as median (p25-p75); ²*N* = 150; ³*N* = 148; ⁴*N* = 153; ⁵*N* = 142; ⁶*N* = 147. BMI: Body mass index; AFP: Alpha-feto protein; MELD: Model of end-stage liver disease.

(Stata Corp, College Station, TX).

RESULTS

Between January 2002 and September 2012, 158 consecutive patients who underwent potentially curative LT for HCC were included. One hundred and twenty-two (77.2%) patients in the IBS group and 36 (22.8%) patients in the non-IBS group were compared. Patients and clinicopathological presentation were compared between groups and are summarized in Table 1. Briefly, the demographic and clinicopathological characteristics were comparable between the two groups. The only significant difference was the presence of liver cirrhosis, which was more prevalent in the non-IBS group (100% vs 84.8%, $P = 0.014$).

Survival analysis

The median follow-up time for all patients was 27 mo; 25 mo for the group who received IBS and 32 mo for the group who did not ($P = 0.049$). The median follow-

Table 2 Univariate and multivariate analyses for predictors of overall survival

	Total	5-yr survival (%)	Median survival (mo)	Univariate analysis <i>P</i>	HR	95%CI	Multivariate analysis <i>P</i>
Overall	158	59.7	-	-			
Age (\geq 60 yr)	-	-	-	0.133			
Gender				0.097			
Male	122	61.5	-		0.88	0.45-1.74	0.714
Female	36	55.4	-				
BMI (\geq 28)				0.080			
Yes	37	48.2	46		1.55	0.81-2.98	0.186
No	113	63.6	-				
Pre-op AFP (\geq 100 ng/dL)				0.087			
Yes	19	51.8	-		1.50	0.68-3.32	0.316
No	129	60.8	-				
Cirrhosis	-	-	-	0.950			
Alcohol related				0.048			
Yes	22	86.4	-		0.30	0.09-1	0.051
No	131	55.5	-				
Hepatitis B infection	-	-	-	0.156			
Hepatitis C infection	-	-	-	0.130			
Others	-	-	-	0.281			
Blood type	-	-	-	0.470			
Rhesus	-	-	-	0.554			
Radiofrequency	-	-	-	0.821			
MELD (\geq 15)	-	-	-	0.721			
Chemo-embolization	-	-	-	0.877			
Tumor alcoholization	-	-	-	0.118			
Graft/body % (\geq 2)	-	-	-	0.163			
No. of lesions ($>$ 3)	-	-	-	0.819			
Largest lesion (\geq 30 mm)	-	-	-	0.640			
Edmond-Steiner degree				0.013			
III-IV	88	48.9	51		2.19	1.07-4.47	0.031
0-II	59	74.4	-				
Vascular invasion	-	-	-	0.290			
Microsatellite lesions	-	-	-	0.283			
Cholangiocarcinoma	-	-	-	0.957			
IBS				0.510			
Yes	122	59.5	-		1.56	0.74-3.30	0.237
No	36	64.5	-				

BMI: Body mass index; AFP: Alpha-feto protein; IBS: Intraoperative blood salvage; MELD: Model of End-Stage Liver Disease. The number of patients included in multivariate model is 141.

up time for survivors was 38 mo; 37 mo for the group who received IBS and recurred and 41 mo for the group who did not ($P = 0.017$). The estimated 3- and 5-year OS rates were 68% and 59.7%, respectively. When OS was adjusted for the use of IBS or not, no difference was detected ($P = 0.51$), as depicted in the Figure 1A. The univariate and multivariate analyses for death were performed and are shown in Table 2. Briefly, no differences were detected according to MELD either as a continuous variable (recurrence, $P = 0.633$; death, $P = 0.286$) or as binominal, as demonstrated in Tables 2 and 3. Only elevated Edmond-Steiner degree of tumor differentiation (III-IV) remained significant for the risk of death, as shown in Table 2. The estimated 3- and 5-year RFS rates were 87.7% and 83.3%, respectively. When RFS was adjusted for the use of IBS or not, no difference was detected ($P = 0.953$; Figure 1B). The univariate analysis for recurrence is shown in Table

3. Briefly, elevated Edmond-Steiner degree of tumor differentiation (III-IV), pre-operative alpha-feto protein level equal to or higher than 100 ng/dL and presence of microsatellite lesions were independent predictors of recurrence, as demonstrated in Table 3.

Regarding the group of patients who received IBS (122 patients), the infusion volume was additionally analyzed as a continuous variable, and no differences were found in either recurrence ($P = 0.512$) or death ($P = 0.055$), as demonstrated in Figure 2A and B. Analyses of outcomes at 90 d or longer were performed and no differences in recurrence ($P = 0.518$) or death ($P = 0.518$) were detected (Figure 2C and D).

DISCUSSION

The IBS is largely accepted as an option for blood transfusion. However, the contra-indications are based on

Table 3 Univariate analysis for predictors of recurrence

	Total	5-yr survival (%)	Median survival (mo)	Univariate analysis <i>P</i>
Overall	158	83.3	-	-
Age (≥ 60 yr)	-	-	-	0.319
Male gender	-	-	-	0.410
BMI (≥ 28)	-	-	-	0.166
Pre-op AFP (≥ 100 mg/dL)	-	-	-	0.001
Yes	19	59.4	84.5	
No	129	85	-	
Cirrhosis	-	-	-	0.163
Alcohol related	-	-	-	0.207
Hepatitis B infection	-	-	-	0.911
Hepatitis C infection	-	-	-	0.568
Others	-	-	-	0.794
Blood type	-	-	-	0.912
Rhesus	-	-	-	0.494
MELD (≥ 15)	-	-	-	0.694
Radiofrequency	-	-	-	0.758
Chemoembolization	-	-	-	0.133
Tumor alcoholization	-	-	-	0.373
Graft/body % (≥ 2)	-	-	-	0.605
Number of lesions (> 3)	-	-	-	0.496
Largest lesion mm (≥ 30)	-	-	-	0.429
Edmond-Steiner degree	-	-	-	0.0162
III-IV	88	73	84.5	
0-II	59	94.3	-	
Vascular invasion	-	-	-	0.071
Yes	26	74.8	84.5	
No	132	86.3	-	
Microsatellite lesions	-	-	-	0.007
Yes	26	-	-	
No	132	86.5	-	
Cholangiocarcinoma	-	-	-	0.375
IBS	-	-	-	0.953
Yes	122	85	84.5	
No	36	78.8	-	

BMI: Body mass index; AFP: Alpha-feto protein; IBS: Intraoperative blood salvage; MELD: Model of End-Stage Liver Disease.

the use of contaminated blood as in chronic diseases like hepatitis or other viral infections, bile infection or colonization, and intra-operative contamination^[4,8]. The same rationale is applied to avoid tumor dissemination in patients with liver cancer already identified. Although this apprehension has been justifying its practice, no clear relation between the use of IBS and cancer recurrence has already been proved. Operations with high blood loss including cancer surgery have been demanding IBS use, however retrospective series did not show any suggestive association between the increase of recurrence and IBS use^[14].

Concerning HCC patients, IBS use was described in a few series for resection and LT. One series described no increase in recurrence with IBS, showing no differences in higher stages and even better results for patients who used IBS in early stage disease^[15,16]. Two series of LT, respectively, with 31 and 40 patients in the IBS groups vs 16 and 96 patients as control group, were described^[17,18]. Despite the theoretical risk of tumor cell

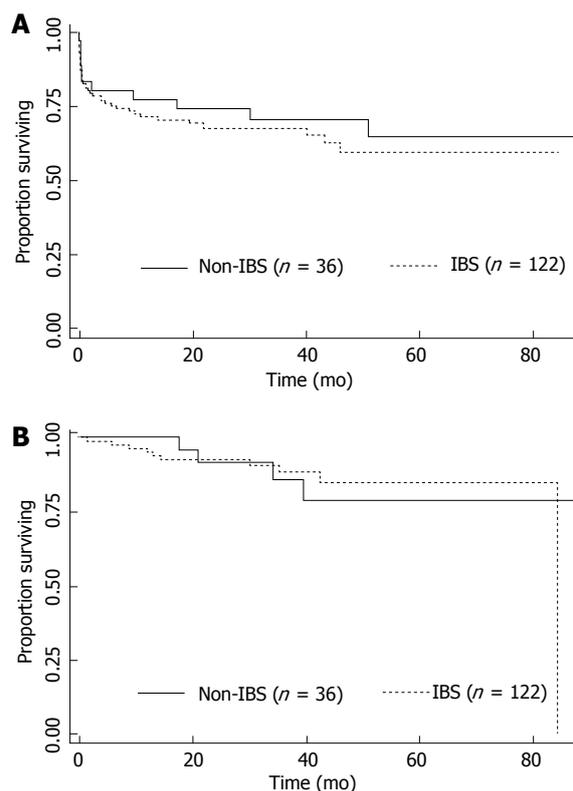


Figure 1 Kaplan-Meier estimates of survival from the date of liver transplantation according to the use of autologous intraoperative blood salvage. A: Overall survival ($P = 0.51$); B: Recurrence free survival ($P = 0.953$). IBS: Intraoperative blood salvage.

dissemination, the recurrence rates were not increased by IBS use in both series^[17,18].

The purpose of our study was to compare long-term outcomes for patients undergoing LT for HCC who received IBS or not. In our study population, the groups were comparable except for the remarkable presence of cirrhosis in the IBS group. As expected, patients with cirrhosis are technically challenging and the blood loss is usually elevated, more justifying IBS. With regard to oncologic outcomes, the use of IBS or not was not significantly associated with recurrence or death. The predictors associated with recurrence were presence of satellite lesions and elevated Edmond-Steiner tumor degree. This was also an independent predictor of death in the multivariate model. The principal finding of this study is that in a large patient population from a single institution there were no measurable differences in outcomes based on the IBS use for patients who underwent LT for HCC.

Regarding only the IBS group, differences in the volumes infused were associated with death but not with recurrence, as depicted in Figure 2. The volume infused changed when the time point of 90 d was used. In the earlier period, higher volumes were associated with death but not with recurrence. This performance translates the IBS volume as surrogate of estimated blood loss, which is an independent predictor of mortality and transfusion as well^[19]. Patients in the earlier

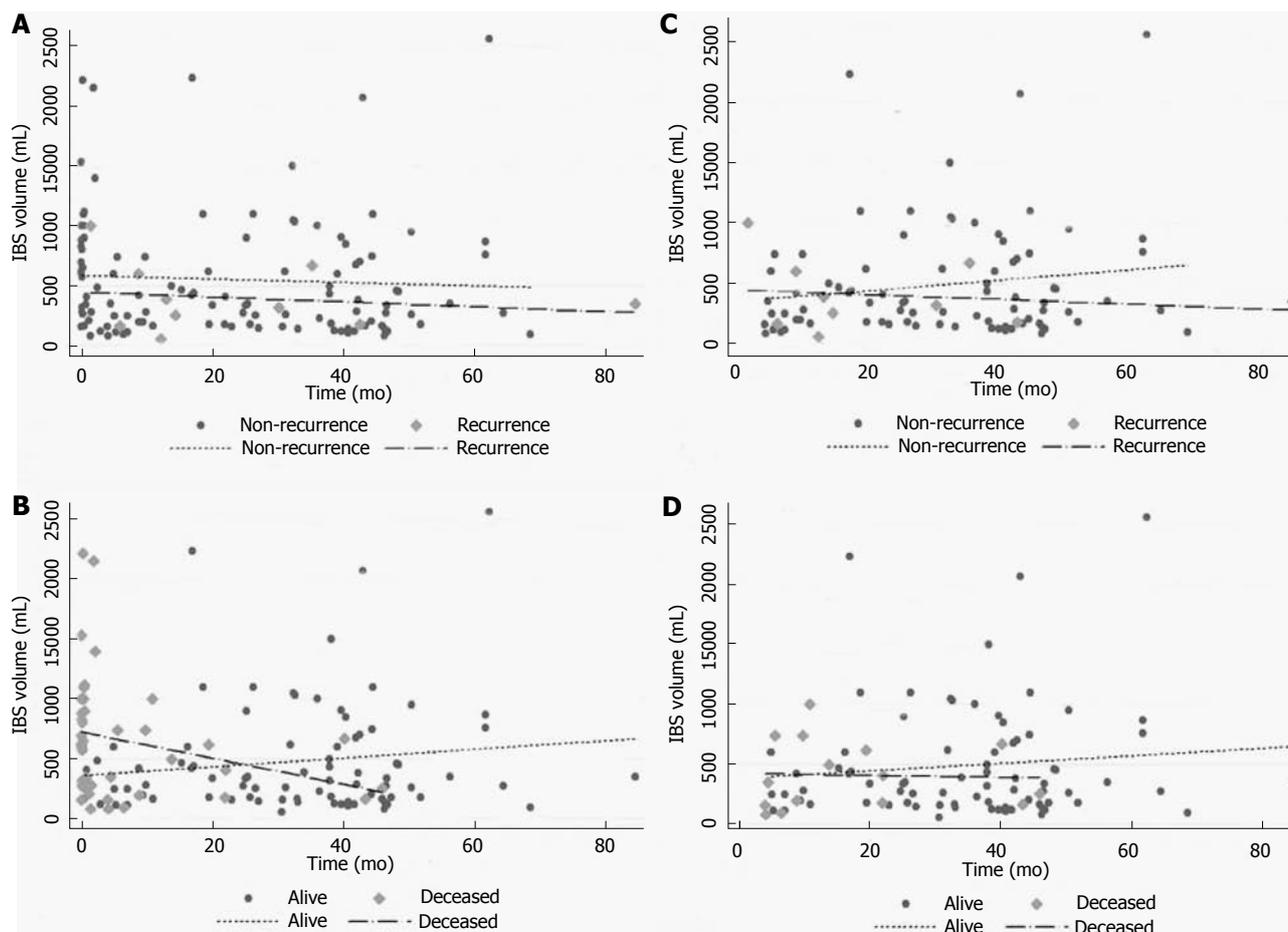


Figure 2 Scatter plots of the infusion volume of autologous intraoperative blood salvage over time. Overall distribution (total, $n = 122$) according to the time for recurrence (A: Recurrence, 10/91) and death (B: Death, 41/92). Distribution at 90 d and longer according to the time for recurrence (C: Recurrence, 9/91) and death (D: Death, 15/92). IBS: Intraoperative blood salvage.

period died in a short follow-up period and they could not have presented recurrence. With regard to longer follow-up (90 d or longer), the IBS volumes fit similarly for the distribution of recurrence or death. Long-term outcomes were not affected for the IBS volume in our series.

The limitations of the study are those associated with the immeasurable biases seen in all retrospective studies. We recognize that selection bias based on several nonobjective, undocumented criteria may have contributed to some of the differences between the two study groups. The estimated blood loss was not fully available and thus it was not described or analyzed.

The major finding of this analysis is the lack of any association between the use of IBS and oncologic outcomes. The results of this study should not be misinterpreted as an endorsement for the IBS use for all cancer patients. On the contrary, our data claim for more translational and clinical investigations of this issue. The operative hemorrhage in LT remains significant and blood transfusion is often demanded. The IBS should be applied as much as necessary, however the rationale of tumor cell reinfusion is a common concern^[4,14,17,18,20-22]. Studies *in vitro* and retrospective series suggest that the use of LDF is effective enough

to avoid tumor cell recirculation^[5-7]. We believe that this finding is convincing and perhaps it is a reasonable explanation for no differences in recurrence or death in our series, since the LDF was used in all cases.

Moreover, a recent meta-analysis, including only non-randomized trials, showed an increase of risk for death and recurrence in patients with HCC who received allogeneic blood transfusion during hepatic resection^[23]. Patients in the allogeneic group had a 16% more chance of recurrence at 5 years as well as a 60% more chance of all-case death in the same period. The reasons for the worse outcomes remain uncertain but it has been assumed that suppressive effects in the host immune system may have been responsible. The postulated mechanisms are allogeneic mononuclear cells; leucocytes-derived soluble mediators; and soluble HLA peptides circulating in allogeneic plasma inducing the host immune suppression^[24]. These effects could be prevented by the autologous transfusion^[24].

In summary, the present study shows that in a large consecutive series of patients undergoing LT for HCC in this single institution, there were no measurable differences in RFS or OS between patients who received IBS or not. With the lack of randomized clinical trials comparing the use of IBS for oncologic patients, its use could

be considered a reasonable option for individualized patients. Based on these data, a trial looking for no inferiority comparing the use of IBS and conventional blood transfusion for LT for HCC is justified and should be designed to detect small differences in outcomes.

COMMENTS

Background

Blood transfusion is usually necessary for liver transplantation (LT). Intraoperative blood salvage has generally been used in LT to avoid deleterious effect of allogeneic blood transfusion. However, autologous blood transfusion has not been recommended in patients with hepatocellular carcinoma (HCC) since there is a putative risk of reinfusion of neoplastic cells.

Research frontiers

Although there is a putative risk of reinfusion of cancer cells into circulation during surgery, there is no data yet demonstrating that it would really impact on oncologic outcomes. This study did not demonstrate impact on clinical and oncologic outcomes. However, since the data are retrospective, our finding claims for trials looking for no inferiority comparing the two modalities of blood transfusion in patients who underwent LT for HCC, to detect small differences in outcomes.

Application

This study addresses an alternative option for allogeneic blood transfusion during LT for HCC. The autologous blood salvage in LT, in this series, did not impact recurrence or death. This suggests that autologous blood transfusion should be considered an option avoiding the deleterious effects of allogeneic blood transfusion.

Innovations and breakthroughs

The use of intra-operative blood salvage would have immunological and economic impact during postoperative course. Circulating cancer cells were already demonstrated, however it also seems that leucocyte filters are safe enough to block those cells. Then, the use of auto-transfusion devices associated with leucocytes filters seems to be a potential resource to help patients who undergo LT for HCC

Terminology

IBS: Autologous intraoperative blood salvage; HCC: Hepatocellular carcinoma; LDF: Leucocyte depletion filter; LT: Liver transplantation; MELD: Model of End-Stage Liver Disease; OS: Overall survival; RFS: Recurrence free survival; RBC: Red blood cell.

Peer-review

Autologous IBS is generally used in liver transplantation to minimize the effect of intraoperative bleeding. However, the peripheral blood of HCC patients may be contaminated with cancer cells or cancer-inducing virus, which can lead to potential risks of recurrence. In this study, authors investigated the association between the intraoperative use of IBS and survival of HCC patients. According to the data of a postoperative follow-up cohort, they reported that the use of IBS cannot influence the survival of HCC patients. This is an interesting study and is useful for clinicians.

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Laparoscopic surgery for small-bowel obstruction caused by Meckel's diverticulum

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Abstract

A 26-year-old woman was referred to our hospital because of abdominal distention and vomiting. Contrast-enhanced computed tomography showed a blind loop of the bowel extending to near the uterus and a fibrotic band connecting the mesentery to the top of the bowel, suggestive of Meckel's diverticulum (MD) and a mesodiverticular band (MDB). After intestinal decompression, elective laparoscopic surgery was carried out. Using three 5-mm ports, MD was dissected from the surrounding adhesion and MDB was divided intracorporeally. And subsequent Meckel's diverticulectomy was performed. The presence of heterotopic gastric mucosa was confirmed histologically. The patient had an uneventful postoperative course and was discharged 5 d after the operation. She has remained healthy and symptom-free during 4 years of follow-up. This was considered to be an unusual case of preoperatively diagnosed and laparoscopically treated small-bowel obstruction due to MD in a young adult woman.

Key words: Surgery; Human; Meckel's diverticulum; Small-bowel obstruction; Laparoscopic surgery

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Core tip: Meckel's diverticulum (MD) is a rare innate anomaly of the gastrointestinal tract caused by incomplete obliteration of the omphalomesenteric duct. It sometimes causes small bowel obstruction. However, as its symptoms are so non-specific, it may be difficult to make a correct diagnosis without exploratory laparotomy. This is a successful case of small-bowel obstruction caused by MD that was diagnosed preoperatively using multi-

dimensional contrast-enhanced computed tomography and treated by elective laparoscopic surgery.

Matsumoto T, Nagai M, Koike D, Nomura Y, Tanaka N. Laparoscopic surgery for small-bowel obstruction caused by Meckel's diverticulum. *World J Gastrointest Surg* 2016; 8(2): 169-172 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i2/169.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i2.169>

INTRODUCTION

Meckel's diverticulum (MD) is one of the most common congenital anomaly of the gastrointestinal tract that results from an incomplete obliteration of the omphalomesenteric duct^[1,2]. It has an incidence of 1%-2% among the general population, and most cases remain asymptomatic^[2]. The rate of developing complicated MD is reported to be about 4% throughout lifetime^[3], which comprises bleeding, inflammation or obstruction.

Intestinal obstruction may occur in cases where there is a volvulus or an internal hernia around a diverticulum, intussusception, or incarceration of the diverticulum in an inguinal (Littre) hernia^[1]. However, as its symptoms, such as abdominal pain, distention, vomiting or constipation, are so non-specific, it may be difficult to make a correct diagnosis, and exploratory laparotomy is often required.

Here we report a case of small-bowel obstruction caused by MD that was diagnosed preoperatively using multi-dimensional contrast-enhanced computed tomography (CECT) and treated by elective laparoscopic surgery.

CASE REPORT

A 26-year-old woman was admitted to our hospital complaining of abdominal pain and recurrent vomiting. She had been hospitalized because of ovarian hyperstimulation syndrome 2 years previously, and had also suffered an episode of small-bowel obstruction 1 year prior to admission, which had been diagnosed as food impaction. She had no episode of hematochezia.

Physical examination demonstrated abdominal distention, with a soft abdomen and no tenderness or rebound pain. Her bowel sounds were hyperactive. Results of a hematologic examination were normal, and a urine pregnancy test gave a negative result.

Abdominal plain X-ray examination demonstrated a ladder-like series of distended small-bowel loops (Figure 1). Multi-dimensional CECT showed a blind-ending U-shaped loop of bowel in the pelvis and a fibrotic band connecting the mesentery to the blind end of the bowel, suggesting MD and a mesodiverticular band (MDB) (Figure 2). A change in the caliber of the ileum was



Figure 1 Abdominal plain X-ray examination demonstrated a ladder-like series of distended small-bowel loops.



Figure 2 Contrast-enhanced computed tomography (coronal section image) showing a blind loop of the bowel extending near the uterus (arrowhead) and a fibrotic band connecting the mesentery to the top of the bowel (arrow) suggesting Meckel's diverticulum and a mesodiverticular band. The terminal ileum appeared to be conglutinated to the band and a change in caliber was ascertained.

evident adjacent to the band.

We diagnosed the patient as having small-bowel obstruction, probably caused by adhesion to the MDB of MD, without any sign of vascular compromise.

A long tube was placed and her small intestine was successfully decompressed. After the tube had been removed, scintigraphy with 99mTc-Na-pertechnetate was performed, and this revealed uptake in the lower abdomen (Figure 3).

Although surgical treatment was proposed, the patient expressed a wish to temporarily leave hospital because of pressing business matters. She was therefore discharged after 1 wk of hospitalization.

Two months after discharge, we performed elective laparoscopic surgery using three 5-mm ports. MD was dissected from the surrounding adhesion and MDB was divided intracorporeally. Then subsequent Meckel's diverticulectomy was performed extracorporeally *via* a 2 cm mini-laparotomy. The postoperative course was uneventful and the patient was discharged on postoperative day 5, and she has since remained healthy and symptom-free during 4 years of follow-up.

Histological examination confirmed the presence of

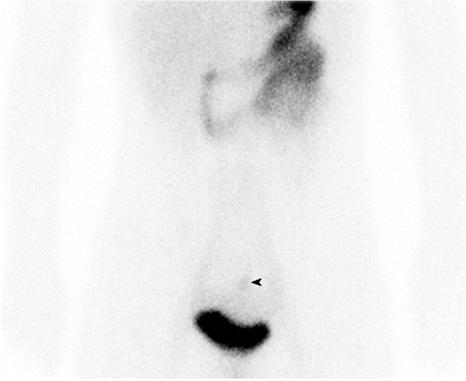


Figure 3 ^{99m}Tc -Na-pertechnetate revealed uptake in the lower abdomen (arrowhead).



Figure 4 The resected Meckel's diverticulum and adjunctive small intestine. The cut mesodiverticular band is seen at the blind end of the diverticulum (arrowhead).

a MDB (Figure 3) and heterotopic gastric mucosa in the mucosa of the diverticulum (Figures 4 and 5).

DISCUSSION

MD is an innate anomaly of the gastrointestinal system caused by incomplete closure of the omphalomesenteric duct^[1]. MD was so named in 1809 after its discoverer, the German anatomist Johann Friedrich Meckel. The presence of MD can be explained in terms of intrauterine evolution of the bowel. The omphalomesenteric duct is the embryonic communication between the yolk sac and the developing midgut. By the 10th week of embryogenesis, the omphalomesenteric duct becomes a thin fibrous band. However, incomplete atrophy of the omphalomesenteric duct may result in a variety of anomalies, they are, umbilicoileal fistula, omphalomesenteric duct cyst or MD^[4].

The diverticulum originates from the antimesenteric border of the small bowel, within 40-100 cm of the ileocecal valve^[4,5]. Blood is supplied *via* the vitelline artery, which is a branch of the ileocecal artery. The diverticulum is ordinarily lined by intestinal mucosa, but the heterotopic gastric mucosa or pancreatic tissue was frequently observed by the histological examination^[4,5].

Reportedly, 25% of MD become symptomatic

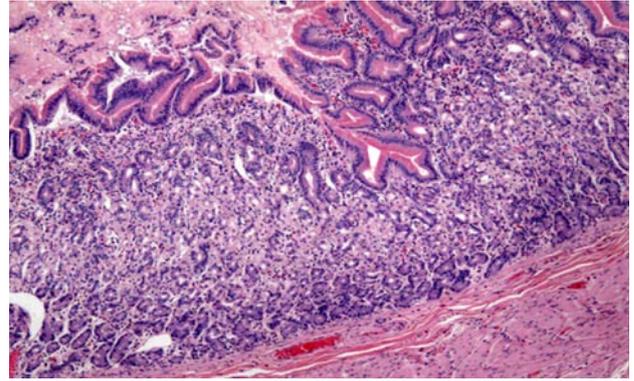


Figure 5 Histological features of the diverticulum. Heterotopic gastric mucosa was seen in the mucosa of the diverticulum (hematoxylin-eosin staining, $\times 100$).

throughout the lifetime^[4]. Bleeding, inflammation or obstruction are the main cause of complication^[2]. Statistically, hemorrhage is the most common presentation in children aged 2 years or younger^[6], whereas intestinal obstruction is the commonest presentation among adults^[7]. Intestinal obstruction due to MD is the most common presentation in adults and the second most common in children^[6,7].

The clinical symptoms are non-specific; patients may have abdominal pain and distension, vomiting or constipation. MD-related small-bowel obstruction occurs so infrequently that most articles have reported only small series or isolated cases. Moreover, many patients with MD have non-specific abdominal symptoms, often making a correct preoperative diagnosis difficult, especially in an emergency setting^[8,9].

The present case illustrates that abdominal CECT has the potential to identify the MDB and MD as the cause of small-bowel obstruction. Multi-dimensional CECT, especially in the coronal view, may yield more information about the cause of the small-bowel obstruction and the presence of a MDB. CECT is less invasive and speedier than other examinations such as Tc scintigraphy, interventional radiology or a gastrointestinal series, and therefore is more preferable in an emergency setting, yielding information about the cause of the small-bowel obstruction, such as internal hernia or other intestinal mass. CECT can also reveal the presence of strangulation. In the present case, we were able to confirm by CECT that there was no sign of vascular compromise, enabling us to start intestinal decompression in preparation for elective laparoscopic surgery.

Laparoscopic surgery for MD has been widely used recently. However, as it is not clear whether laparoscopic surgery is preferable to laparotomy in the setting of small-bowel obstruction^[10], we performed intestinal decompression first. MD can be resected either extracorporeally or intracorporeally^[9,11]. Although some reports have indicated intracorporeal laparoscopic diverticulectomy, we selected laparoscopy-assisted diverticulectomy *via* a small incision in the lower abdomen to allow palpation of the MD, thus helping

to rule out any mass or thickening of the base, and allowing a more complete assessment for the presence of any ectopic gastric mucosa^[12].

In conclusion, we successfully treated MD causing small bowel obstruction by laparoscopic surgery. Multi-dimensional CECT may yield to detect both the etiology of small-bowel obstruction and the presence of strangulation in such unusual settings.

COMMENTS

Case characteristics

A 26-year-old woman with past history of small bowel obstruction presented with abdominal pain and recurrent vomiting.

Clinical diagnosis

Physical examination demonstrated abdominal distention, with a soft abdomen and no tenderness or rebound pain. Her bowel sounds were hyperactive.

Differential diagnosis

Small bowel obstruction due to food impaction, due to internal hernia, or due to intestinal tumor.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Multi-dimensional contrast enhanced computed tomography showed a blind-ending U-shaped loop of bowel in the pelvis and a fibrotic band connecting the mesentery to the blind end of the bowel, suggesting Meckel's diverticulum (MD) and a mesodiverticular band (MDB).

Pathological diagnosis

MDB and heterotopic gastric mucosa in the mucosa of the MD.

Treatment

Long tube decompression and subsequent laparoscopic diverticulectomy.

Related reports

MD occurs with an incidence of 1%-2% among the general population, and most cases remain asymptomatic. Complications result most commonly from bleeding, inflammation, or obstruction.

Term expression

The MDB is an embryologic remnant of the vitelline circulation which carries the arterial supply to the Meckel's diverticulum. In the event of an error of involution, a patent or nonpatent arterial band persists and extends from the mesentery to the apex of the anti-mesenteric diverticulum.

Experiences and lessons

This is a successful case of small-bowel obstruction caused by MD that was

diagnosed preoperatively using multi-dimensional contrast-enhanced computed tomography and treated by elective laparoscopic surgery.

Peer-review

This is an interesting report on a rare etiologic factor of bowel obstruction in young adults.

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Pneumatosis intestinalis with obstructing intussusception: A case report and literature review

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Abstract

Pneumatosis intestinalis (PI) often represents a benign condition that should not be considered as an argument for surgery. We report a patient with PI and obstructing intussusception who underwent urgent colectomy and review the literatures regarding PI with intussusception. A 20-year-old man presented at our hospital with a 3-d intermittent lower abdominal pain history. He underwent steroid therapy for membranoproliferative glomerulonephritis for 4 years. Computed tomography revealed ascending colon intussusception with air within the wall. Intraoperative colonoscopy revealed numerous soft polypoid masses with normal overlying mucosa and right hemicolectomy was performed. Histological examination of colonic wall sections revealed large cysts in the submucosal layer. The pathological diagnosis was PI. Nine cases of intussusception associated with primary PI have been reported. Although primary PI often represents a benign condition that should not be considered as an argument for surgery, if the case involves intussusception and obstruction, emergent laparotomy should be considered.

Key words: Pneumatosis intestinalis; Intussusception; Urgent surgery; Immunosuppressive drug; Ischemia of the intestine

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Core tip: We report a patient with pneumatosis

intestinalis (PI) and obstructing intussusception who underwent urgent colectomy and review the literatures regarding PI with intussusception. A 20-year-old man presented at our hospital with abdominal pain, and has undergone steroid therapy for 4 years. Computed tomography revealed ascending colon intussusception with air within the wall, and colectomy was performed. Histological examination of colonic wall sections revealed large cysts in the submucosal layer. Nine cases of intussusception associated with primary PI have been reported. Although primary PI often represents a benign condition, if the case involves intussusception and obstruction, emergent laparotomy should be considered.

Itazaki Y, Tsujimoto H, Ito N, Horiguchi H, Nomura S, Kanematsu K, Hiraki S, Aosasa S, Yamamoto J, Hase K. Pneumatosis intestinalis with obstructing intussusception: A case report and literature review. *World J Gastrointest Surg* 2016; 8(2): 173-178 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i2/173.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i2.173>

INTRODUCTION

Pneumatosis intestinalis (PI) is a rare condition characterized by the presence of gas within the wall of the gastrointestinal tract. This condition can result from a wide variety of pathologies, including chronic obstructive lung disease, collagen diseases, necrotizing enterocolitis in premature infants, intestinal infections, ischemic bowel disorders, and immunosuppressive drug therapy^[1]. PI often represents a benign condition that should not be considered as an argument for surgery^[2]; however, immediate surgery may be required in some life-threatening circumstances such as the presence of bowel obstruction, perforation, or ischemia^[3].

Here we describe a case of PI in the ascending colon with obstructing intussusception for which urgent surgery was performed, and review the available published literature on PI with intussusception. Written informed consent was obtained from the patient.

Search strategy

The literature search strategy for this study was based on published systematic review guidelines^[4]. Literature databases such as PubMed MEDLINE (National Library of Medicine) were searched from 1980 to 2015 using the following medical subject headings: "PI (or Pneumatosis cystoides intestinalis)" and "intussusception" or "PI (or Pneumatosis cystoides intestinalis)" and "invagination". In addition, references within the retrieved articles were reviewed. We identified 24 manuscripts using this search strategy and selected 8 case reports for this review. Nineteen articles were excluded because their content was not applicable to this review and 7 articles were excluded because they were not written in English.

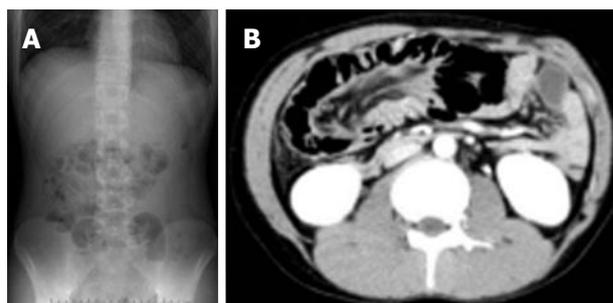


Figure 1 Abdominal radiograph. It showing multiple distended loops of small bowel with fluids and multiple air pockets (A) and computed tomography showing multiple gas-filled cysts, a streaky collection of air in the bowel wall, and an intussusception of the colon (B).



Figure 2 Intraoperative findings showed intussusception of the ascending colon with palpable soft polypoid masses.

CASE REPORT

A 20-year-old man presented our hospital with a 3-d history of intermittent lower abdominal pain. He had been on steroid therapy (methylprednisolone 25 mg/d) for membranoproliferative glomerulonephritis for 4 years. A physical examination revealed tenderness in the lower right quadrant of the abdomen. His body temperature was 37.7 °C and pulse was 81 beats per minute. All serum levels tested were within the normal range, with the exception of serum total bilirubin (1.5 mg/dL; normal range, 0.3-1.2 mg/dL). White blood cells (WBCs) (21000/μL), hemoglobin concentration (17.1 g/dL), and the C-reactive protein concentration (0.5 mg/dL) were also elevated, indicating acute inflammation and dehydration, with a level of base excess of 2.4 mmol/L. Abdominal X-ray showed multiple air-filled lucencies in the right upper quadrant and multiple distended loops of small bowel with fluid (Figure 1A). Computed tomography (CT) revealed intussusception of the ascending colon with air within the wall (Figure 1B). We performed an urgent laparotomy under the diagnosis of acute abdomen with obstructing intussusception. The colo-colic intussusception that was caudal to the polypoid lesion easily resolved using Hutchinson's maneuver and soft polypoid masses were palpable from the cecum to the ascending colon (Figure 2). Intraoperative colonoscopy revealed the presence of numerous soft polypoid

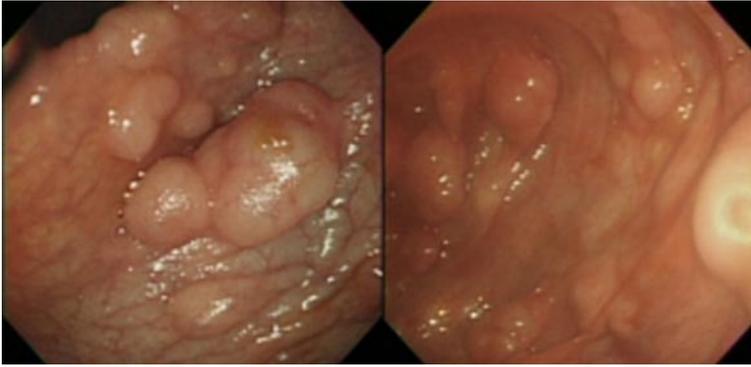


Figure 3 Intraoperative colonoscopy showed numerous soft polypoid masses with normal overlying mucosa located between the ascending colon and middle part of transverse colon.

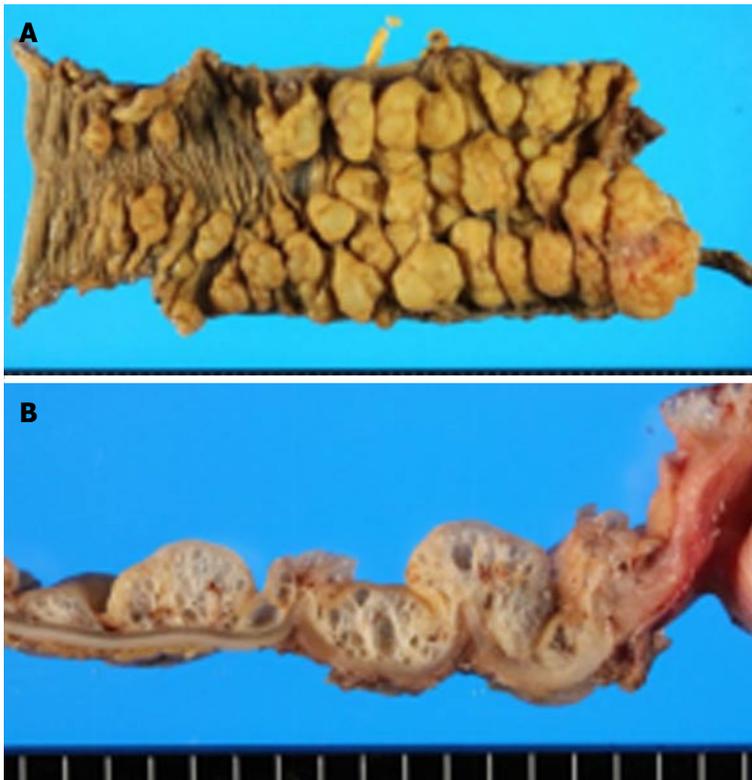


Figure 4 The resected specimen revealed polypoid lesions with normal mucosa and cystic structures (A), submucosal cysts had a spongy consistency (B).

masses with normal overlying mucosa (Figure 3). A right hemicolectomy was performed because other polyposis diseases or intussusception relapse could not be ruled out, and to help make a final pathological diagnosis. A gross examination showed that the mucosa of the resected colon appeared normal with no evidence of ulceration or ulcer-related lesions, but instead a number of soft, yellowish cystic masses (Figures 4). A histological examination of sections of the colonic wall revealed large cysts in the submucosal layer (Figure 5A). The cysts were empty, but were surrounded by a distinct fibrous wall and were lined by macrophages that frequently coalesced to form multinucleated giant cells (Figure 5B). Based on these findings, the patient was diagnosed with pneumatosis cystoides intestinalis. The postoperative course was uneventful and the patient was discharged on postoperative day 9. No recurrence was noted on radiographic imaging performed on postoperative 14 mo.

DISCUSSION

Classically, PI can be subdivided into 2 distinct groups: primary PI, representing 15% of cases, and secondary PI, representing 85% of cases^[5]. Secondary PI, where the gas accumulates as linear collections and reflects a pathological condition, has been attributed to endoscopic procedures, immunological disturbances, bowel mucosal disruptions, and intra-abdominal pathologies. In contrast to secondary PI, primary PI is characterized by intramural gas that is cystic and benign in nature and does not always require urgent laparotomy^[6]. Although PI may occur in association with acquired immunodeficiency^[7], transplant status^[8], cancer treatment^[9,10], scleroderma^[11], cystic fibrosis^[12], systemic lupus^[13], inflammatory bowel disease^[2], intestinal ischemia^[14], colitis^[15], or trauma^[16], the exact etiology of both primary and secondary PI remains unknown.

There is currently no consensus on the appropriate

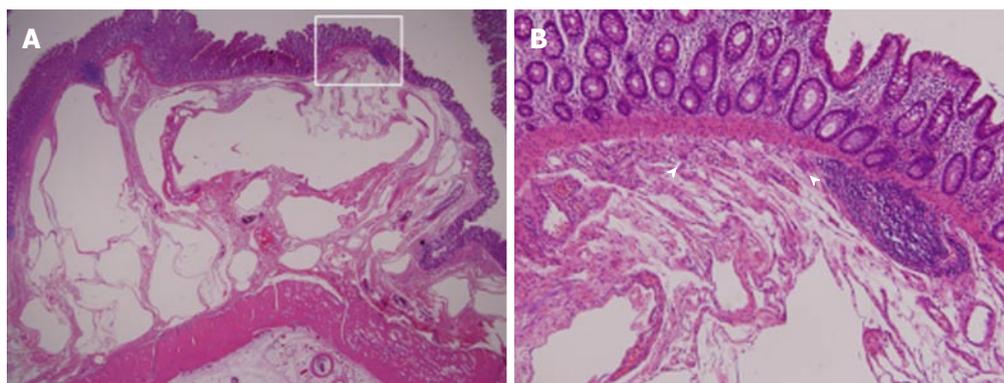


Figure 5 Histopathological examination revealed cystic air-filled spaces within the submucosa, which were partially lined by clusters of foreign-body macrophages (arrow heads) (hematoxylin-eosin stain; A: × 40, B: × 400).

Table 1 Reported cases that had intussusception associated with primary pneumatosis intestinalis										
Ref.	Year	Sex	Immunosuppressive drug	Ischemia	PVG	Site	Treatment	Indication of surgery	Co-morbidity	
Nagata <i>et al</i> ^[20]	23 yr	Male	No	No	No	A/C	CS→Surgery	Abdominal pain	None	
Emanuel <i>et al</i> ^[21]	48 yr	Male	NR	NR	NR	D/C	Surgery	Obstruction	Hybrid perineurioma-schwannoma	
Sugita <i>et al</i> ^[22]	5 yr	Female	Yes	No	Yes	A/C	BE	-	CML	
Stern <i>et al</i> ^[23]	32 yr	Male	No	No	No	A/C	BE	-	None	
Morrison <i>et al</i> ^[24]	3 mo	NR	Yes	Yes	NR	T/C	BE→Surgery	could not resolved intussusception	Peter's anomaly	
Dubinsky <i>et al</i> ^[25]	1 yr	Male	Yes	NR	NR	A/C	Surgery	Obstruction	Crohn's disease	
Navarro <i>et al</i> ^[26]	13 yr	Male	No	No	NR	T/C	BE→Surgery	Obstruction	None	
Ahrar <i>et al</i> ^[27]	29 yr	Male	No	No	NR	A/C	BE→Surgery	NR	None	
Our case	20 yr	Male	Yes	No	No	A/C	Surgery	Obstruction	MPGN	

NR: Not referred; PVG: Portal venous gas; A/C: Ascending colon; D/C: Descending colon; T/C: Transverse colon; CS: Colonoscopy; BE: Barium enema; CML: Chronic myelogenous leukemia; MPGN: Membranoproliferative glomerulonephritis.

management of PI, although many mechanical, bacterial, and pulmonary hypotheses have been proposed regarding PI etiopathogenesis, and its management can be challenging for surgeons^[17]. Many studies have investigated the use of risk factors as predictors of a compromised bowel and the probable need for surgery, such as patient age and the presence of hypotension, peritonitis, renal failure, or serum lactate levels^[18]. Other studies have attempted to create algorithms for PI management that, while helpful, are also tedious and may be difficult to apply clinically in circumstances where the patient requires rapid evaluation^[19]. In this case, we performed urgent laparotomy because he had intestinal obstruction due to intussusception and several inflammatory symptoms.

Although the course of primary PI may be benign or may not frequently result in a need for urgent surgery, laparotomy should be considered in cases with intestinal obstruction due to intussusception. To our knowledge, 9 reported cases, including the present case, had intussusception associated with primary PI (Table 1)^[20-27]. The mean patient age was 19.0 ± 16.0 years (range 0-48 years), which is younger than has been reported previously^[19]. It is notable that more than

44% of these patients received an immunosuppressive drug, and few patients appeared to have intestinal ischemia. All patients had the intussusception in the colon, particularly on its right side. Five out of 9 patients had co-morbidities, most of which required an immunosuppressive drug. With the exception of the article placed as reference number 22, no other articles referred to the presence of portal venous gas, which often indicates ischemic bowel disease. Only 2 cases experienced successful reduction of the intussusception with barium enema^[22,23], although long-term outcomes were not reported. Among the 4 cases with initial successful reduction of the intussusception by colonoscopy or barium enema, all of these patients eventually needed surgery: One case had persistent abdominal pain after solution of intussusception; in one case, the intussusception could not be completely resolved; one case had bowel obstruction; and for one case the indication of surgery was not clearly stated. For the present case, we performed an urgent laparotomy because of bowel obstruction with intussusception of the ascending colon. Right hemicolectomy for this case was performed because of the possibility of there being another polyposis disease present and because relapse

of the intussusception could not be ruled out.

In conclusion, although primary PI often represents a benign condition that should not be considered as an argument for surgery, emergent laparotomy should be considered for cases with intussusception, obstruction, and unsuccessful resolution of intussusception by colonoscopy or barium enema.

COMMENTS

Case characteristics

A 20-year-old man presented our hospital with a 3-d history of intermittent lower abdominal pain.

Clinical diagnosis

The authors performed an urgent laparotomy under the diagnosis of acute abdomen with obstructing intussusception.

Differential diagnosis

A right hemicolectomy was performed because other polyposis diseases or intussusception relapse could not be ruled out.

Laboratory diagnosis

All serum levels tested were within the normal range, with the exception of serum total bilirubin (1.5 mg/dL; normal range, 0.3-1.2 mg/dL). White blood cells (WBCs) (21000/ μ L), hemoglobin concentration (17.1 g/dL), and the C-reactive protein concentration (0.5 mg/dL) were also elevated.

Imaging diagnosis

Computed tomography revealed intussusception of the ascending colon with air within the wall.

Pathological diagnosis

A gross examination showed that the mucosa of the resected colon appeared normal with no evidence of ulceration or ulcer-related lesions, but instead a number of soft, yellowish cystic masses, suggesting that to be pneumatosis cystoides intestinalis.

Treatment

A right hemicolectomy was performed because other polyposis diseases or intussusception relapse could not be ruled out, and to help make a final pathological diagnosis.

Related reports

To our knowledge, 9 reported cases, including the present case, had intussusception associated with primary pneumatosis cystoides intestinalis.

Experiences and lessons

Although primary pneumatosis intestinalis (PI) often represents a benign condition that should not be considered as an argument for surgery, emergent laparotomy should be considered for cases with intussusception, obstruction, and unsuccessful resolution of intussusception by colonoscopy or barium enema.

Peer-review

This is an interesting article summarising a case of PI and intussusception with a review of the cases in the literature.

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Assessment of lymph node involvement in colorectal cancer

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Abstract

Lymph node metastasis informs prognosis and is a key factor in deciding further management, particularly adjuvant chemotherapy. It is core to all contemporary staging systems, including the widely used tumor

node metastasis staging system. Patients with node-negative disease have 5-year survival rates of 70%-80%, implying a significant minority of patients with occult lymph node metastases will succumb to disease recurrence. Enhanced staging techniques may help to identify this subset of patients, who might benefit from further treatment. Obtaining adequate numbers of lymph nodes is essential for accurate staging. Lymph node yields are affected by numerous factors, many inherent to the patient and the tumour, but others related to surgical and histopathological practice. Good lymph node recovery relies on close collaboration between surgeon and pathologist. The optimal extent of surgical resection remains a subject of debate. Extended lymphadenectomy, extra-mesenteric lymph node dissection, high arterial ligation and complete mesocolic excision are amongst the surgical techniques with plausible oncological bases, but which are not supported by the highest levels of evidence. With further development and refinement, intra-operative lymphatic mapping and sentinel lymph node biopsy may provide a guide to the optimum extent of lymphadenectomy, but in its present form, it is beset by false negatives, skip lesions and failures to identify a sentinel node. Once resected, histopathological assessment of the surgical specimen can be improved by thorough dissection techniques, step-sectioning of tissue blocks and immunohistochemistry. More recently, molecular methods have been employed. In this review, we consider the numerous factors that affect lymph node yields, including the impact of the surgical and histopathological techniques. Potential future strategies, including the use of evolving technologies, are also discussed.

Key words: Colorectal cancer; Lymphatic metastases; Lymph node metastasis; Neoplasm staging; Tumor node metastasis classification; Sentinel lymph node biopsy; Lymph node excision; Histopathological assessment; Surgery

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Core tip: The number of lymph nodes in surgical resection specimens is influenced by numerous factors. Good practice by surgeons and pathologists is essential to maximize lymph node yields, but there are non-modifiable factors related to patient and tumour. Extended lymphadenectomy, extra-mesenteric lymph node dissection, high arterial ligation and complete mesocolic excision, all increase lymph node yields, but a definite benefit in prognosis is not proven and the optimal extent of surgical resection remains contentious. Conversely, further development in sentinel lymph node biopsy techniques could allow selective lymphadenectomy, whilst providing appropriate information to guide adjuvant therapy.

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INTRODUCTION

Lymph node metastasis (LNM) informs prognosis and is a key factor in deciding further management, particularly adjuvant chemotherapy. As such, lymph node metastasis has had a role in colorectal cancer staging from the earliest classification systems. Its importance in prognosis has been borne out by successive classification systems and is reflected in all contemporary staging systems, in particular the widely used tumor node metastasis (TNM) staging system, developed and maintained by the Union for International Cancer Control and American Joint Committee on Cancer (AJCC).

Patients with node-negative disease have 5-year survival rates of 70%-80% in contrast to 30%-60% in those with node-positive disease. Survival is improved in the latter group by adjuvant chemotherapy. The 20%-30% disease recurrence in apparently completely excised tumours without lymph node metastases is thought to be due to occult lymph node disease. If this subset could be identified by better lymph node staging, they might also benefit from adjuvant chemotherapy.

There are several prognostic factors other than lymph node disease status that also identify patients who might benefit from adjuvant treatment. These include venous invasion, peri-neural invasion, tumour perforation, serosal involvement and incomplete resection^[1,2]. However, lymph node assessment remains a mainstay of deciding adjuvant chemotherapy. To achieve accurate staging, surgeons and pathologists must exercise due diligence in their respective practices. Most authorities recommend examination of a minimum of 12 lymph nodes, although the evidence base for this is weak. Behind this apparently simple number are numerous complex issues, many without

clear solutions. In this review, we consider the factors that affect lymph node yields including the influence of surgical and histopathological techniques. Evolving concepts and technologies that are not in widespread use, such as sentinel lymph node evaluation, are also discussed.

FACTORS INFLUENCING LYMPH NODE ASSESSMENT

In order to identify and maximise the diagnostic information from lymph nodes within a specimen, it is important to understand the factors that influence the lymph node harvest (LNH). This relates to a range of different factors: The pathologist, the surgeon and factors inherent to the patient and tumour. While tumour and patient characteristics cannot be changed, the pathologist can employ various techniques to maximise both the LNH and gain additional diagnostic information from enhanced study of the lymph node. The surgeon can modify the surgical procedure to excise more tissue or use ancillary techniques to aid selection and examination of lymph nodes by the pathologist.

ROLE OF THE HISTOPATHOLOGIST

Contemporary lymph node staging

There are several tumour staging systems, of which the TNM staging system is the most widely used internationally. It seems self-evident that lymph node metastasis indicates the presence of tumour cells within a lymph node. However, precise definition of different types of burden is crucial. Metastatic disease is often sub-classified into isolated tumour cells (ITCs, < 0.2 mm), micrometastases (defined as > 0.2 mm but < 2 mm) and macrometastases (\geq 2 mm). More recently, the concept of molecular positivity has been introduced. The classification of nodal disease (N-stage) under the current 7th edition of the TNM staging system (TNM7) is summarised in Table 1.

A universally agreed definition of what constitutes lymph node metastasis is important for communication between all parties involved in treating, diagnosing and researching colorectal cancer. It facilitates uniformity for the purposes of entry to clinical trials, subsequent applicability of the ensuing results and interpretation of historical trends. Any criteria should be objective, reproducible, evidence-based and met with broad agreement. However, significant changes to the criteria in successive editions of TNM have been criticised for lacking some of the above qualities.

Detailed analysis of the changes wrought by the two most recent TNM editions is presented elsewhere^[3-5]. The main changes are summarised diagrammatically in Figure 1, but a few points warrant discussion. In the 6th edition (TNM6)^[6] of the TNM staging system, isolated tumour cells became classed as N0 for the purposes of grouping tumours into AJCC stage I to IV, in contrast to N1 in the 5th edition (TNM5)^[7]. Secondly, extra-mural

Table 1 Nodal staging in the 7th edition of the tumor node metastasis staging system

N Stage	Description
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N0 (i-)	No regional lymph node metastases histologically, negative IHC
N0 (i+)	Isolated tumour cells, identified by H&E and/or IHC
N0 (mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
N0 (mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
N1mi	Micrometastases
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2b	N2b Metastasis in seven or more regional lymph nodes
N2a	N2a Metastasis in 4-6 regional lymph nodes

IHC: Immunohistochemistry. RT-PCR: Reverse transcription-polymerase chain reaction.

deposits are difficult to classify. In a study of 69 tumour deposits, step sections were performed on what were initially diagnosed as tumour deposits. A significant proportion were found to represent other patterns of tumour spread^[8]. The “3 mm rule” stipulated in TNM5 was not based on published data, but had the advantage of being objective and reproducible^[9], in contrast to the assessment of “contour” introduced in the 6th edition (TNM6)^[10]. The “contour rule” was dropped in the 7th edition (TNM7), but explicit criteria were not provided to replace it. Left to the discretion of the pathologist, classification of extra-mural tumour is fraught with inter-observer variability^[11]. Unsurprisingly, there has been stage migration as a result of these changes, making it difficult to compare historical data. Data from the Surveillance, Epidemiology and End Results population-based registries showed that 10% of colorectal cancer cases had “tumour deposits”, of which 30%-40% occurred without concomitant lymph node metastases. Compared to TNM6, this represented up-staging of 2.5% of colon and 3.3% of rectal cases to N1c, a significant stage migration from stage I to stage III^[12]. There have also been misgivings over the use of TNM7 following neoadjuvant treatment, where patchy tumour regression may give the false appearance of lymph node metastasis or discontinuous tumour deposit. Finally, the changes in definition tend to reduce lymph node counts^[13], a concern where LNH is being used as a marker of “quality”. It is hoped that the 8th edition, due to be published this year, will resolve some of these issues.

Dissection

In many pathology laboratories, macroscopic examination and dissection of colorectal cancer specimens is

delegated to trainee pathologists, sometimes with limited experience and expertise. These large resection specimens tend to be left to the end of the “cut-up” session when time may be limited. Even in experienced hands, the detection of minute lymph nodes in mesenteric fat by palpation and dissection is painstaking and time-consuming. Marked variation in the assessment of colorectal cancer in the pathology laboratory, particularly in lymph node yields, is not a new issue^[14,15], but there is now more awareness of the crucial role of dissection. Results from staff pathologists^[16] and non-pathologist dissectors^[17-19] may be superior, but it is likely that a major factor is not the expertise of the operator, but rather the time devoted to searching for lymph nodes. de Burtet *et al.*^[20] studied LNH in gastrointestinal tumour resection specimens. Twenty minutes was allocated to an initial lymph node search, followed by an extra 5 and 10 min, which increased yields by 12% and 20% respectively. Twenty additional minutes added a mean of 6 lymph nodes, albeit with a diminishing rate of lymph node discovery. The United Kingdom Royal College of Pathologists’ Guidelines on Staffing and Workload allocates 8 points for cutting-up a colorectal resection, corresponding to an anticipated time spent of 31-50 min^[21]. This would appear to underestimate the time required for a thorough job if de Burtet *et al.*^[20] findings are correct. Often little thought is given to the ergonomics around cut-up. To optimise lymph node yields, we recommend that large specimens should be dealt with first when the operator is still fresh.

Handling

Current practice in handling of lymph nodes is not uniform. The United Kingdom Royal College of Pathologist guidance recommends embedding each lymph node whole, if < 4 mm, and a central block through longest axis for larger nodes^[22]. It is common practice to bisect or serially slice larger lymph nodes.

Typically, a single haematoxylin and eosin stained section is cut from each lymph node block, representing only a tiny volume of the lymph node in a single axis. Cutting more sections increases detection of lymph node metastases, including up-staging of several cases^[23], but the workload implications for the laboratory and histopathologist makes routine application of this unfeasible. Similarly, identification of small deposits of tumour by immunohistochemistry increases detection, but once again, has significant cost and workload implications.

Lymphatic mapping, the process of injecting tracer at the tumour site and following lymphatic flow to identify lymph nodes, has been used to identify sentinel lymph nodes (SLN). These SLNs are then subject to more intensive histopathological scrutiny, so-called ultrastaging^[24], typically consisting of additional levels and/or immunohistochemistry and in some cases molecular techniques^[25]. The utility of SLN ultrastaging is hampered by the limitations of current

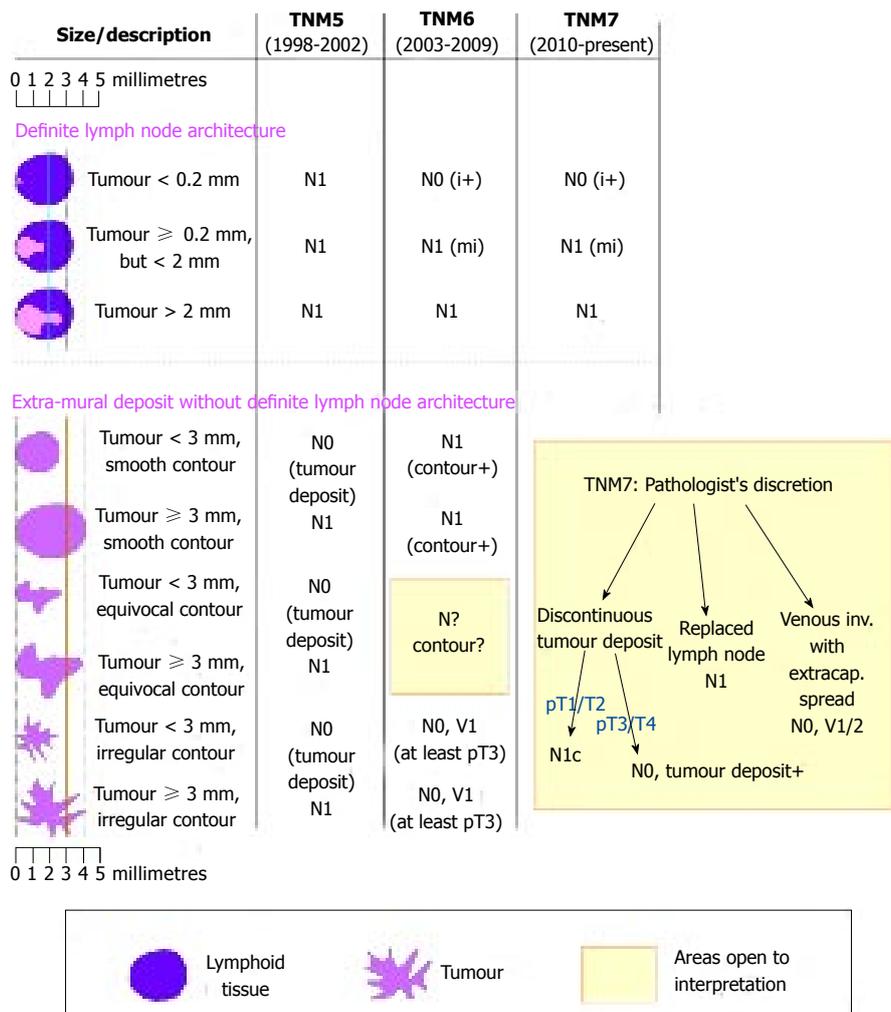


Figure 1 Changes in successive editions of the tumor node metastasis staging system. Top 3 rows: Size of deposit within definite lymph node. Under the 5th edition of the TNM staging system (TNM5)^[7], the volume of tumour cells is immaterial, but from the 6th edition (TNM6) onwards^[6], tumour burden is sub-classified by size; bottom 6 rows: Extra-mural deposits. TNM5 uses a 3 mm threshold; above this, the deposit is regarded as a lymph node metastases, below this, the deposit is regarded as a discontinuous extension of the main tumour. TNM6 relies on assessment of contour; smooth deposits are counted as nodes, whereas irregular contours are considered vascular invasion and upstaged in the T category. TNM7 leaves the decision to the judgement of pathologist with a wide range of outcomes.

SLN procedures, namely false negatives, skip lesions and failure to identify a SLN (see later section on SLN). The significance on prognosis of isolated tumour cells identified in this way is also contentious^[25] and is discussed in the later section on the size of tumour deposits.

Several other ancillary techniques have been employed to aid the LNH. Modified lymphatic mapping can be achieved by injection of India ink at the time of surgery^[26,27] and, similarly, *ex vivo* intra-arterial injection of methylene blue can accentuate lymph nodes^[28,29]. Chemical fat clearance can be performed with a variety of chemical regimens, typically a mixture of fixatives and organic solvents, such as glacial acetic acid, xylene, acetone, and alcohol. With the fat partially removed, nodes are accentuated, facilitating manual dissection and increasing yields. The clearance techniques are not in universal usage due to the slight delay introduced in finalizing a report and safety issues related to the disposal of the volumes of hazardous chemicals generated. The entire mesentery can be embedded

without fat clearance, so-called entire residual mesenteric tissue examination, which also increases yields^[30]. There is no doubt that many of these techniques increase LNH, but there are not currently enough data to show that they result in significant up-staging^[31].

Molecular techniques

The disadvantage of conventional ultrastaging is that it still relies on examination of a tiny volume of the lymph node. Lymph nodes harvested fresh can be processed to extract nucleic acids that can be analysed using reverse transcriptase and polymerase-based technologies. Some studies have used conventional polymerase chain reaction, but loop-mediated isothermal amplification, also known as one-step nucleic acid amplification (OSNA) can be performed in less than an hour and can be used intra-operatively. The results are quantitative and should reflect mRNA copy number. Thresholds are set to give grades of molecular lymph node involvement equivalent to conventional nodal staging, typically

≥ 250 copies for micrometastases and ≥ 5000 for macrometastases, although these figures are based on work done with breast cancer cases. Typical markers including carcinoembryonic antigen, cytokeratins 19/20 and guanylyl cyclase C. OSNA can be performed on the entire node^[32-34] or half of the node in combination with conventional sections^[35]. While up-staging was described in most series, there have been discrepancies not entirely explained by tissue allocation, suggesting conventional methods, albeit with ultrastaging-type protocols may have superior sensitivity and specificity. The data on how OSNA results correlates with the performance of single section histopathological analysis is sparse, particularly when isolated tumour cells are not included as a molecular category. Application of the OSNA technique to all lymph nodes harvested is not currently feasible outside of the research setting and practically-speaking, its main role is likely to be for the purposes of analysing sentinel lymph nodes.

Sentinel lymph node biopsy

The principle of sentinel lymph node biopsy (SLNB) is well established in melanoma and breast cancer, where the aim is to avoid unnecessary and potentially morbid lymphadenectomy. Unlike these two malignancies, where lymphadenectomy is a separate procedure, lymphadenectomy in elective colorectal cancer surgery is typically performed as part of a single surgical procedure. The lymphadenectomy component carries a low, but not entirely negligible morbidity. In a review of SLNB, Cahill questions the assumption that additional surgery carries no or minimal risk, particularly if radical lymphadenectomy is performed^[36]. The effects of excising unnecessary tissue are difficult to quantify. However, if SLNB can readily and reliably determine lymph node status, permitting more conservative surgery, then reduced tissue dissection, shortened operative time and better bowel function are all desirable outcomes.

Another scenario where SLNB may be informative is in early T-stage colorectal cancers, particularly pT1 polyp cancers identified by bowel cancer screening programmes. Adequate local excision of these polyp cancers is often achieved by endoscopic resection, but there is uncertainty about whether segmental resection for lymphadenectomy is indicated, a particular dilemma in patients with significant co-morbidities. While certain tumour characteristics predict lymph node metastases^[37-40], a SLNB should provide a definitive answer. SLNB can be performed laparoscopically^[41,42] and potentially *via* other minimally invasive techniques, *e.g.*, a transcolonic approach using with natural orifice transluminal endoscopic surgery^[43].

In this context, SLNB data specific to pT1/T2 tumours is of particular relevance, but many studies are small, typically include all T-stages or, in some studies, omit T-stage data. SLNB may have less of a role in pT3/T4 tumours as they are more likely to harbour lymph node metastases and therefore less likely to benefit

from initial SLNB^[44]. Additionally, an increased rate of false negatives has also been described in pT3/pT4 tumours^[36].

Broader adoption of SLNB, however, is limited by the guarded results from existing studies. SLNB is beset by a number of problems: Failure to identify a SLN, false negatives and skip lesions^[45-47]. Skip lesions have been hypothesised to be due to blocked lymphatic flow into involved lymph nodes, but this is not entirely explained by some data. It is unclear if the poor results are explained by technical problems, sub-optimal implementation of the technique or whether the concept is fundamentally flawed because of the inherently unpredictable pattern of lymph node involvement^[36,48]. Further evaluation of these techniques is required to determine whether they should be generally adopted.

ADDITIONAL HISTOPATHOLOGICAL ASPECTS IN LYMPH NODE ASSESSMENT

The most obvious measurable parameter relating to lymph nodes is the total LNH. Sampling as many lymph nodes as possible is ideal, but the focus on absolute counts alone ignores the complex and sometimes interacting factors that influence LNH. A detailed analysis of lymph node counts is presented later in this review, but other characteristics related to lymph nodes are discussed here.

Size of tumour deposit and/or lymph node

There are two separate aspects to consider. Firstly, does lymph node size, irrespective of tumour involvement, have implications on LNH or prognosis? Secondly, if a lymph node is involved, is the size of the deposit within the lymph node significant?

Chirieac *et al.*^[49] showed that nodal size significantly predicted overall survival in patients with node-negative colorectal cancer. They also speculated that high numbers of bulky negative lymph nodes were a product of an active host immune response, which ultimately contributed to improved patient prognosis and survival.

In some studies, LNM were more likely to be found in larger lymph nodes^[50,51], perhaps because they are easily palpable and therefore preferentially sampled. In node-positive disease, the size of the lymph node (as opposed to the tumour deposit) appears to have no significance on outcome^[52,53]. These studies and several others have demonstrated that many, if not the majority, of LNM occur in lymph nodes < 5 mm^[51,54]. The relevance of this is that small LNs are harder or impossible to palpate and are therefore less likely to be sampled during pathological dissection. Secondly, it is hard to completely separate the size of the tumour deposit from the size of the lymph node as the deposit obviously cannot exceed the size of the node. According to TNM7 rules, a positive 1.9 mm lymph node will either be involved by isolated tumour cells or micrometastases, but never a macrometastases (Figure 1).

This leads to the next question: Is the size of LN tumour deposit significant? The size of the largest lymph node tumour deposit appears to be prognostic^[55], but the overall volume of lymph node tumour burden appears to be less important than the number of involved lymph nodes^[56].

There is also considerable debate about the significance of isolated tumour cells. The data shows a wide variation in the incidence of isolated tumour cells and micrometastases, ranging from 11% to 59%. Some demonstrate an adverse effect on survival^[57-60], but others show no significance^[61-64]. The discrepancy reflects the differences in study design such as method of detection, length of follow-up and whether other confounding factors were considered. As previously discussed, more thorough scrutiny of lymph nodes with ultrastaging and/or molecular methods may increase detection of tumour, but it is unclear what significance this has on prognosis as direct comparison of data difficult. A 2014 meta-analysis suggests micrometastases have an adverse prognosis whilst isolated tumour cells do not^[65], but this distinction is not always straight-forward: The size cut-off of 0.2 mm is arbitrary and other definitions in terms of total cell numbers are hard to apply consistently.

Oncological practice in the United Kingdom continues to use the TNM5 definitions of lymph node metastasis, which defines the presence of any metastatic disease as N-positive, warranting adjuvant chemotherapy. Practice in other parts of the world differs, particularly in countries that have already adopted TNM7, which classifies isolated tumour cells as N0.

Extracapsular spread

Extracapsular extension is typically associated with more aggressive and infiltrative tumours. Heide *et al*^[66] noted that extracapsular extension in rectal resections was connected with adverse local control and a higher rate of distant metastases. In another study, the survival rates and disease-free survival rates for patients with metastatic lymph nodes showing an extracapsular invasion pattern were significantly worse than cases showing no evidence of extracapsular extension^[67].

Lymphoid hyperplasia/sinus histiocytosis

LNs negative for tumour may show reactive patterns such as follicular, parafollicular hyperplasia, as well as sinus histiocytosis. These have been regarded as indicators of active host immune response and are associated with an improved prognosis and 5-year survival rate^[68]. A survival advantage has also been established in metastatic lymph nodes that also demonstrate a background of benign reactive inflammatory changes^[69]. The host-response hypothesis may also explain why patients with lower lymph node yields are generally found to have a poorer prognosis, although reactive lymph nodes are more easily identified and may result in higher LNH and more accurate staging.

Ratio of involved lymph nodes

The use of the ratio of positive nodes to total LNH was first proposed by Berger *et al*^[70] in 2005 as an additional prognostic factor. Several subsequent studies have corroborated the original findings^[71-77], although what threshold to use is not clear. The results are not entirely consistent and there may also be differences between colonic and rectal tumour^[78]. A minimum LNH is required to make the ratio valid. Conversely, large numbers of lymph nodes obtained through techniques such as fat clearing may increase the overall denominator, disproportionately reducing the ratio.

Mucin pools

LNM from tumours showing prominent mucinous differentiation may manifest as pauci-cellular mucin pools. Following neoadjuvant treatment, these may be rendered acellular. Further step levels are helpful to exclude viable tumour cells, but if no cells are found, these are regarded by most pathologists as lymph node negative^[79,80].

ROLE OF THE SURGEON

The role of the surgeon is to excise the primary tumour and an appropriate amount of mesenteric tissue with clear margins, to allow adequate staging, whilst minimising potential complications. This raises the question of how much tissue should be removed to achieve optimal oncological outcomes.

Lymphadenectomy - therapeutic or prognostic?

How much tissue to remove is guided by the interpretation of the fundamental purpose of lymphadenectomy. There are divergent views on whether it is directly therapeutic or whether it provides mainly staging and prognostication^[81]. The model espoused by Halsted at the end of the 19th century assumes sequential and step-wise spread of tumour outwards from the primary site. Radical surgery to remove all tumour not only provides staging information, but also potentially cures the tumour. In contrast, the Cady *et al*^[82] paradigm assumes systemic spread may occur early in tumour growth and that improved outcomes derive from delivery of the optimum adjuvant treatment as determined by accurate staging. The Halsted radical mastectomy has been consigned to surgical history, but it is unclear if principles gleaned from breast cancer can be extrapolated to colorectal cancer.

Indirect evidence for a therapeutic effect has been inferred from studies looking at lymph node counts. The Intergroup Trial INT-0089 showed 5-year overall survival increased from 51% to 71% for N2 disease if > 35 lymph nodes were harvested compared to < 35^[83]. Given this was N2 disease, better staging and stage migration cannot entirely explain the results which showed superior survival to that of published trials using optimal adjuvant chemotherapy, implying a curative component. Other explanations are possi-

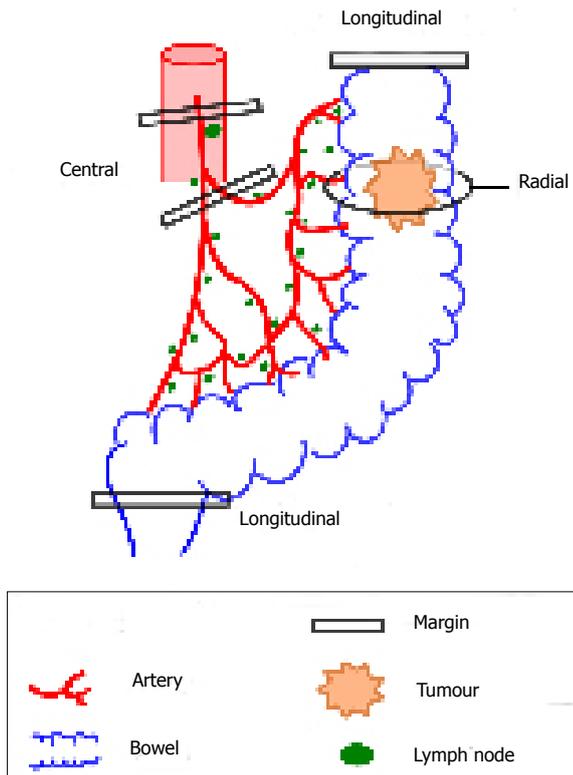


Figure 2 Anatomical extent of surgery. Schematic representation of the 3 anatomical boundaries of colorectal surgery.

ble, *e.g.*, high lymph node counts representing good host inflammatory response, but it is likely that lymphadenectomy is both prognostic and therapeutic, particularly in the rectum where total mesorectal excision (TME) achieves simultaneous local control and lymphadenectomy, with both components inherently inseparable. It is no surprise that when more mesenteric tissue is removed, LNH also increases. In theory, this leads to more accurate staging and potential therapeutic removal of involved lymph nodes. However, for many of the surgical techniques described below, the highest levels of evidence are lacking. It is therefore unclear whether the benefits of removing more tissue outweigh the increased operating time and potential morbidity associated with these procedures. A detailed review of surgical practice is beyond the scope of this review, but salient issues are considered below and readers are directed to other surgical guidelines^[84-87].

What is adequate surgery?

Margins can be thought of as extending to 3 anatomical boundaries (Figure 2). Firstly, the longitudinal margin as determined by the axial extent of the bowel excised. Secondly, the extent of mesenteric tissue excised, in a centripetal direction towards the root of the supplying artery. Thirdly, radial margins, in the broadest sense, which may include *en bloc* excision of advanced local spread, *e.g.*, the abdominal wall or adjacent organs, but also encompasses the circumferential margin, or more accurately, the non-peritonealised margin.

Frequently, these three margins cannot be manipulated independently of each other, but as a general rule, increasing the first two margins also increases lymph node yields.

Longitudinal margins

Typically, the segment of bowel containing the tumour is excised along with the mesentery delineated by its arterial supply. For colonic tumours, at least 5 cm of longitudinal clearance is advised to minimise anastomotic recurrence^[88,89]. In the rectum, 5 cm proximal and 2 cm distal appears sufficient^[90]. The Japanese Society for Cancer of the Colon and Rectum guidelines recommend at least 5 cm in the direction of lymph flow and 10 cm in opposite direction^[91]. In practice, it is the vascular supply that dictates the extent of surgery. If the tumour straddles two arterial branches, both segments should be excised. Anatomical and functional considerations may also extend resection beyond oncological requirements. For instance, in left-sided tumours, many surgeons avoid anastomoses with the sigmoid colon as it is regarded as a “high pressure” segment and also receives no contribution from the marginal artery.

The length of bowel resected may be extended in several scenarios on the basis that spread of tumour beyond normal segmental boundaries has been described, a finding partially borne out by intra-operative lymphatic mapping. Extended lymphadenectomy can be achieved by performing an extended right hemicolectomy for proximal right-sided tumours^[92,93]. Extended right hemicolectomy is also common performed for transverse colon and splenic flexure tumours, although there are no randomised, controlled trials to support this. Similarly, for left-sided tumours, one of the few randomised controlled trials in this area showed no benefit of left hemicolectomy over segmental resection^[94]. The type of surgery employed, particularly the length of specimen, has a clear influence on LNH, but without lymphatic mapping, is not clear when extended surgery should be performed.

Central margins and extra-mesenteric lymphadenectomy

Classically, colonic tumour spreads along lymphatics in the distribution of the arterial supply^[92,95,96]. Depending on their anatomical distribution, lymph nodes in the colon are described as pericolic, intermediate and apical/central/main, broadly corresponding to D1, D2 and D3 in the Japanese notation^[87]. Lymphadenectomy can be performed up to and flush with the level of the origin of the artery^[97], so-called complete vascular ligation, one of the key components of complete mesocolic excision (see below). This manoeuvre takes the apical node which is involved in about 3%-11% of tumours^[93,97,98]. In tumours of the sigmoid colon and upper rectum, high ligation of the inferior mesenteric artery has been advocated as oncologically superior. This was first promulgated by Moynihan in 1908^[99] and the debate on its value has continued for more than a

century. Despite good results in several, mainly cohort studies, other studies have shown no benefit (see systematic reviews in^[100-103]). No benefit was seen in sigmoid tumours in a multicentre randomised controlled trial^[94]. The issue, however, has not entirely been laid to rest and a randomised controlled trial of high ligation in the context of laparoscopic surgery is on-going^[104].

Routine excision or sampling of lymph nodes outside the typical lymph node basin has also been advocated. Tumours around the hepatic flexure may spread to infra-pyloric nodes^[97]. In the rectosigmoid region, the arterial supply is variable and spread to lateral (extra-mesorectal) pelvic lymph nodes may occur^[96]. One paper describes lateral pelvic node involvement in up to 18%, rising to 36% in the sub-group of Dukes' C tumours^[105]. Proponents of radical lymphadenectomy argue it is oncologically superior, both in achieving better staging but also therapeutically by removing all diseased lymph nodes. However, all of the above additions and modifications to "standard" lymphadenectomy may result in additional morbidity, particularly damage to neighbouring structures.

Depending on the anatomical site, this includes the duodenum, ureters and nerve plexuses^[106]. Vascular compromise may occur from direct vascular damage or *via* reduction in collateral flow^[107]. As extra-mesenteric and apical lymph node involvement is present only in a minority of cases, routine extended dissection represents unnecessary surgery for most patients. A selective approach has been advocated^[98], but patients with the highest rates of aberrant lymph node involvement are those with high T-stage, the same group where lymphadenectomy is least likely to be curative due to the increased risk of systemic disease. The benefit of these procedures is unproven and potential morbidity may outweigh the benefits^[108,109].

Radial margins

TME has been established as the optimal surgical technique for rectal tumours. Pioneered by Heald, introduction of the technique reduces local recurrence^[110,111]. The same anatomical and oncological principles have been extrapolated to colonic tumours, so-called complete mesocolic excision (CME)^[112]. Although a relatively new concept in the West, CME shares many features with D3 excisions that have been performed routinely in East Asia^[113,114]. It is associated with better LNHS^[115]. However, while it is supported by some compelling oncological and anatomical concepts, it encompasses many of the unproven surgical elements discussed above. The technique may prove itself in the fullness of time, but there is presently insufficient evidence to support it^[116,117]. Furthermore, the unsuccessful attempts by European surgeons to adopt D3 lymphadenectomy for gastric cancer is a salutary reminder of how challenging it is to "import" purportedly superior surgical techniques from established centres^[118].

Type of surgery

Laparoscopic and laparoscopic-assisted surgery is increasingly the default surgical approach to colorectal cancer resection. Superior peri-operative recovery and oncological equivalence has been demonstrated by several randomised controlled trials, including no significant difference in lymph node counts^[119]. Many of techniques described above can be achieved laparoscopically, *e.g.*, CME^[120-126], although randomised controlled trials are difficult to undertake. Laparoscopic CME therefore still lacks a convincing body of supportive evidence. The data on robotic surgery are promising^[127], but at present only includes a single randomised-controlled trial.

INTRA-OPERATIVE PROCEDURES

A number of procedures can be performed intra-operatively to assist in lymph node staging. As previously discussed, lymphatic mapping entails injecting a tracer at the tumour site, which travels along lymphatics and facilitates identification of lymph nodes^[24], including the sentinel lymph node. SLNs can be excised intra-operatively and for immediate results, can be subject to frozen section histological examination or OSNA^[128]. Other technologies that provide immediate intra-operative results are the subject of on-going research, *e.g.*, optical coherence tomography and real time elastography^[129].

Outside these techniques, the default histological analysis is performed on sections cut after formalin-fixation and paraffin embedding of the SLN. The results are therefore not available to influence immediate operative management. The exception is where the lymphatic mapping process identifies tracer in "aberrant" lymph node territory. The surgeon can choose to sample the abnormal lymph nodes or perform more radical lymphadenectomy. In 2 studies, *in vivo* lymphatic mapping changed the procedure in 9% and 22% of cases respectively^[129,130]. In the latter study, nodal positivity was higher in patients undergoing a change of procedure.

THE INFLUENCE OF PATIENT AND TUMOUR CHARACTERISTICS

Patient

Several patient characteristics have been identified that influence LNHS^[131]. However, factors identified in some studies are not corroborated by others. Fewer lymph nodes are generally obtained from specimens from older patients^[132-134]. Gender seems to have no effect, while low counts have an inconsistent association with obesity, as measured by body mass index^[135,136].

Tumour characteristics

Several histological characteristics of the primary

tumour have been shown to be associated with an increased risk of LNM. One meta-analysis identified 42 different factors. Only 15 were reported in 2 or more studies and not all are routinely analysed during standard reporting procedures^[137]. Factors that are easily assessed during routine histological reporting include tumour site^[133,134,138], stage^[133] and differentiation. Higher counts are seen in tumours with micro-satellite instability^[139]. While not an exhaustive list, many of these features lack reproducibility, sensitivity and/or specificity. It is therefore uncertain whether any single feature in isolation is reliable enough to influence decisions on adjuvant treatment. Neoadjuvant chemotherapy and/or radiotherapy typically reduces the numbers of nodes sampled^[133,140].

Predictive factors in submucosal (pT1) tumours are of particular interest as these are typically resected endoscopically and may require segmental resection for lymphadenectomy. Adverse factors in this group include poor tumour differentiation, depth of invasion and lymphovascular invasion^[37-40]. If sentinel lymph node biopsy techniques can be refined, this would greatly aid decision-making in this group on whether additional surgery is appropriate.

LYMPH NODE YIELDS AS A MEASURE OF QUALITY

Many of the surgical and histopathological techniques discussed are based on the presumption that increased lymph node yields invariably leads to more accurate stage. This assumption warrants critical appraisal. Many organizations such as the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the United Kingdom Royal College of Pathologists have guidance stipulating a minimum lymph node yield of 12 lymph nodes per case. The choice of 12 was proposed in 1990 by the Working Party Report to the World Congress of Gastroenterology in Sydney^[141], partly supported by subsequent studies, but has a poor evidence base.

Others have suggested alternative minimum numbers depending on the T-stage of tumour^[142], with more numbers required for low T-stage disease. While it has been clearly demonstrated in numerous studies that prognosis improves with the number of lymph nodes sampled^[143-146], this association does not prove causation. Furthermore, the association of lymph node counts and survival applies even in node-negative disease^[147] which lends support to the alternative explanation that high lymph node yields are a surrogate marker of a vigorous host immune response to tumour. Conversely, low lymph node counts are associated with a worse survival and may, in itself, be an indication for adjuvant treatment. Much of the existing evidence is based on studies where LNs were harvested without recourse to special techniques and it is unclear if the same survival associations apply when additional or

special techniques "inflate" the number of lymph nodes sampled. Not all studies have demonstrated a beneficial effect of higher lymph node yields^[148]. Yet others have observed a trend of increased lymph node yields over several years, most likely reflecting better surgical and histopathological practice, but without a corresponding increase in the detection rate of LNM^[149,150]. Similarly, the use of special techniques fares no better^[151]. At the risk of repetition, we need to clearly distinguish the principle of association from causality. Increased lymph node yields show an association with survival, but do not cause it. Various techniques may increase the lymph node count, but may not change the underlying nature of the disease. It is established that lymph node yields are multifactorial, influenced by a combination of patient, tumour, surgical and pathological factors^[131,152].

Clearly, there must be minimum standards in both surgical and histopathological practice. Surgery that fails to remove enough mesentery for staging and a cursory, hurried dissection by a pathologist, sampling only a handful of lymph nodes are likely, in combination, to lead to under-staging. However, for the majority of practitioners, the message about the importance of achieving accurate lymph node staging has been heard and implemented. Audit of LNHS is good practice, but the unthinking pursuit of ever higher lymph node yields should be resisted. In particular, it is unreasonable to link lymph node yields with quality payments, particularly when it is established that many factors influencing lymph node yields are outside the control of both surgeon and pathologist.

CONCLUSION

The importance of colorectal cancer lymph node staging cannot be over-emphasised. We have discussed many of the controversies associated with this challenging area and provided guidance about the rational application of additional techniques. TNM7 has not been universally adopted internationally^[22], but publication of TNM8 is anticipated in this year. The authors anticipate that this will address some of the issues and lead to a consensus approach. The variable contribution of surgical, pathological, patient and tumour related factors means that this remains a contentious subject. This complex area continues to evolve with new developments, surgically and pathologically, providing novel methods to evaluate nodal disease.

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Relevance of fecal calprotectin and lactoferrin in the post-operative management of inflammatory bowel diseases

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Abstract

The role of fecal lactoferrin and calprotectin has been extensively studied in many areas of inflammatory

bowel disease (IBD) patients' management. The post-operative setting in both Crohn's disease (CD) and ulcerative colitis (UC) patients has been less investigated although few promising results come from small, cross-sectional studies. Therefore, the current post-operative management still requires endoscopy 6-12 mo after intestinal resection for CD in order to exclude endoscopic recurrence and plan the therapeutic strategy. In patients who underwent restorative proctocolectomy, endoscopy is required whenever symptoms includes the possibility of pouchitis. There is emerging evidence that fecal calprotectin and lactoferrin are useful surrogate markers of inflammation in the post-operative setting, they correlate with the presence and severity of endoscopic recurrence according to Rutgeerts' score and possibly predict the subsequent clinical recurrence and response to therapy in CD patients. Similarly, fecal markers show a good correlation with the presence of pouchitis, as confirmed by endoscopy in operated UC patients. Fecal calprotectin seems to be able to predict the short-term development of pouchitis in asymptomatic patients and to vary according to response to medical treatment. The possibility of both fecal markers to be used in the routine clinical practice for monitoring IBD patients in the post-operative setting should be confirmed in multicentric clinical trial with large sample set. An algorithm that can predict the optimal use and timing of fecal markers testing, the effective need and timing of endoscopy and the cost-effectiveness of these as a strategy of care would be of great interest.

Key words: Calprotectin; Lactoferrin; Fecal markers; Inflammatory bowel disease; Post-operative; Surgery; Crohn's disease; Ulcerative colitis

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Core tip: Inflammatory bowel diseases (IBDs) are chronic conditions, requiring life-long therapy and monitoring. Surgery is not curative and the disease

might recur after operation as post-operative recurrence in Crohn's disease patients and pouchitis in ulcerative colitis patients. In both cases, endoscopy with histology is the gold standard procedure to assess disease activity. Non-invasive markers of intestinal inflammation, such as fecal calprotectin and lactoferrin, might be useful in the post-operative management of IBD patients, in order to identify individuals requiring endoscopy, so that they can avoid unnecessary invasive investigations. This paper reviews the current knowledge on the use of fecal markers in this specific setting.

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INTRODUCTION

Inflammatory bowel disease (IBD) is chronic, relapsing-remitting inflammatory conditions of the gastrointestinal tract. Both Crohn's disease (CD) and ulcerative colitis (UC) might require surgical intervention for different indications. Operated patients, both CD and UC patients, need to be followed-up regularly, because the risk of post-operative recurrence (CD patients) and of pouchitis (UC patients) is very common. However, the post-operative management is not clearly defined, in terms of needs of medications and timing of clinical, biochemical and endoscopic follow-up. Therefore, patients often undergo several invasive procedures to re-assess disease activity and exclude complications.

The role of non-invasive markers has been extensively studied in the diagnosis, management and monitoring of IBD patients. In particular, fecal markers, calprotectin (FC) and lactoferrin (FL), represent intestinal infiltration by leukocytes and correlate with the severity of endoscopic and histological intestinal inflammation^[1,2].

Calprotectin is a calcium- and zinc-binding protein of neutrophils, that is released in case of activation or apoptosis/necrosis^[3]. It displays several physiological roles in inflammatory and infectious processes and has anti-proliferative capability. The long stability of FC at room temperature (up to 7 d) is an advantage for its use in clinical practice. Lactoferrin is an iron-binding glycoprotein of neutrophils that, after degranulation, regulates their margination and diapedesis through the intestinal wall in case of inflammation^[4]. Unlike calprotectin, its stability at room temperature is guaranteed only for 2 d.

More recently, a meta-analysis confirmed the usefulness of C-reactive protein (CRP) and FC in excluding IBD in patients with symptoms of irritable bowel syndrome^[5]. Another meta-analysis showed that CRP, FC, and FL might aid in the triage of IBD patients for endoscopic evaluation when they are symptomatic^[6].

Currently, FC and FL do not replace endoscopy with histology, however this might become the future approach.

Still now, due to limited studies on the efficacies of FC and FL as non-invasive biomarkers, no consistent conclusion was made about their use in post-operative management of IBD patients. In this context, we aimed to review the efficacy of FC and FL from the available studies for use of FC and FL as non-invasive diagnostic markers of inflammation in post-operative CD and UC.

CD

CD is a chronic progressive destructive, disabling disease, clinically characterized by relapsing-remitting behavior. Even during periods of clinical remission the disease progresses, leading to structural and irreversible bowel damage in the majority of patients^[7]. In the natural history of CD, intestinal resection is often required to treat strictures, fistula, or abscesses. Historical population-based studies reported that, overall, the cumulative risk for surgery 10 years after diagnosis is around 40%-55%^[8]. There are emerging data suggesting that the early use of immune-modulators and biologics might delay disease progression and thus the timing of first surgical intervention. In an Australian population-based registry, authors observed indeed a fall in surgery rates (the one and 5 year resection rates were 13% and 23%, respectively)^[9]. Similarly, a Hungarian population based study showed that reduction of surgery rates was independently associated with early introduction of immune-modulators^[10].

Although, surgery is not curative and the disease often recurs in many cases (in the neoterminal ileum or in the ileo-colonic anastomosis), that leads to progressive loss of intestinal function and disability. Post-operative recurrence can be clinical, endoscopic, radiological or surgical. The reported incidence rates of post-operative recurrence depend on the definition used, the time of observation and the study design. Unfortunately, the available epidemiological data are heterogeneous and difficult to interpret. Buisson *et al.*^[11] summarized the data coming from randomized controlled trials; referral centers studies and population-based studies. Clinical recurrence was higher in population-based studies and referral center studies, reaching 61% at 10 years. Data about endoscopic recurrence at one year derived mainly from referral center studies (rates ranging from 48% to 93%) and randomized controlled trials (rates ranging from 35% to 85%). However, the definition of endoscopic post-operative recurrence was heterogeneous.

The established risk factors for post-operative recurrence are smoking, prior intestinal resection, fistulizing behavior, perianal disease and extensive disease (> 50 cm)^[11]. It is fundamental to identify high-risk patients and offer efficient treatment in order to maintain remission. However, the most appropriate therapeutic approach has still to be established. At present, the only universally accepted preventive measure for post-

operative recurrence is to quit smoking^[12,13].

Landmark studies by Rutgeerts *et al.*^[14,15] demonstrated that the post-operative clinical course of CD is predicted by the severity of endoscopic lesions during the first year after surgery. The presence of severe endoscopic lesions (Rutgeerts' score \geq i2) gives a high risk of early clinical relapse and complications^[14], but this can be observed already 6 mo after curative resection^[16].

As mentioned, detection of post-operative recurrence is mainly based on endoscopic appearance. Therefore, patients soon after surgery are expected to undergo endoscopy and repeat several evaluations, which timing is still need to be determined.

Fecal markers might be the most realistic alternative to ileocolonoscopy; their reliability as markers of intestinal inflammation has been proved in different settings and they are entering routine management. However, data about their use in the post-operative setting are poor.

Clinical and biochemical recurrence

The correlation between fecal markers and clinical and serological activity is controversial also in the post-operative setting.

We observed in 63 operated CD patients that levels of both FL and FC remained high after a median follow-up of 40.5 mo even in case of clinical remission, suggesting the persistence of subclinical inflammation^[17]. However, episodes of clinical flares predicted higher levels of FL. Only FL significantly correlated with CRP, showing a potential also as a maker of systemic inflammation. We investigated the correlation between FL levels and systemic inflammation in other 36 CD patients in clinical remission after ileo-colonic resection^[18], and demonstrated a significant correlation with IL-6 and CRP and an inverse correlation with albumin and serum iron. A major limitation of both studies was the absence of endoscopic evaluation to confirm endoscopic recurrence and its correlation with fecal markers.

Lamb *et al.*^[19] followed-up a small cohort of 13 CD patients for one year after surgery with regular FC and FL measurements. In case of early normalization of these biomarkers (within two months), a subsequent two-fold increase in the upper limit of FC and FL correlated with a relapse. Both markers demonstrated better performance than CRP. The authors studied also a second post-operative cohort of 104 patients in a cross-sectional study. In this study, both FC and FL correlated significantly with the Harvey Bradshaw Index (HBI) of clinical activity; in particular, severely active patients (HBI \geq 6) had higher levels of fecal markers (more than twice the upper normal limit). However, surprisingly there was no significant difference between the FC and FL values in those with endoscopic post-operative recurrence (25 patients out of 43 patients who underwent endoscopic assessment) and those without.

Yamamoto *et al.*^[20] prospectively investigated the relationship between the severity of endoscopic inflammation and fecal markers in 20 CD patients in remission during 6-12 mo after ileocolic resection. All patients underwent ileocolonoscopy at study entry and were then followed for 12 mo. Both fecal markers were significantly higher in patients (30%) who developed clinical recurrence. A cutoff value of 170 μ g/g for FC had 83% sensitivity and 93% specificity to predict a risk of clinical recurrence within 12 mo from the baseline endoscopy, while a cutoff value of 140 μ g/g for FL had a sensitivity of 67% and a specificity of 71%.

Endoscopic recurrence

The correlation of fecal markers with the presence of endoscopic recurrence should be the major endpoint in studies evaluating their role in post-operative recurrence. Orlando *et al.*^[21] observed that amongst 50 CD patients who underwent intestinal resection a FC level > 200 mg/L had 63% sensitivity and 75% specificity to diagnose endoscopic post-operative recurrence one year after the operation.

In the study performed by Yamamoto *et al.*^[20] both FC and FL correlated with the presence of endoscopic post-operative recurrence according to Rutgeerts' score. On the contrary, laboratory measurements (white blood cell count, platelet count and CRP level) did not significantly correlate with the endoscopic score.

A recent study performed in Sweden did not confirm the promising results of fecal markers in the post-operative setting proposed by the earlier studies^[22]. Authors evaluated the correlation between FC and the endoscopic findings one year after ileo-caecal resection in 30 CD patients; they observed that the median FC values did not significantly differ between patients in endoscopic remission or recurrence. However, most patients with low values were in remission and all patients with FC > 600 μ g/g had recurrence. The collection of the stool sample for FC measurement after colonoscopy might influence FC levels. This happened for only six patients, who collected the sample 1-4 wk after the endoscopy, and might not be sufficient to explain the absence of statistically significant difference between the groups of patients. Furthermore, the longitudinal part of the study, in which stool samples were delivered monthly until ileocolonoscopy, showed an important variability in FC concentrations. According to these findings, a single measurement of calprotectin might not be significant in the decision making process, and this was already demonstrated in the follow-up of patients undergoing anti-TNF treatment^[23].

Recently, results from the Post-Operative Crohn's Endoscopic Recurrence (POCER) Trial became available^[24] and data about the role of FC in monitoring and detecting post-operative recurrence were extracted^[25]. It is a prospective, randomized, controlled, multicenter trial, which evaluated a therapeutic strategy based on risk stratification of patients, with treatment step-up in case of recurrence detected at ileocolonoscopy, performed at

6 and 18 mo after surgery^[26]. This trial clarified that an active strategy based on the postoperative endoscopic monitoring, together with treatment intensification for early recurrence, is more effective (at least in the short term) than standard drug therapy alone and waiting for clinical recurrence. The surgically induced and verified remission (after resection of the macroscopically involved intestine) is an ideal starting point for the use of a noninvasive marker to monitor for recurrent inflammation. In the POCER trial FC concentration was increased markedly before surgery and decreased substantially after resection of all macroscopic diseased segments at 6 mo. Combined 6- and 18-mo FC levels correlated significantly with endoscopic recurrence, whereas CRP and CDAI did not. A cutoff of FC > 100 mg/g detected patients with endoscopic recurrence with 89% sensitivity and 58% specificity; the negative predictive value (NPV) was 91%. In this cohort, colonoscopy could be avoided in 47% of cases without endoscopic recurrence, but at the cost of missing 11% of patients with endoscopic recurrence. FC could be useful also in treatment monitoring, since it decreased in patients who underwent treatment intensification. A FC level of < 51 µg/g in patients in remission at 6 mo after surgery predicted maintenance of remission at 18 mo, with NPV 79%; sensitivity, specificity and PPV in this particular situation were less satisfying (50%, 68% and 36%, respectively), therefore the FC measurement remains of modest value in predicting long term future endoscopic recurrences.

Rapid test

Usually fecal markers are determined through the conventional ELISA method, that is effective, but time-consuming. A new rapid test for FC (FC-QPOCT) has been evaluated for the prediction of endoscopic remission in 115 CD patients^[27]. Twenty nine out of these patients were previously resected and endoscopic activity was scored according to the Rutgeerts' score. Median FC-QPOCT levels were able to discriminate between patients with and without endoscopic post-operative recurrence (98 µg/g vs 234.5 µg/g, respectively; $P = 0.012$). There was no significant difference in FC levels between the different degrees of the Rutgeerts' score. The accuracy of FC-QPOCT in predicting post-operative recurrence presented an AUC of 71.53. A 283 µg/g cut-off value had 67% sensitivity and 72% specificity (similar results were obtained with the ELISA method). However, accuracy was lower than that obtained in non-resected patients (AUC 0.933). Neither clinical activity nor serological biomarkers had a significant correlation with post-operative recurrence.

The validation of rapid fecal tests could be of further utility in the out-patient management of operated patients, avoiding the waiting time of laboratory reports.

Taken these results together, serial measurement of FC at regular intervals in the postoperative period might be the best way to predict future endoscopic behavior^[25,28].

It has been proposed that an algorithm combining FC and colonoscopy, based on the stratification of patients according to the risk of permanent bowel dysfunction, could be a cost-effective strategy to detect asymptomatic recurrence^[28]. This approach need further validation in larger, prospective trials, but might be a cost-effective strategy for the management of operated CD patients.

Results of the major studies in CD patients are reported in Table 1.

UC

The clinical course of UC may range from prolonged periods of remission to acute severe colitis requiring intensive medical treatment. Emergency colectomies are required in case of life-threatening complications of colitis in hospitalized patients unresponsive to medical treatment. Elective colectomy is indicated for refractory disease, intolerance to medical treatment and colonic neoplasia.

Surgery rates at 10 years from diagnosis are approximately 10%^[29,30], showing a decline over the years for elective colectomies (probably due to immunomodulators)^[31]; in contrast, emergent colectomy rates remain stable. Extensive colitis at diagnosis is proposed as a risk factor for colectomy in several studies across different cohorts of patients^[29,30].

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients with UC requiring colectomy. Pouchitis is a non-specific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC^[32,33]. The incidence of a first episode of pouchitis depends on the duration of follow up, occurring in up to 45% of patients 10 years after surgery^[34,35]. Pouchitis recurs in more than 50% patients and up to 10% of patients develop chronic pouchitis; refractory pouchitis is rare^[33]. Increased bowel movements, urgency, and abdominal pain in patients with IPAA may be caused by different inflammatory conditions (pouchitis, cuffitis, or CD) or non-inflammatory conditions (irritable pouch syndrome). The diagnosis of pouchitis requires therefore endoscopic confirmation with mucosal biopsies^[36,37]. The Pouchitis Disease Activity Index (PDAI) was developed to standardize diagnostic criteria and assess the severity of pouchitis, combining symptoms, endoscopy and histology^[36]; a total PDAI score ≥ 7 is diagnostic for pouchitis. Patients with suspected pouchitis need endoscopy for a proper diagnosis. The use of fecal markers for the detection of pouch inflammation might avoid the repetition of such invasive investigation^[38].

The literature on fecal markers in the post-operative setting in UC patients is quite scarce. Furthermore, the majority of studies was conducted on small samples of patients and have a cross-sectional design, which do not permit to clarify the evolution over time of the disease and the consensual behavior of the fecal markers. However, these studies form the basis of evidence that FC and FL are useful as inflammatory markers also in

Table 1 Studies evaluating fecal calprotectin and lactoferrin in operated Crohn's disease patients

Ref.	FC/FL	Method	No. of patients	Aim	Best cut-off	Sens %	Spec %	Main findings
Scarpa <i>et al</i> ^[17]	FC and FL	ELISA	63 (22 endoscopy)	Role as marker of intestinal inflammation after ileocolonic resection	/	/	/	High FC and FL levels at long-term follow-up after resection even in case of clinical remission Correlation between FL and CRP Higher levels of FL in case of clinical recurrence
Ruffolo <i>et al</i> ^[18]	FL	ELISA (IBD-scan)	36	Correlation with systemic inflammation and prognostic value in terms of need of surgery for recurrence	/	/	/	FL as expression of subclinical intestinal inflammation (through IL6-CRP cascade)
Lamb <i>et al</i> ^[19]	FC and FL	ELISA (PhiCal) ELISA (IBD-Scan)	13 (prospective cohort) 104 (cross-sectional cohort; 43 endoscopy)	Evaluation of the course of FL and FC after ileocaecal resection. Identification of postoperative recurrence; Correlation between FC and FL	/	/	/	Prospective cohort: Normalization of fecal markers by 2 mo after surgery in uncomplicated patients Cross-sectional cohort: Significant correlation between FC and FL Significant correlation of fecal markers with HBI No significant difference between the FC and FL values in those with endoscopic recurrence and those without
Yamamoto <i>et al</i> ^[20]	FC and FL	ELISA (Cell Science) and Colloidal Gold Agglutination reagent (Auto Lf-Plus, respectively)	20	Evaluation of the relationship between endoscopic activity and FC/FL Assessment of Fc and FL predictive value for future clinical recurrence	FC 170 mg/g FL 140 mg/g (for prediction of clinical relapse)	83 67	93 71	Significant correlation between FC and FL Correlation with endoscopic activity Ability to predict clinical post-operative recurrence
Orlando <i>et al</i> ^[21]	FC	ELISA	50 (39 endoscopy)	Evaluation of the one year postsurgical endoscopic recurrence	200 mg/L	63	75	FC > 200 mg can be an indication to colonoscopy in patients with negative ultrasound in order to detect early recurrence
Lasson <i>et al</i> ^[22]	FC	ELISA (Buhlmann)	30	Correlation of FC with the endoscopic findings one year after ileocaecal resection Evaluation of the variation of FC in individual patients during 6 mo prior to the ileocolonoscopy	/	/	/	No difference in the concentrations of FC between patients in endoscopic remission and patients with recurrence one year after ileocaecal resection Significant variability of FC concentrations over time
Wright <i>et al</i> ^[25]	FC	ELISA (fCAL, Buhlmann)	135 (319 fecal samples)	To assess whether monitoring FC can substitute endoscopy and be used as surrogate marker of recurrent post-operative disease	100 µg/g	89	58	FC correlated with the presence of recurrent disease at endoscopy and with endoscopic severity FC has sufficient sensitivity and negative predictive values to monitor for recurrence FC can be used to monitor response to treatment after detection of recurrence FC has better diagnostic performance than CRP and clinical index of activity
Lobatón <i>et al</i> ^[27]	FC	ELISA (Buhlmann) FC-QPOCT (Quantum Blue)	115 (29 resected)	To evaluate the performance of a new rapid test for FC in predicting endoscopic remission (in both operated and non-operated CD patients)	283 µg/g	67	72	Significant correlation between ELISA and rapid test FC was able to discriminate between the presence or absence of endoscopic recurrence, but not distinguish different levels of severity

CD: Crohn's disease; CRP: C-reactive protein; ELISA: Enzyme-linked immunoassay; FC: Fecal calprotectin; FL: Fecal lactoferrin; HBI: Harvey Bradshaw Index; Sens: Sensitivity; Spec: Specificity.

the post-operative setting.

In 24 patients with ileo-anal pouch (both UC patients and with familial adenomatous polyposis) FC showed a strong association with pouchitis ($P = 0.0002$), and correlated with the severity of inflammation detected at endoscopy and histology in the 9 patients having pouchitis^[39]. A cut-off of 92.5 $\mu\text{g/g}$ feces in 54 patients who underwent restorative proctocolectomy (46 UC patients and 8 with familial adenomatous polyposis coli) reached 90% sensitivity and 76.5% specificity in diagnosing pouchitis^[40]. No difference was found in symptom scores of patients with FC concentrations above or below 50 $\mu\text{g/g}$ ($P = 0.155$), confirming that the clinical presentation is aspecific.

Thirty-two patients with pediatric-onset of UC who underwent proctocolectomy with IPAA were enrolled in a cross-sectional study to assess whether FC was related to pouchitis^[41]. Patients with recurrent pouchitis had significantly higher FC levels ($832 \pm 422 \mu\text{g/g}$) followed by those with a single episode ($290 \pm 131 \mu\text{g/g}$) and those with no history of pouchitis ($71 \pm 50 \mu\text{g/g}$) ($P = 0.019$). FC levels correlated also with the amount of neutrophilic infiltration of the distal ileum at histology. The cross-sectional design of the study and the small sample size are of course important limits of the study.

Also FL showed satisfactory results in detecting pouch inflammation (due to either pouchitis, cuffitis or CD). In 60 patients with IPAA, a cut-off of 13 $\mu\text{g/mL}$ could distinguish irritable pouch syndrome from pouchitis, cuffitis, or CD, with 97% sensitivity and 92% specificity^[42]. FL levels correlated with the PDAI score (correlation coefficient 0.73; $P < 0.001$), especially with the endoscopic subscore. Although the cut-off level of 13 $\mu\text{g/mL}$ showed the best combination of specificity and sensitivity, authors recommended a cutoff level of 7 $\mu\text{g/mL}$ to decrease the possibility of false negative results. In case of higher levels, pouch endoscopy with biopsy is necessary to distinguish among different causes of inflammation. Lim *et al.*^[43] achieved similar results in 2008, evaluating the levels of FL in 32 patients with IPAA, showing 100% sensitivity and 86% specificity in diagnosing pouchitis, according to PDAI.

We evaluated the interplay between the ileal-pouch microbiota and several inflammatory parameters in the pathogenesis of pouchitis in 32 consecutive patients^[44]. Although it was not the primary aim of the study, we observed that FL correlated with the presence of mucosal ulcers, neutrophils and monocytes infiltration and the histologic diagnosis of pouchitis, confirming the ability of the fecal marker in detecting mucosal inflammation.

Recently, Yamamoto *et al.*^[45] conducted a longitudinal study to assess the utility of sequential dosage of FC and FL for the early diagnosis and prediction of pouchitis after restorative proctocolectomy for UC. Sixty patients were followed up (with clinical and biochemical assessments) every 2 mo for one year after the ileostomy closure. In case of symptoms suggestive of pouchitis, endoscopic examination was

immediately undertaken; otherwise, asymptomatic patients performed endoscopy at one year. Between 4 and 10 mo before the diagnosis of pouchitis (10 patients, 17%), the median FC and FL levels remained low and stable. However, these levels significantly increased 2 mo before the diagnosis of pouchitis, although patients were asymptomatic. In contrast, in 50 patients without pouchitis fecal levels did not change. In particular, a cut-off value of 56 $\mu\text{g/g}$ for FC had a NPV of 100% and a diagnostic accuracy of 87% to predict pouchitis; a cut-off value of 50 $\mu\text{g/g}$ for FL had a NPV of 98% and a diagnostic accuracy of 88% to predict pouchitis. Again, there was no significant correlation between the clinical subscore of PDAI and fecal biomarkers (FC: $r = 0.230$, $P = 0.08$ and FL: $r = 0.163$, $P = 0.21$); on the contrary, both fecal markers correlated with the endoscopic and histological subscores. In patients with pouchitis who responded to antibiotics (8/10) median FC levels dropped from 106 to 34 $\mu\text{g/g}$ and FL levels from 89 to 31 $\mu\text{g/g}$; in non-responders the levels of these fecal biomarkers increased, suggesting their usefulness for evaluating the efficacy of medical treatment and possibly for the early detection of pouch inflammation without repeating endoscopy.

In summary, fecal proteins demonstrated the potential to monitor intestinal inflammation in UC patients after proctocolectomy with IPAA. The early detection of subclinical inflammation with serial measurements of fecal markers might facilitate pre-emptive treatments in asymptomatic patients. Prospective studies need to confirm the cost-effectiveness of such strategy, especially evaluating the reduction of rates of chronic pouchitis and pouch failures^[46].

Results of the major studies in UC patients are reported in Table 2.

CONCLUSION

The role of fecal markers in the post-operative management of IBD patients seems promising. Preliminary data in CD patients came from small studies, sometimes relying only on clinical activity, without endoscopic confirmation of recurrence, and produced inconsistent data. More recently, studies have revealed the potential use of fecal markers, especially FC, in the post-operative management of CD, for the diagnosis of post-operative recurrence and possibly for monitoring the response to therapy. In UC patients, studies, although heterogeneous, have more consistently showed the correlation between fecal markers and the presence of inflammation of the pouch. Furthermore, there are no data showing that the early diagnosis of post-operative recurrence in CD patients and of pouchitis in UC patients might alter the long term outcome. The evidence of the reliability of FC and FL as markers of inflammation in the post-operative setting in both CD and UC should be strengthened in larger, longitudinal, multicentric studies, addressing the aim to refine an algorithm that stratifies the use and the optimal timing of fecal markers testing

Table 2 Studies evaluating fecal calprotectin and lactoferrin in operated ulcerative colitis patients

Ref.	FC/FL	Method	No. of patients (No. of patients with inflammation of the pouch) and type of disease	Aim	Best cut-off	Sens %	Spec %	Main findings
Thomas <i>et al</i> ^[39]	FC	ELISA	24 (9) UC and familial polyposis coli	Comparison between single and 24-h stool collections in patients with and without pouchitis (endoscopic, histologic and immunohistochemical indices)	/	/	/	Mean first morning stool concentration correlated with 24-h collection Levels of FC were significantly higher in patients with pouchitis Correlation with % of mature granulocytes and activated macrophages
Johnson <i>et al</i> ^[40]	FC	ELISA (PhiCal)	54 (20) UC and familial polyposis coli	Differentiation between inflamed and noninflamed pouches Correlation with inflammation severity	92.5 µg/g	90%	76.50%	FC levels significantly higher in pouchitis (> 50 µg/g had higher endoscopic and histological scores) Correlation with endoscopic score ($r = 0.605$) and histological score ($r = 0.708$)
Pakarinen <i>et al</i> ^[41]	FC	ELISA (PhiCal)	32 (22) UC	Cross-sectional assessment of FC after proctocolectomy for pediatric onset UC	300 µg/g (for detection of recurrent pouchitis)	57%	92%	Higher levels of FC in patients with recurrent pouchitis, followed by those with a single episode and those without (832, 290, 71 µg/g respectively, $P = 0.019$) Correlation with neutrophilic infiltration and overall inflammatory activity in the distal ileum
Parsi <i>et al</i> ^[42]	FL	In-house test	60 (30) UC	Evaluate the usefulness of FL in symptomatic patients with IPAA	13 µg/mL	97%	92%	Higher levels in patients with inflammation of the pouch Not able to distinguish between pouchitis, cuffitis and CD Not able to distinguish between asymptomatic patients and those with irritable pouch syndrome Correlation with PDAI (better for endoscopic subscore)
Lim <i>et al</i> ^[43]	FL	Rapid immunochromatographic test	32 (11) Healthy controls and pouchitis patients	Diagnostic yield for pouchitis	/	100%	86%	Sensitive method for the non-invasive diagnosis of pouchitis
Scarpa <i>et al</i> ^[44]	FL	ELISA (IBD-scan)	32 UC	Evaluate the relationship between ileal-pouch microbiota and inflammatory parameters	/	/	/	Correlation with histological inflammation Correlation with mucosal ulcers, mucosal immune infiltration Inverse correlation with <i>Eubacteriaceae spp.</i> , <i>Burkholderiaceae spp</i> and <i>Moraxellaceae spp.</i> counts
Yamamoto <i>et al</i> ^[45]	FC FL	ELISA (Cell Science) and Colloidal Gold Agglutination reagent (Auto Lf-Plus, respectively)	60 (10) UC	Evaluate the significance of consecutive monitoring of fecal markers for early diagnosis and prediction of pouchitis	56 µg/g 50 µg/g	100% 90%	84% 86%	Elevation of FC and FL already 2 mo before the diagnosis of pouchitis Correlation with PDAI score (correlation with endoscopic and histological subscores, but not with the clinical subscore) Correlation with response to therapy

CD: Crohn's disease; CRP: C-reactive protein; ELISA: Enzyme-linked immunoassay; FC: Fecal calprotectin; FL: Fecal lactoferrin; PDAI: Pouch disease activity index; Sens: Sensitivity; Spec: Specificity; UC: Ulcerative colitis.

and the effective need of colonoscopy. This should be based on patients-tailored approach, in order to

improve the cost-effectiveness of several postoperative fecal testing and examine the ability of such a strategy to prevent both clinical relapse and subsequent surgical resections in CD patients and the early identification with prompt treatment of pouchitis in UC patients.

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Current perspectives on pancreatic serous cystic neoplasms: Diagnosis, management and beyond

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Abstract

Pancreatic cystic neoplasms have been increasingly recognized recently. Comprising about 16% of all resected pancreatic cystic neoplasms, serous cystic neoplasms are uncommon benign lesions that are usually asymptomatic and found incidentally. Despite overall low risk of malignancy, these pancreatic cysts still generate anxiety, leading to intensive medical investigations with considerable financial cost to health care systems. This review discusses the general background of serous cystic neoplasms, including epidemiology and clinical characteristics, and provides an updated overview of diagnostic approaches based on clinical features, relevant imaging studies and new findings that are being discovered pertaining to diagnostic evaluation. We also concisely discuss and propose management strategies for better quality of life.

Key words: Pancreatic cystic neoplasm; Serous cystic neoplasm; Diagnosis; Management strategy; Surgery

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Core tip: Pancreatic cystic neoplasms (PCNs) have been more frequently recognized clinically in recent years and serous cystic neoplasms (SCNs) account for a large proportion of all PCN cases. Recent reviews have paid much attention to general aspects of PCNs and have discussed various subtypes of PCNs, but there is still a lack of comprehensive review exclusively focused on SCNs. This review attempts to provide a concise overview and outlook of pancreatic SCN and propose management strategies.

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INTRODUCTION

Pancreatic cystic neoplasms (PCNs) are increasingly being recognized incidentally with widespread use of advanced imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). According to the most recent WHO classification^[1], PCNs comprise serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs) and solid pseudopapillary neoplasms (SPENs). SCNs account for nearly 16% of surgically resected PCNs and > 30% of all clinically diagnosed PCNs^[2-4], hence, they have become of concern and have posed a challenge to primary care clinicians and general practitioners. Not surprisingly, SCNs harbor some already known epidemiological characteristics. SCNs largely affect women (approximately 75% of all cases), and the mean age of patients who underwent pancreatic surgery for SCNs was 56 years in Europe, 58 years in Asia and 62 years in the United States^[5,6]. SCNs tend to be larger if they occur in male patients^[4]. In contrast with other premalignant or malignant PCNs (MCNs, IPMNs and SPENs), SCNs are usually benign, and the malignant variant serous cystadenocarcinoma is rare. To date, only approximately 30 cases of serous cystadenocarcinoma are reported in the literature^[7]. Therefore, correct diagnosis is needed to avoid unnecessary surgical interventions and exclude other malignancies.

Morphologically, SCNs can be divided into four subtypes: Microcystic, macrocystic or oligocystic (< 10% of cases), mixed form (micro-macrocystic) and a solid variant form^[8]. SCNs may arise in any part of the pancreas and occasionally can spread throughout the organ. The majority of SCNs are the microcystic lesions, which occur predominantly in the body and tail of the pancreas, whereas the oligocystic lesions normally arise from the head of the pancreas^[9,10]. When multiple lesions are identified, Von Hippel-Lindau (VHL)-disease-associated pancreatic cysts should be taken into consideration^[11]. VHL disease is a genetic disease, driven by mutation of the VHL tumor suppressor gene located on chromosome 3, which leads to development of several tumors, primarily hemangioblastoma of the central nervous system, retinal hemangioblastoma, renal cell carcinoma, adrenal pheochromocytoma and pancreatic tumors, mainly represented by pancreatic endocrine tumors and cystic tumors^[12]. It is reported that SCNs are involved in 2.7%-9.5% of patients with VHL disease^[13].

Histologically, SCN cystic walls are lined with cubic flat epithelia consisting of glycogen-rich, watery-fluid-producing cells^[14] (Figure 1). The cytoplasm is

either clear or eosinophilic and the nuclei are normally centrally located, small and hyperchromatic; mitoses are not commonly found^[15]. Although some controversy still exists, it is widely accepted that SCNs originate from the centroacinar cells^[16]. They normally express cytokeratins AE1/AE3, CAM 5.2, CK7, CK8, CK18 and CK19, epithelial membrane antigen, α -inhibin, and mucin 6^[16,17].

CLINICAL PRESENTATION AND DIAGNOSIS OF SCN

According to a study led by Tseng *et al.*^[4], approximately 47% of patients with SCN were asymptomatic and diagnosed incidentally. As for symptoms, they are not specific and often attributed to mass effects or to infiltration of adjacent structures. Abdominal pain (25%), palpable mass (10%) and jaundice (7%) are the main clinical manifestations. It also has been shown that when lesions are > 4 cm, symptoms do occur more frequently if compared to lesions < 4 cm (72% vs 22%, $P < 0.001$)^[4], which is in line with several studies reported elsewhere^[18,19]. A more recent multinational study of 2622 cases of SCN revealed that patients could present with nonspecific abdominal pain (27%), pancreaticobiliary symptoms (9%), diabetes mellitus (5%), or other symptoms (4%), with the remaining patients being asymptomatic (61%)^[20].

Given that SCNs are usually benign and asymptomatic, better surveillance and management strategies for these cysts call for accurate preoperative diagnosis. CT, MRI and EUS are three most commonly used imaging techniques for revealing SCNs. A recent study stated that the accuracy of preoperative diagnosis of PCN remains low, reaching approximately 60%, and in light of the exact diagnosis by pathology, surgical resection, most of which were Whipple resections, should not have been performed in approximately 8% of patients^[21]. In another study cohort, 9% of PCN patients underwent pancreatic resection for a non-neoplastic condition^[22], which further demonstrated the difficulty in differentiation between benign and premalignant lesions and that better preoperative diagnosis is urgently needed. Pancreatic cysts are readily identified in up to 20% of MRI studies, and 3% of CT scans^[23,24]. Both CT and MRI predict the presence of malignancy in pancreatic cysts with 73%-79% accuracy^[25]. In addition to routine radiological studies, EUS has emerged as a useful tool because it provides high-resolution imaging of the pancreas through the lumen of the stomach or duodenum and helps obtain detailed information of the cystic lesions, such as wall, margins, internal structures and parenchyma^[26,27]. In a recent prospective cross-sectional study of the prevalence of incidental pancreatic cysts during routine outpatient EUS, the prevalence of incidental pancreatic cyst was 9.4% and most were < 1 cm^[28]. The accuracy of EUS to differentiate benign from malignant neoplastic tumors and from non-neoplastic

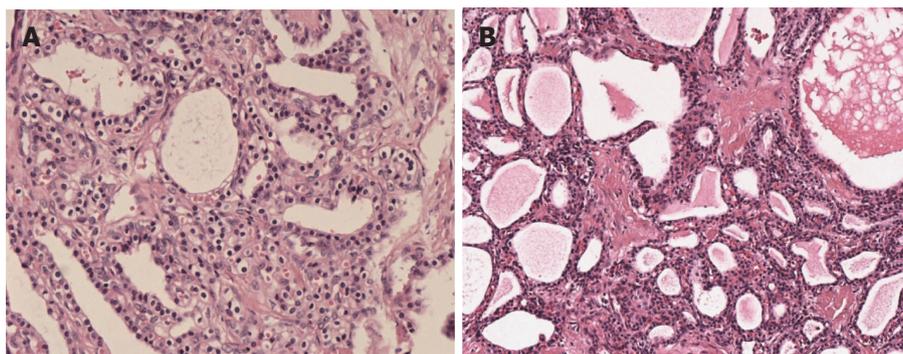


Figure 1 Pathological examinations revealing that serous cystic neoplasm cystic walls are lined with cubic flat epithelia consisting of glycogen-rich, watery-fluid-producing cells (hematoxylin and eosin $\times 100$). A: Pathology of a microcystic SCN of the pancreas; B: Pathology of a macrocystic SCN of the pancreas. SCN: Serous cystic neoplasm.

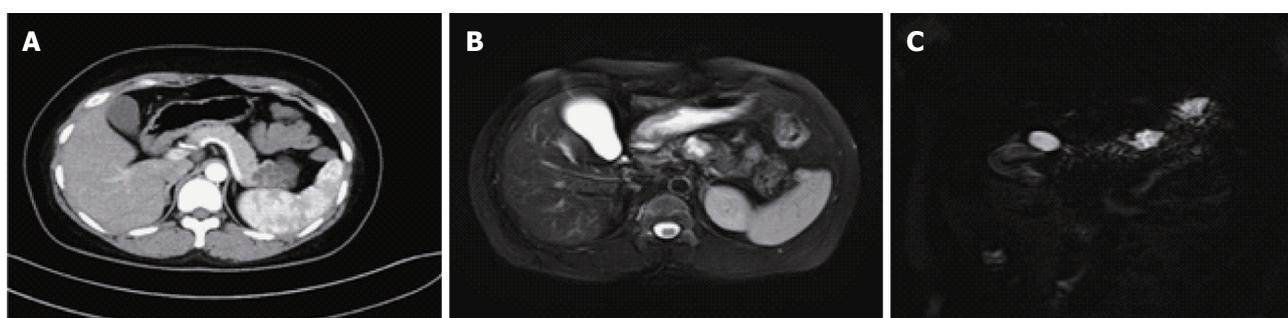


Figure 2 Microcystic pancreatic serous cystic neoplasm presentation on computed tomography/magnetic resonance imaging. A: A microcystic pancreatic SCN lesion was revealed in the tail of the pancreas; B: MRI showed a microcystic lesion in the body of pancreas; C: A microcystic SCN lesion was revealed by magnetic resonance cholangiopancreatography. Images B and C came from the same patient. SCN: Serous cystic neoplasm; MRI: Magnetic resonance imaging.

cysts remains debatable. Some studies have stated an accuracy of $> 90\%$, while others have expressed doubt, especially when there is a lack of evidence of a solid mass or invasive tumor^[29-31]. Despite this debate, another major advantage of EUS is its ability to collect fluid from cystic lesions *via* fine-needle aspiration (FNA) for cytological and biochemical analysis, such as carcinoembryonic antigen (CEA), amylase, and *KRAS* mutations^[32].

Compared to other cystic neoplasms, accurate preoperative diagnosis of SCNs seems more feasible. As mentioned before, SCNs can be divided into four subtypes: Microcystic, macrocystic or oligocystic ($< 10\%$ of cases), mixed form (micro-macrocytic) and solid variant form^[8]. VHL-disease-associated pancreatic cysts should be considered when other cystic lesions exist. A Japanese multicenter study of 172 SCNs diagnosed by resection and typical imaging findings noted highest diagnostic accuracy for microcystic SCN (85%), with lower diagnostic rates (17%-50%) for macrocystic and mixed types. CT alone is approximately 23% accurate at diagnosing SCN^[33]. Diffusion-weighted MRI has proved to be a powerful tool with 100% sensitivity and 97% specificity for differentiating mucinous cysts from SCNs^[34]. The pathognomonic central scar, which is formed by central coalescence of the septa and commonly contains foci of calcification on imaging, is present in only approximately 30% of these

cysts^[35].

On CT/MRI, microcystic SCN typically appears as an isolated, lobulated, well-marginated, multilocular lesion, comprising a cluster of multiple (usually > 6) small cysts separated by a thin septum^[26,36] (Figure 2). Each of the small cysts is usually < 2 cm^[37]. Occasionally, the "honeycomb" pattern, characterized by numerous, sub-centimeter cysts appears as a solid mass on CT (Figure 3), but has high signal intensity when T2-weighted MRI is applied^[37]. Macrocystic SCN is characterized by a limited number of cysts, usually < 6 , showing a diameter > 2 cm, or even one single cyst^[38] (Figure 4). This subtype can be seen in approximately 10% of all cases of SCN but poses difficulty for differentiating it from MCN and branch-duct (BD)-IPMN, based on the findings of CT or MRI^[39]. In addition, if a patient has a reported history of pancreatitis, pseudocyst should be considered^[40]. The mixed micro-macrocytic type is depicted as a combination of the above two types of lesions. As for the solid variant, it consists of small cysts separated by multiple, thick fibrous septa^[41]. VHL-disease-associated pancreatic cysts, which can occur in 50%-80% of the patients with VHL disease, and are occasionally misdiagnosed as macrocystic SCNs, tend to form multiple lesions and are even diffuse throughout the pancreas^[42,43].

Generally, microcystic SCNs on EUS are imaged as numerous (> 6) small ($< 1-2$ cm) fluid-filled cysts with

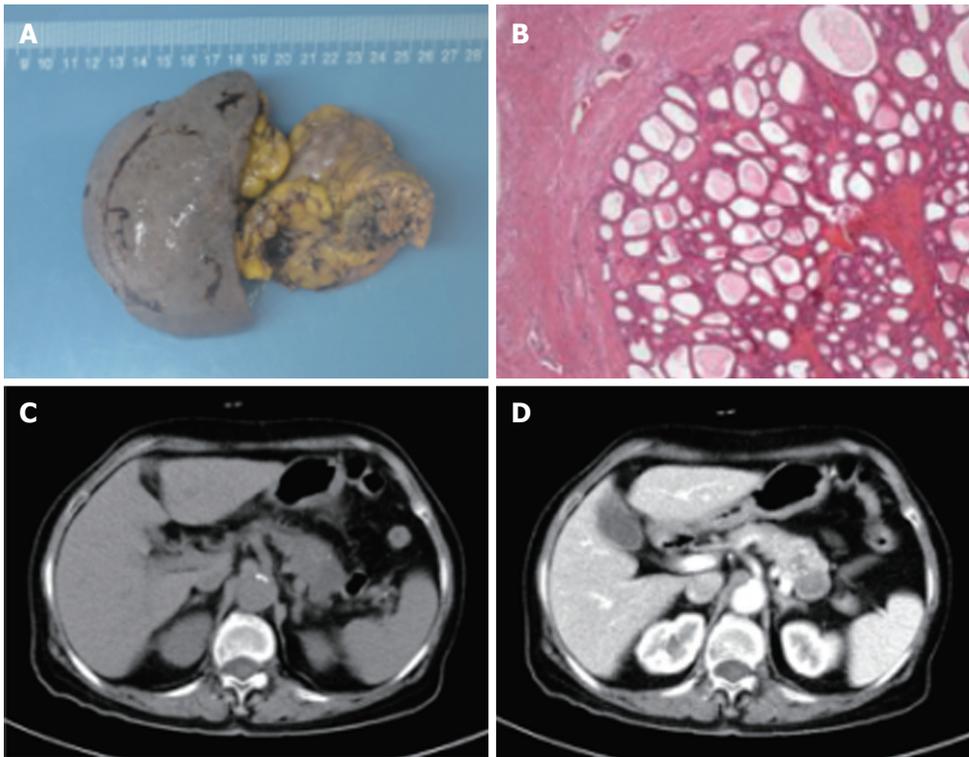


Figure 3 Solid variant microcystic serous cystic neoplasm with honeycomb characteristics. A: Gross pathology of a solid variant microcystic SCN; B: Histology of solid variant microcystic SCN; C: Solid variant lesion was detected by CT; D: Solid variant lesion was detected by contrast-enhanced CT. These four images were acquired from the same patient. SCN: Serous cystic neoplasm; CT: Computed tomography.

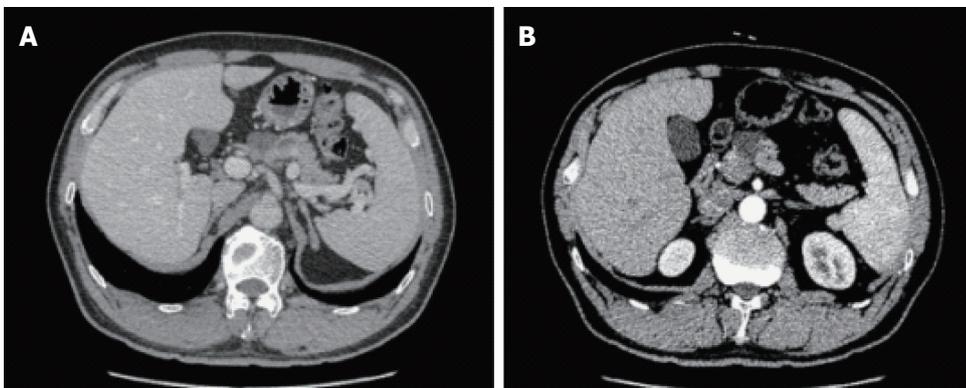


Figure 4 A macrocystic pancreatic serous cystic neoplasm was detected on computed tomography with (B) and without enhancement (A).

thin-walled septa and possibly calcification of the central septum^[44,45] (Figure 5). The honeycomb variants are interspersed within dense fibrous septa, with or without central fibrosis or calcification^[46,47]. The less common oligocystic SCNs usually contain larger (> 2 cm) cysts^[48]. However, the solid variant, which is defined when lesions are predominantly solid (< 10% cystic portion) and might resemble a ductal carcinoma on CT, contains numerous tiny cysts (1-2 mm) and appears as a hypoechoic mass on EUS^[49].

Management and surveillance of SCNs depend on correct preoperative diagnosis. One major concern is potential misdiagnosis of a malignancy or premalignancy as a benign SCN, which was more frequent in the past;

it was reported in seven of 28 patients in one study and in two of 49 patients in another^[50,51]. Among SCNs, macrocystic SCNs are frequently undistinguishable from MCNs and BD-IPMNs. BD-IPMNs may also present in a polycystic pattern, similar to microcystic SCNs^[52]. Typically, unlike IPMNs, SCNs are characterized by lack of communication with the main pancreatic duct. However, the absence of communication does not allow for the exclusion of IPMN, although this absence may favor the diagnosis of MCN over SCN^[53,54]. In contrast to MCNs, which usually exhibit a smooth oval shape and varied signal intensity (depending on the fluid viscosity of each lobule), macrocystic SCNs typically present with a thin wall and lobulated contours and can be



Figure 5 A microcystic pancreatic serous cystic neoplasm was discovered by endoscopic ultrasonography.

found in the head of the pancreas^[55]. A central calcified scar is virtually pathognomonic for SCNs (Figure 6), whereas peripheral calcifications are frequently observed in MCNs^[56]. Many solid variant SCNs show arterial hypervascularity on imaging studies and are frequently misdiagnosed as pancreatic neuroendocrine tumors (pNETs)^[57-59]. A recent study found that the frequency of hypervascular solid-appearing SCNs was 7.3% among surgically confirmed SCNs and unenhanced CT and MR features can help to differentiate solid variant SCNs from pNETs^[60].

Despite various potential complications of EUS-FNA, such as bleeding caused by injury of the subepithelial vascular plexus of SCNs, pancreatitis, infection, and even the seeding of malignant cells along the tract of the needle have been suggested^[61-63], EUS-FNA-related morbidity and mortality rates have remained low^[64] and the widespread use of EUS-FNA has yielded a wealth of information for cytological, chemical and molecular analysis of SCNs.

A 22- or 25-gauge needle is often used when aspirating cyst fluid during EUS-FNA. SCNs usually contain little fluid and the fluid usually contains few cellular components, and FNA cytological analysis has an unreliable sensitivity of only 30%-40%^[65]. For chemical analysis, assessment of tumor markers such as CEA, carbohydrate antigen (CA)19-9, CA15-3, CA72-4, and enzymes like amylase and lipase is often carried out, although it has proved of limited diagnostic value^[66]. Fluid from SCNs universally has low CEA levels. A level < 5 ng/mL is 95% specific for SCN, pseudocyst or pNET^[67]. However, an elevated CEA level favors a mucinous lesion, although the exact cut-off level is still in debate. It is also important to mention that the CEA threshold varies in different centers, ranging from 5 ng/mL to > 100 ng/mL^[68]. When a classic CEA cut-off level of 192 ng/mL is applied, it yields 73% sensitivity and 84% specificity for mucinous cysts^[69]. An amylase level < 250 U/L favors diagnosis of SCN over pseudocyst, with a sensitivity of 44%, specificity of 98% and overall accuracy of 65%^[68]. Other than CEA and amylase, recent studies have revealed that levels of cystic fluid

metabolites glucose and kynurenine are markedly elevated in SCNs compared to MCNs, which aids the diagnosis of SCNs^[70,71]. Although large prospective studies are warranted to validate these promising results, they shed light on a new path to seek better biomarkers. Molecular analysis of cystic fluid has gained in interest in recent years, in parallel with the advent of new techniques on sequencing. DNA analysis of KRAS mutations may help identify mucinous cysts with 54% sensitivity and 100% specificity, as demonstrated in a study containing 142 surgically resected cysts. When CEA and KRAS analysis were collectively applied, the sensitivity climbed to 83% while the specificity dropped to 85%^[72]. More interestingly, data from whole-exome sequencing of PCNs revealed that the application of a panel of five genes (*VHL*, *RNF43*, *KRAS*, *GNAS* and *CTNNB1*) allowed correct distinction of mucinous from nonmucinous cysts. All eight SCNs had intragenic mutations of *VHL* or loss of heterozygosity in or adjacent to *VHL* and did not contain mutations of the other four genes. Furthermore, point mutations of *VHL* gene were detected in cystic fluid analysis in half of the SCNs. Nevertheless, IPMNs had alterations of *RNF43*, *GNAS* or *KRAS* and never had *VHL* or *CTNNB1* mutations. MCNs always harbored *KRAS* or *RNF43* mutations but never contained *GNAS*, *CTNNB1* or *VHL* mutations^[73]. Another study stated that *GNAS* mutations were present in 10% of their cases of SCN, which was still significantly lower than in IPMNs^[74]. Thereafter, the identification of *GNAS* mutation may help discrimination of SCN from IPMN. Another mainstay of research of cystic molecular analysis gives insights into miRNAs. A panel of four miRNAs comprised miR-31-5p, miR-483-5p, miR-99a-5p and miR-375 has been developed to differentiate SCNs accurately from mucinous lesions, with 90% sensitivity and 100% specificity^[75]. While promising, these results were based on surgically archived specimens but not on cystic fluid, therefore, validation in cystic fluid samples should be addressed in future studies to fit these findings better in preoperative scenarios.

MANAGEMENT AND INTERVENTION STRATEGY FOR SCNs

As mentioned before, most SCNs follow a benign course and malignant SCNs (serous cystadenocarcinoma) are rare (< 1% of all cases). According to an investigation of 193 SCNs, along with a literature review, the clinicopathological characteristics of solid and macrocystic SCN variants are similar to those of their microcystic counterpart, and there are no deaths that are directly attributable to dissemination/malignant behavior of SCNs^[76]. It is also recommended to consider and manage SCNs as benign neoplasms initially^[77]. For this reason, correct preoperative diagnosis of SCNs could spare many unnecessary interventions and guide optimal management strategies. Currently, there

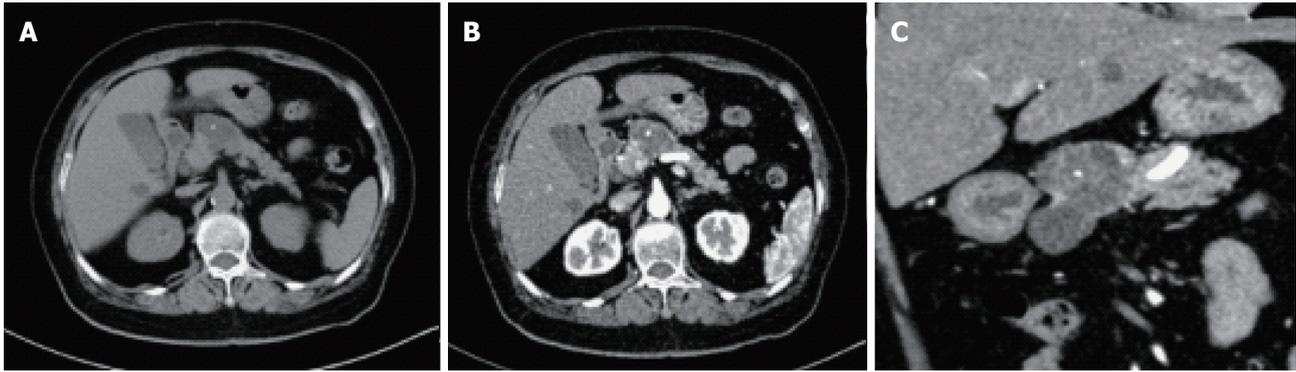


Figure 6 Central calcifications were found by computed tomography with and without enhancement (A and B), and also shown after three dimensional reconstruction (C).

is no universal consensus on the best management strategy, but it is widely accepted that not every single case should be surgically resected, regardless of how advanced surgical technology has been developed, and symptomatic, local invasive or potential malignant SCNs should be resected^[37,54,78]. It is also advised that resection should be considered for large (> 4 cm), rapidly growing SCNs, given that such SCNs are more likely to cause symptoms^[4,33]. However, it is difficult for a clinician to predict whether and when an incidentally found asymptomatic SCN will grow to cause symptoms. One older study claimed that a more rapid growth rate of approximately 1.98 cm/year was observed in cysts > 4 cm, whereas the growth rate was approximately 0.12 cm/year in cysts < 4 cm^[4]. A more recent multicenter study failed to confirm those results. In that same study, a rate of growth of 6.2% per year or a doubling time of 12 years was calculated for the nonresected SCNs, while resected SCNs grew faster (17% per year for a doubling time of 4.5 years)^[18]. In addition, there is also a paucity of knowledge about the relationship between growth rate and potential malignancy^[7]. Obviously, symptoms do occur when fast-growing SCNs are left unresected^[79]. It is tempting to conclude that initial size is neither associated with malignant transformation, nor proportionally related to developing symptoms. However, growth rate is more powerful to predict if and when the symptoms occur. Thus, the growth rate should be weighed when considering if an SCN should be subjected to surgical intervention. One multinational study stated that, in patients followed beyond 1 year ($n = 1271$), size increased in 37% (growth rate: 4 mm/year), was stable in 57%, and decreased in 6%, hence, surgical treatment should be proposed only in cases in which diagnosis remains uncertain after complete work-up^[20].

Surgery is considered curative. Despite increasing experience and advanced surgical techniques, pancreatic surgery holds a perioperative morbidity of 15%-30% and a mortality rate of 1%-2%, even in high-volume centers^[3]. The indications for surgical intervention are as follows: (1) presence of symptoms; (2) Uncertain diagnosis. MCNs and IPMNs can mimic SCNs

on radiology scans, especially macrocytic SCNs. When premalignant MCNs and IPMNs cannot be excluded, the lesions can be managed as IPMNs when the cysts are < 4 cm^[80] and are advised to be surgically removed accordingly following the International consensus in 2012 and the European consensus in 2013^[81,82]; and (3) growth rate of the neoplasm. As discussed above, large SCNs are not correlated with an increased risk of malignancy. Also, growth rate is not linked with initial size. The notion that any cyst > 4 cm or even > 5 cm be resected should be abandoned. In this regard, clinicians need to remain cautious when neoplasms grow rapidly, and make decisions on a case-by-case basis, including patient's age, comorbidity and tumor location. Large SCNs can always be closely observed first and then sent for surgery once they grow faster and cause unrelieved symptoms.

From an anatomical point of view, surgical resection of an SCN largely depends on the location of the lesion. As a result of the benign nature of SCN, as a general rule, it is recommended that pancreatic functions are protected and preserved as much as possible for better outcome and quality of life. If SCNs are localized in the pancreatic head, pylorus-preserving pancreatoduodenectomy or Begar procedure is often carried out. If SCNs are located in the body or tail of the pancreas, spleen-preserving distal pancreatectomy should be the first choice. For patients whose SCNs are located in the neck of the pancreas, central segmental pancreatectomy is an alternative procedure, preserving islet cell mass and reducing the risk of iatrogenic insulin-dependent diabetes. Enucleation is not recommended because greater morbidity (up to 35%) and associated complications such as pancreatic fistula^[83] have been reported.

As mentioned above, clinicians are encouraged to manage SCNs in a conservative manner, which means that, initially, these lesions do not require surgery but serial follow-up when radiological diagnosis is certain and symptoms are absent. However, to date, the best follow-up strategy has not been standardized. Some advocate follow-up imaging every 12 mo, while others suggest biennial surveillance^[84,85]. The European con-

sensus in 2013 suggests that asymptomatic nonresected patients should enter a follow-up program, initially repeated after 3-6 mo, and then individualized depending on growth rate^[81]. Once SCNs are resected, no further surveillance imaging is needed.

CONCLUSION AND FUTURE DIRECTIONS

Comprising about 16% of all resected PCNs, SCNs are uncommon benign lesions that are asymptomatic and found incidentally. Despite overall low risk of malignancy, the presence of these pancreatic cysts still generates anxiety, leading to extensive medical investigation with considerable financial cost to health care systems. CT and MRI alone are not powerful enough to characterize cystic pancreatic lesions fully, and more specifically, to differentiate macrocystic SCNs from MCNs. However, EUS, with or without addition of FNA, adds more diagnostic value to conventional imaging techniques. CEA, although not perfect, plays a role in differentiating pancreatic cystic lesions. New cystic fluid markers from chemical and molecular analyses are just beginning to emerge, paving a new way to future research. As for treatment and management strategy, surgery should be limited only to symptomatic SCNs and lesions that show aggressive behavior, while the majority of patients should be strictly monitored and followed up by serial imaging. Further investigations on best follow-up strategy are warranted. Patients would benefit from multidisciplinary management and receive precise medical advice once gastroenterology, surgery, pathology and radiology are all involved in individual patient care as a team. As such, patient care based on a multidisciplinary team is encouraged if applicable.

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Duodenal adenocarcinoma: Advances in diagnosis and surgical management

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Abstract

Duodenal adenocarcinoma is a rare but aggressive malignancy. Given its rarity, previous studies have traditionally combined duodenal adenocarcinoma

(DA) with either other periampullary cancers or small bowel adenocarcinomas, limiting the available data to guide treatment decisions. Nevertheless, management primarily involves complete surgical resection when technically feasible. Surgery may require pancreaticoduodenectomy or segmental duodenal resection; either are acceptable options as long as negative margins are achievable and an adequate lymphadenectomy can be performed. Adjuvant chemotherapy and radiation are important components of multi-modality treatment for patients at high risk of recurrence. Further research would benefit from multi-institutional trials that do not combine DA with other periampullary or small bowel malignancies. The purpose of this article is to perform a comprehensive review of DA with special focus on the surgical management and principles.

Key words: Duodenal cancer; Duodenal adenocarcinoma; Periampullary; Whipple; Pancreaticoduodenectomy; Segmental resection; Small bowel

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Core tip: Duodenal adenocarcinoma is a rare but aggressive malignancy. Complete surgical resection is recommended when technically feasible. Pancreaticoduodenectomy or segmental duodenal resection may be employed, depending on the tumor location, and either are acceptable options as long as negative margins and adequate lymphadenectomy can be achieved. Although specific data are limited, adjuvant chemotherapy and radiation should be considered for patients at high risk of recurrence.

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INTRODUCTION

Although the majority of small bowel adenocarcinomas arise in the duodenum, duodenal adenocarcinoma (DA) still represents less than 1% of all gastrointestinal cancers^[1,2]. Not surprisingly, given the rarity of the disease, there is limited data to guide treatment decisions. Early studies grouped DA with other periampullary tumors (pancreatic, ampullary, distal bile duct) when discussing their management options. However, in general, DA has a more favorable outcome. For example, compared to some other periampullary malignancies, DA is more likely to be amenable to curative resection and has more favorable long term outcomes^[3]. As a result, treatment strategies have tended to favor aggressive surgical resection. The purpose of this article is to provide a comprehensive review of the epidemiology, presentation, diagnosis, management and prognosis of DA with a special emphasis on surgical principles.

Epidemiology

Small bowel malignancies are relatively rare, accounting for only 2% of all gastrointestinal cancers in the United States^[4]. Among small bowel tumors, most malignancies arise from the ileum, followed by the duodenum and lastly the jejunum. While most tumors of the ileum are neuroendocrine in origin, adenocarcinoma is the most common duodenal cancer^[4-6]. One large population-based analysis found the duodenum to be the location of 55.7% of adenocarcinomas of the small bowel^[5]. The majority of DA arise in the second portion of the duodenum, followed by D3/D4, with cancers of the first portion of the duodenum, especially the duodenal bulb, extremely rare^[7,8].

The causative factors for DA have not been clearly identified. Dietary factors, such as increased intake of bread, pasta, sugar and red meat or reduced intake of fruits and vegetables, are risk factors for small bowel adenocarcinoma (SBA) as they are for colorectal cancer^[9]. Ingestion of alcohol, coffee and use of tobacco also seem to be risk factors^[10]. Nevertheless, the strength of these associations are small and the majority of cases of DA are not associated with any known causative agents. However, duodenal adenomas, such as those that occur in familial adenomatous polyposis (FAP) and Gardner syndrome, are associated with elevated risk of DA^[11,12]. Similarly, patients with duodenal polyps are also at increased risk^[13]. Although less investigated than in colon cancer, the adenoma-carcinoma sequence is still largely accepted in SBA as well^[14,15].

CLINICAL PRESENTATION

Since patients do not typically present until tumors have grown to sufficient size to cause symptoms, the diagnosis of DA is difficult and often delayed. When symptoms do appear they are nonspecific and include abdominal pain, nausea, vomiting, fatigue,

weakness, and weight loss. Anemia, gastrointestinal obstruction and jaundice are symptoms associated with advanced disease. Abdominal pain is the most common presenting symptom, associated with 56% of cases^[16]. As a result of these delays in diagnosis, many cases of DA are not resectable at presentation due to local and distant invasion. Less often, patients undergoing screening programs may be found to have early DA or even adenoma with dysplasia before symptoms begin^[17].

DIAGNOSIS

Imaging

Since early symptoms are typically vague, most patients initially undergo either esophagogastroduodenoscopy or cross sectional imaging. Endoscopy is the preferred diagnostic modality as it allows simultaneous visualization and biopsy. Evaluation by an experienced endoscopist is critical as examination of the entire duodenum is required. While lesions in the third or fourth portion of the duodenum can be technically challenging to view endoscopically, the use of extra-long fiber optic scopes may be helpful^[18]. Lesions in the distal duodenum may be missed on initial endoscopic evaluation, resulting in further diagnostic delays. Careful attention to proximity of pertinent structures such as the ampulla of Vater should be given. Endoscopic ultrasound may be performed simultaneously to evaluate local extension or lymphadenopathy. In addition, it may facilitate tissue diagnosis when attempts at luminal biopsy are not successful. Upper gastrointestinal series with oral contrast may facilitate precise localization, evaluate for obstruction and rule out other causes of patients' symptoms. Contrast-enhanced computed tomography is important for assessing involvement of nearby structures, determining resectability and planning surgery. In cases without a confirmed diagnosis, sensitive but non-specific radiographic features suggestive of malignancy include an exophytic or intramural mass, central necrosis and ulceration^[19]. While the role of conventional abdominal ultrasound is limited, especially for tumors < 2 cm in size, lesions appear as irregularly marginated hypoechoic masses^[20].

Pathology

Diagnosis of DA requires a thorough histopathologic examination of tissue specimens. Adenocarcinoma of gastric, pancreas, distal bile duct and ampullary origin must be ruled out. The degree of associated dysplasia should be assessed. Among extra-ampullary DA, several distinct subtypes have been described: intestinal, gastric, pancreaticobiliary and indeterminate (Table 1)^[21,22]. Interestingly, intestinal type DA has been associated with more favorable prognosis compared to other histological subtype^[22-24]. Variable expression of the classic cytokeratin markers CK7 and CK20 have made them largely unhelpful in diagnosing DA^[25,26]. However, CDX2, a sensitive marker for colorectal

Table 1 Histopathologic subtypes of duodenal adenocarcinoma

Phenotype	Histological characteristics	Histologically similar	Immunophenotype markers	Prognosis
Intestinal	Tubular/cribiforming glands lined by columnar neoplastic cells	Colonic adenocarcinoma	MUC2, CD10, CDX2	+
Gastric	Tubular/papillary proliferation with foveolar or pyloric-type differentiation	Gastric adenocarcinoma	MUC5AC, MUC6	-
Pancreaticobiliary	Simple glands of cuboidal/columnar cells with rounded pleomorphic nuclei; prominent desmoplastic stroma	Pancreatic and Extrahepatic bile duct adenocarcinoma	MUC1	-
Indeterminate	Poor differentiation	None	MUC1	-

Adapted from Ushiku *et al.*^[22].**Table 2** 7th edition of the American Joint Committee on Cancer's staging system for small bowel adenocarcinoma

Primary tumor (T)	Regional lymph nodes (N)		Distant metastases (M)
Tx - Primary tumor cannot be assessed	Nx - Regional lymph nodes cannot be assessed		Mx - Distant metastases not assessed
Tis - Carcinoma <i>in situ</i>	N0 - No regional node metastasis		M0 - Distant metastases not present
T1a - Tumor invades lamina propria	N1 - Metastasis in 1-3 regional nodes		M1 - Distant metastases present
T1b - Tumor invades submucosa	N2 - Metastasis in 4 or more regional nodes		
T2 - Tumor invades muscularis propria	Stage grouping		
T3 - Tumor invades into the subserosa	Stage 0	Tis	N0
	Stage I	T1-T2	N0
	Stage IIA	T3	N0
T4 - Tumor perforates visceral peritoneum; or invades pancreas/bile duct	Stage IIB	T4	N0
	Stage IIIA	Any T	N1
	Stage IIIB	Any T	N2
	Stage IV	Any T	Any N

carcinoma, is more often expressed in DA and SBA^[25,27]. Expression of Her2 in DA has been inconsistently reported in the literature^[25,28], perhaps because expression may be limited to gastric subtypes of DA^[22]. Conversely, Overman *et al.*^[25] found EGFR and VEGF expression rates of 71% and 91%, respectively, in a large series of SBA which was primarily comprised of DA.

Staging

Staging of DA is based on the 7th edition of the American Joint Committee on Cancer's TNM staging system that was published in 2010 (Table 2)^[29]. Accurate nodal staging depends on adequate lymphadenectomy at the time of surgery^[30,31].

SURGICAL MANAGEMENT

Relevant anatomy

The duodenum is the first of portion of the small intestine and functions as a conduit between the stomach and the jejunum while regulating the emptying of gastric contents and enzymatically breaking down the chyme received from the stomach. The surgical management of duodenal cancers varies by the portion of the duodenum involved, and hence the basic anatomic divisions merit review. The first segment of the duodenum is suspended by the hepatoduodenal ligament, lies intraperitoneally, begins caudal to the pylorus and extends 5 cm to the duodenal flexure.

Moving retroperitoneally, the second segment spans approximately 7.5 cm and is fixed to and curves around the head of the pancreas to travel medially at the level of L3. The transverse, or third, portion of the duodenum is 10 cm in length and lies anterior to the aorta and inferior vena cava but posterior to the superior mesenteric vein and artery. The ascending, or fourth, segment of the duodenum is approximately 2.5 cm in length and heads superior and laterally to become intraperitoneal again as it reaches the ligament of Treitz at the anatomical boundary of the duodenojejunal junction.

Surgical approach

Tumors located in the second portion of the duodenum typically require pancreaticoduodenectomy (PD) because of proximity to head of the pancreas, distal bile duct and ampulla of Vater. Conversely, tumors occurring in the first, third or fourth portion of the duodenum may be managed by either PD or segmental resection (SR). Some will argue that PD should be used for all DAs, regardless of location, to ensure wide margins and adequate regional lymphadenectomy. This opinion is based on the results of early series reporting few long-term survivors of SR^[32-39]. Still others will argue for SR of tumors in either the very proximal or very distal duodenum provided that wide margins can be achieved^[40-42] in order to avoid the morbidity of PD. Most studies that compared outcomes of two approaches found no statistically significant difference

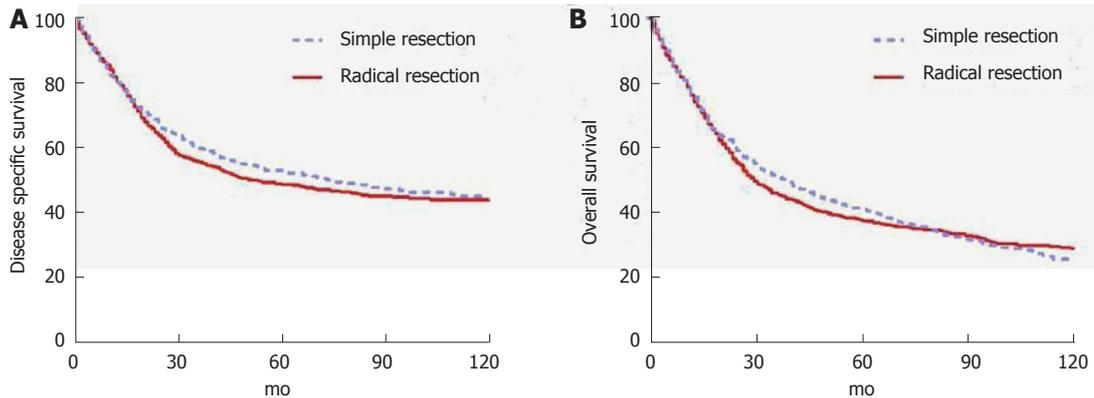


Figure 1 Outcomes of surgery for duodenal adenocarcinoma based on type of surgery. Used with permission: Cloyd *et al*^[49].

in outcomes, but were limited by small sample sizes and retrospective design^[13,42-48]. Cloyd *et al*^[49] recently utilized the surveillance, epidemiology and end results database to retrospectively compare the outcomes of radical resection (defined as a resection of the primary duodenal tumor *en bloc* with an adjacent organ, as is performed in PD) vs SR across a population-based cohort of patients with DA. In this study of 1611 patients from 1988 to 2010, radical resection was associated with a greater number of LNs excised but not improved survival (Figure 1). Although PD may be required for technical reasons in some situations, the study suggests that SR is an appropriate strategy as long as negative margins can be obtained^[49].

Regardless of the approach, an R0 resection remains the most important goal for surgery with curative attempt. Margin status directly impacts outcomes. Sohn *et al*^[35] reported the Johns Hopkins experience and showed a 5 year OS of 58% in margin negative patients vs 0% in margin positive patients. Similarly, Poultsides *et al*^[50] reviewed the Memorial Sloan Kettering Cancer Center (MSKCC) experience and found 5 year OS rates of 55% and 0% among R0 and R1 patients, respectively.

Lymphadenectomy

The importance of an adequate lymphadenectomy cannot be underscored. Sarela *et al*^[51] were among the first to report improved prognostic abilities of the N staging system with higher number of lymph nodes retrieved. In fact, a greater lymph node retrieval has independently been associated with improved survival for patients with DA^[2,31,49]. Although the American Joint Committee on Cancer has recommended a minimum pathologic evaluation of 6 lymph nodes, several authors have questioned whether this minimum number should be raised^[50,52]. Intuitively, one might expect operations that enable a better lymphadenectomy, such as a classic PD vs a pylorus-preserving PD or PD vs SR, would therefore be associated with improved survival. However, this has not been found to be the case, either in randomized controlled trials^[53] or population-based analyses^[49]. Although the reasons behind why greater

lymph node retrieval is associated with improved survival may be complex and multifactorial, it is likely primarily secondary to improved stage stratification and prognostication.

Palliative surgery

Among patients with localized DA, approximately 43%-87% will have resectable disease^[54]. Of the remainder, some will require palliation. The goals of palliative surgery for DA may include relief of gastric outlet obstruction, relief of biliary obstruction and/or pain relief. Operative interventions for gastroduodenal obstruction may include gastrojejunostomy or duodeno-jejunosomy; either may be constructed in a roux-en-y or loop fashion. Minimally invasive approaches are possible in the correct context. Surgery for biliary obstruction typically involves a roux-en-y hepatico-jejunosomy. A 13-year prospective study from the United Kingdom examining surgery for DA found that of the 178 patients included in the study, 150 underwent surgery with curative intention and 28 underwent surgery for palliation. Of those who received palliation, 15 had a gastrojejunostomy, 9 had a double bypass and 4 underwent an exploratory laparotomy without further intervention. Median survival in the palliative surgery group was 8 mo. Not surprisingly, those who undergo palliative surgery are more likely to have a larger tumor, greater degree of invasiveness, as well as regional and distant metastases^[55]. For patients who are not already undergoing surgical exploration and require palliation for enteral or biliary obstruction, endoscopically placed duodenal and biliary stents, when technically feasible, are preferable to avoid laparotomy given the limited prognosis.

Pancreas-preserving total duodenectomy

Although a comprehensive discussion is outside the scope of this review article, pancreas-preserving total duodenectomy (PPTD) has emerged as an alternative to PD or SR for patients with benign or pre-malignant conditions of the duodenum, most commonly in the setting of FAP. After total proctocolectomy, upper gastrointestinal cancers are the most common cause

Table 3 Series reporting factors associated with worse survival in duodenal adenocarcinoma

Ref.	Study period	Total No. of patients	No. of patients resected (%)	PD	5-year overall survival after resection (%)	Negative predictors of survival		
						Non-predictor	Univariate	Multivariate
Solaini <i>et al</i> ^[48]	2000-2013	178	150 (84.2)	132	43	T stage, grade, AJCC stage, perineural invasion, size, age	-	Lymphovascular invasion, nodal metastasis
Poultides <i>et al</i> ^[50]	1984-2006	122	122 (100)	122	48	T stage, tumor grade	Tumor grade, positive margins, perineural invasion, nodal metastasis, vascular invasion	Nodal metastasis
Onkendi <i>et al</i> ^[79]	1994-2009	124	99 (79.8)	70	37	Tumor size, positive nodes, surgical approach, adjuvant therapy	-	T stage and pathologic grade
Cecchini <i>et al</i> ^[80]	1982-2010	169	103 (60.9)	87	42	T stage, nodal metastasis, grade, AJCC stage, lymphovascular invasion, size, age	-	Perineural invasion
Liang <i>et al</i> ^[77]	1993-2010	36	36 (100)	31	NA	T stage, grade, AJCC stage, lymphovascular invasion, perineural invasion, size	Age > 75, body weight loss, nodal metastasis	Nodal metastasis
Malleo <i>et al</i> ^[73]	2000-2009	37	25 (67)	25	71 ¹	T stage, nodal metastasis, AJCC stage, lymphovascular invasion, perineural invasion, size, age	-	Tumor grade, lack of post-operative complications
Zhang <i>et al</i> ^[16]	1995-2008	91	59 (65)	NA	49 ¹	T stage, grade, AJCC stage, lymphovascular invasion, perineural invasion, size, age	-	Nodal metastasis, positive margins
Han <i>et al</i> ^[81]	1990-2006	32	28 (88)	18	30	-	Positive margins	-
Struck <i>et al</i> ^[78]	1989-2006	30	30 (100)	25	33 ²	Positive margins, T stage, adjuvant therapy	Positive margins	Nodal metastasis, stage
Lee <i>et al</i> ^[74]	1995-2007	53	28 (53)	26	44	Age, gender, weight loss, CA19-9, grade, tumor size	T stage, nodal metastasis, AJCC stage	Nodal metastasis
Hurtuk <i>et al</i> ^[82]	1984-2005	52	35 (67)	24	NA	Grade, positive margins, nodal metastasis, venous or perineural invasion	Stage T4, tumor size < 3.5 cm	-
Hu <i>et al</i> ^[47]	NA	43	28 (65)	11	27	-	Positive margins	-
Sarela <i>et al</i> ^[51]	1983-2000	137	72 (52.5)	56	71 ¹	Gender, grade, T stage	Age, nodal metastasis	Age, nodal metastasis
Tocchi <i>et al</i> ^[13]	1980-2000	47	25 (53)	9	23	T stage, grade, AJCC stage, lymphovascular invasion, perineural invasion, positive margins, size, age	-	Nodal metastasis
Ryder <i>et al</i> ^[83]	1957-1998	49	31 (63)	27	43	Nodal metastases, location in duodenum, type of resection, adjuvant chemoradiation	-	Tumor size, histologic grade, transmural invasion
Kaklamanos <i>et al</i> ^[43]	1978-1998	63	37 (59)	26	30	Age, gender, grade, T stage	Nodal metastasis	Nodal metastasis
Bakaen <i>et al</i> ^[44]	1976-1996	101	68 (67)	50	54	Histologic grade, tumor size, location in duodenum, adjuvant chemoradiation	Age, weight loss, T stage, nodal metastasis, AJCC stage	Weight loss, positive margins, nodal metastasis, AJCC stage
Sohn <i>et al</i> ^[35]	1984-1996	55	48 (87)	35	53	Nodal metastasis, adjuvant chemoradiation, tumor size, histologic grade	Positive margins, segmental resection, tumor in third/fourth portion of duodenum	-
Sexe <i>et al</i> ^[76]	1987-1991	85	34 (40)	31	23	AJCC Stage	-	-
Rotman <i>et al</i> ^[84]	1978-1988	66	46 (70)	38	45	Gender, age, weight loss, jaundice, T stage, tumor size, pancreatic invasion	-	-
Delcore <i>et al</i> ^[85]	1960-1990	35	28 (80)	21	60	nodal metastasis, location of metastatic nodes	GI bleeding, symptomatic > 4 mo, nodal metastasis	-
Barnes <i>et al</i> ^[40]	1967-1991	67	36 (54)	27	54	Nodal metastasis	Stage	-

Lowell <i>et al</i> ^[42]	1970-1991	17	17 (100)	8	45	-	First/second portion of the duodenum	-
Ouriel <i>et al</i> ^[33]	1950-1981	65	19 (29)	1	30	-	Histologic grade, nodal metastasis	-

Values in parentheses are percentages. ¹R0 resection only; ²Three-year survival. PD: Pancreaticoduodenectomy; AJCC: American Joint Committee on Cancer; NA: Not available.

of death in patients with FAP^[56]. Intense screening programs utilizing duodenoscopy with endoscopic polypectomy have proven effective in reducing the incidence of DA in this high risk population^[57]. In patients with diffuse polyposis or Spigelman stage IV disease, however, prophylactic duodenectomy may be indicated^[56,58,59]. Several techniques of PPTD have been described^[60-63] including minimally invasive options^[64]. Despite the advantages of organ preservation, short term morbidity and mortality rates remain high^[65]. It is important to note that invasive carcinoma in FAP patients should be treated similarly to sporadic DA with either PD or SR (as described above) in order to ensure adequate margins and lymphadenectomy. Pylorus-preserving PD should be avoided in patients with FAP as the residual duodenal bulb remains at risk for new polyp and carcinoma formation^[66].

ADJUVANT THERAPY

Chemotherapy

Unfortunately, little data is currently available to inform the choice of adjuvant chemotherapy following complete surgical resection. The ESPAC-3 trial was a phase 3, multi-institutional, randomized controlled trial comparing observation vs adjuvant fluorouracil vs adjuvant gemcitabine in patients with periampullary cancers (ampullary, bile duct, duodenal or other) who underwent PD with R0 or R1 resection status. Although median survival was not significantly different between the observation and adjuvant therapy groups in the primary analysis (35 mo vs 43 mo), adjuvant chemotherapy was associated with improved OS after multivariable regression (HR = 0.75, 95%CI: 0.57-0.98)^[67]. Importantly, periampullary DA comprised a small subset of this study's population and extra-ampullary DA was not included.

Given its rarity, most therapeutic studies have traditionally combined DA with either other periampullary cancers or small bowel adenocarcinomas. For this reason, chemotherapeutic regimens are not standardized, but increasingly DA is being treated similar to colorectal adenocarcinoma with oxaliplatin-based chemotherapy. Given the tendency of this disease to recur systemically, the role of adjuvant chemotherapy warrants further investigation. Current practice at many centers is to treat patients with high risk features (*e.g.*, nodal metastasis) with oxaliplatin-based chemotherapy^[50].

Definitive, or palliative, chemotherapy should be offered to all eligible patients with metastatic or

unresectable disease. A phase II prospective trial studied 30 patients with metastatic or unresectable small bowel or ampullary adenocarcinoma who received capecitabine and oxaliplatin and noted a 50% overall response rate, 10% complete response. Median time to progression was 11 mo with median overall survival 20 mo^[68,69]. Patients should also be considered for clinical trials as appropriate.

Chemoradiation

The role of adjuvant radiotherapy in the treatment of DA is not well defined. No studies have demonstrated an effect on OS with the use of chemoradiotherapy (CRT). One small study of 14 patients from Johns Hopkins with node-positive DA treated with PD and adjuvant CRT (median dose of 50 Gy, concurrent 5-FU) resulted in improved local control compared with surgery alone (93% vs 67%)^[70]. Similarly, a retrospective study of 32 patients from Duke University Medical Center was able to show modest improvement in local control (70% vs 49%) with adjuvant CRT^[71]. Unfortunately, neither study showed that adjuvant chemoradiation contributed to improved overall survival: 5-year survival 44% vs 43%^[70] and 44% vs 57%^[71], respectively. Other retrospective series have shown similar results with improvements in locoregional control but not OS^[72]. Nevertheless, this approach targeting improved locoregional control may make CRT particularly useful in patients with lymph node metastases. In a study of 122 patients at a single institution who underwent curative resection for DA, adjuvant CRT in patients with a higher prevalence of regional lymph node metastases was associated with a similar overall survival to that of a group of patients with limited or no nodal metastases who did not receive adjuvant therapy^[50].

OUTCOMES

Short term

Surgery for DA can be associated with significant morbidity and mortality. Poultsides *et al*^[50] in their contemporary series of PD at MSKCC, reported a postoperative morbidity rate of 35% and 30-d mortality rate of 2.4%. Solaini *et al*^[48] published a postoperative complication rate of 40% and in-hospital mortality rate of 3.3% for all patients undergoing surgery for DA. In these studies, postoperative pancreatic fistulae (POPF) developed following PD in 14.0% and 10.6% of patients, respectively^[48,50]. The impact of the type of resection on postoperative outcomes is controversial. Some have suggested that SR is associated with

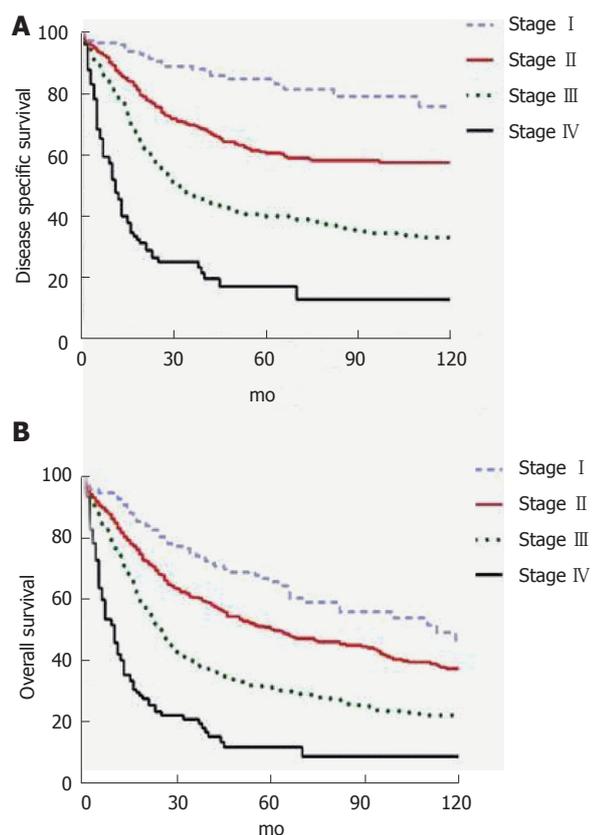


Figure 2 Stage-based disease free (A) and overall (B) survival for patients undergoing surgery for duodenal cancer based on seer data. Used with permission: Cloyd *et al.*^[49].

improved outcomes as it avoids the opportunity for POPF. Tocchi *et al.*^[13] reviewed their series of 47 patients undergoing surgery for DA and found SR to be associated with less postoperative morbidity, mortality and length of hospital stay. Bakaeen *et al.*^[44] found similar complication rates but shorter LOS in the patients undergoing SR. Other studies have failed to find an effect of surgery type on complication rates^[43,48]. The occurrence of a postoperative complication may be associated with worse long term survival^[73].

Long term

DA represents an aggressive cancer but in patients with resectable disease, long term outcomes are better than with other periampullary malignancies. In a retrospective study of 122 patients who underwent PD for DA over a 22 year period at MSKCC, ten-year OS was 41%^[50]. A prospective cohort study of 150 patients from six United Kingdom hepatopancreaticobiliary centers undergoing curative intent surgery for DA from 2000-2013 found 1-, 3- and 5-year OS rates of 83.9%, 66.7% and 51.2%, respectively. Median disease-free survival was 53 mo^[48]. A recent population-based study suggested worse outcomes with 5-year OS rates of 65.9%, 50.4%, 31.4%, and 11.9% for Stage I, II, III and IV, respectively (Figure 2)^[49]. Patients with metastatic or unresectable disease have median survival that ranges from 2-8 mo^[68,69,74,75].

Prognostic factors

Factors associated with worse outcome in DA include patient age, distant metastasis, lymph node metastasis, lymph node ratio, number of lymph nodes harvested, high tumor grade, tumor (T) stage, margin status, lymphovascular or perineural invasion, and overall cancer stage (Table 3). Lymph node metastasis remains one of the most important prognostic determinants^[41,43,44,49-51,74,76-78]. In the largest single institution series of 122 patients who underwent PD for DA, the presence of lymph node metastases was the only independent predictor of decreased survival in multivariate analysis. Five-year survival for node negative (N0) patients was 68% compared to 17% in patients with N2 disease^[50]. Another study calculated 3-year survival for node negative patients to be 87.5% compared to only 21% in patients with nodal disease^[74]. LNR, the ratio of positive LNs to number of LNs excised, may be even a more accurate predictor of prognosis^[2,31,49].

CONCLUSION

Duodenal adenocarcinoma is a rare but aggressive malignancy. Because of the nonspecific symptoms it presents with and the difficulty in confirming a diagnosis, patients may often present with advanced disease. Nonetheless, aggressive surgical resection, when possible, affords the best chance at survival. The decision of whether to perform pancreaticoduodenectomy vs segmental resection depends on the location of the primary tumor as both are acceptable options as long as negative margins can be safely obtained. Lymph node positivity is one of the most important prognostic indicators and a wide lymphadenectomy should be routinely performed. Although data are limited guiding adjuvant therapy options, oxaliplatin-based chemotherapy is typically offered to high risk patients, such as those with positive lymph nodes. In some series, adjuvant radiation is associated with improved local control but no difference in overall survival. Previous research on DA has been limited by small sample sizes and single institutional design. Further research would benefit from multi-institutional trials that do not combined DA with other periampullary or small bowel malignancies.

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Adhesive small bowel adhesions obstruction: Evolutions in diagnosis, management and prevention

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Abstract

Intra-abdominal adhesions following abdominal surgery represent a major unsolved problem. They are the first cause of small bowel obstruction. Diagnosis is based on clinical evaluation, water-soluble contrast follow-through and computed tomography scan. For patients presenting no signs of strangulation, peritonitis or severe intestinal impairment there is good evidence to support non-operative management. Open surgery is the preferred method for the surgical treatment of adhesive small bowel obstruction, in case of suspected strangulation or after failed conservative management, but laparoscopy is gaining widespread acceptance especially in selected group of patients. "Good" surgical technique and anti-adhesive barriers are the main current concepts of adhesion prevention. We discuss current knowledge in modern diagnosis and evolving strategies for management and prevention that are leading to stratified care for patients.

Key words: Adhesive disease; Intestinal obstruction; Diagnosis of adhesive small bowel obstruction; Non-operative management of adhesive disease; Emergency surgical treatment

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Core tip: Adhesive disease is a consequence of all intra-peritoneal surgeries. We decided to carry out a systematic review about the adhesive small bowel

obstruction because it is still difficult to make differential diagnosis and to understand the right time to operate and which surgical technique to perform. Besides there is a way to prevent major adhesive disease: "Good" surgical technique and anti-adhesive barriers are the main current concepts of adhesion prevention. We discuss all current knowledge in this field.

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INTRODUCTION

Adhesive disease is the most frequently encountered disorder of the small intestine; in one review of 87 studies including 110076 patients, the incidence of adhesive small bowel obstruction (ASBO) following all types of abdominal operations was 2.4%^[1].

In North America, there are more than 300000 annual hospital admissions for ASBO accounting for 850000 d of inpatient care, costing more than \$1.3 billion in medical expenditures and contributing to more than 2000 deaths annually^[2].

Dembrowski published the first data on induction of adhesions in an animal model in 1889 and in the following 120 years there have been extensive studies both *in vitro* and *in vivo*^[3].

In the past decade, limited clinical research has produced uncertainty about best practice with subsequent international variation in delivery and in outcome.

There is a diagnostic dilemma on how to distinguish between adhesive SBO and other causes, and how to distinguish between ASBO that needs emergency surgery and ASBO that can be successfully treated conservatively.

ASBO after peritoneal cavity surgery is a well-known disease entity that still harbors challenges regarding prevention, diagnosis and treatment despite general improvements in care. Good surgical technique, *e.g.*, laparoscopy, and anti-adhesive barriers at initial surgery seem to reduce ASBO but reports have conflicting results and only provide general conclusions which do not apply for each individual patient. Contrast enhanced computed tomography (CT) has improved diagnosis of ASBO in general but cannot be performed in each patient (severe vomiting, kidney failure) and fails to accurately identify adhesions as the cause. Also, predicting which treatment should be installed and success of treatment by CT is under debate. Regarding surgical treatment laparoscopy has gained popularity but also is associated with increased risk of iatrogenic complications. Particularly, identifying patients who might benefit from laparoscopic adhesiolysis and who

should not and should be treated by open surgery is a challenge.

Therefore, ASBO diagnosis, treatment and prevention are important for reducing mortality, morbidity and for socioeconomic reasons.

The aim of this review is to provide an update of the current controversies over diagnosis, non-operative/operative management and prevention of ASBO.

LITERATURE RESEARCH

We searched the Cochrane Library, MEDLINE, and EMBASE, limited to the final search date (31/03/2015) and not limited to English language publications.

We used the search terms "small bowel" or "obstruction" in combination with the terms "adhesions" or "adhesive" or "adherences".

We largely selected publications in the past five years, but did not exclude commonly referenced and highly regarded older publications.

We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

We searched ClinicalTrials.gov (01/01/2000-31/03/2015) for current trials in ASBO.

EPIDEMIOLOGY

Intra-abdominal adhesions following abdominal surgery represent a major unsolved problem; in patients with abdominal pain, ASBO is a common cause that accounts for 4% of all emergency department admissions and 20% of emergency surgical procedures^[4].

These fibrous bands are thought to occur in up to 93% of patients undergoing abdominal surgery and can complicate future surgery considerably^[5].

Adhesion formation can result in significant morbidity, mortality and infertility in women, and adhesion-related complications are also responsible for up to 74% cases of ASBO in adults and 30% of re-admissions at 4 years after an incident intra-abdominal surgery^[6].

It is unknown whether the increase in laparoscopic intra-abdominal surgery has translated into fewer postoperative complications due to adhesions; a recent review of 11 experimental studies involving seven animal models and four human studies reported mixed results. Some reported decreased rates of adhesion formation after laparoscopy. However, there was significant heterogeneity among the human studies^[7,8].

Furthermore, some evidence suggests that this decrease in adhesion formation has not necessarily translated to a decrease in adhesion-related obstruction; in a recent randomized, multi-center trial comparing outcomes in laparoscopic vs conventional approaches in colorectal surgery for malignancy, there was no difference between the two groups in obstruction-related complications at 3-year follow-up consultations^[9].

However, in a long-term follow-up study examining the rate of hospitalization due to ASBO for patients

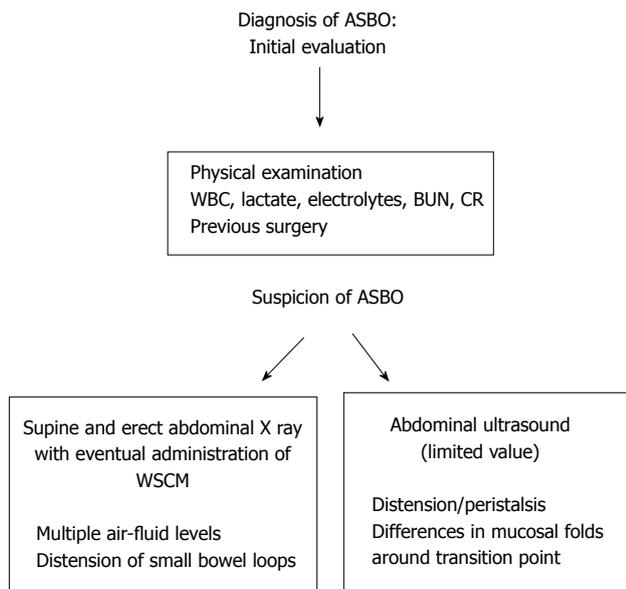


Figure 1 Adhesive small bowel obstruction diagnosis: Initial evaluation. ASBO: Adhesive small bowel obstruction; WBC: White blood cell count; BUN: Blood urea nitrogen; CR: Creatinine; WSCM: Water soluble contrast medium.

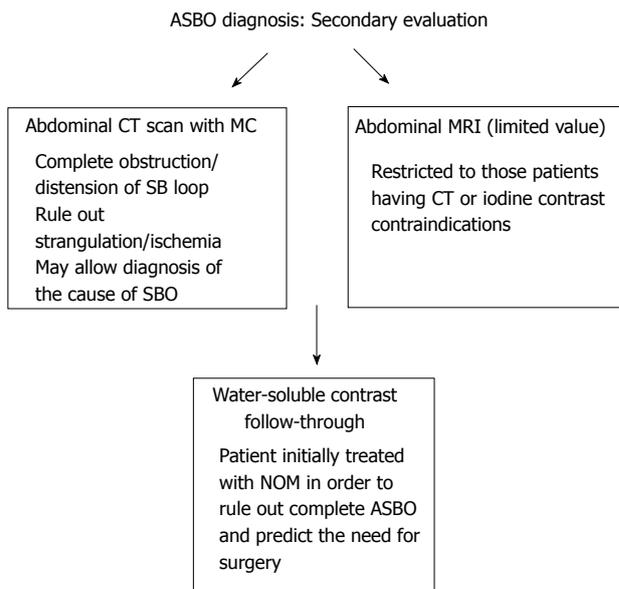


Figure 2 Adhesive small bowel obstruction diagnosis: Secondary evaluation. ASBO: Adhesive small bowel obstruction; NOM: Non operative management; CT: Computed tomography; MC: Medium contrast.

operated on due to suspected appendicitis, the laparoscopic approach resulted in significantly lower rates compared to open surgery. However, frequency of ASBO after the index surgery was low in both groups^[10].

In a recent meta-analysis the incidence of adhesive small bowel obstruction was highest in pediatric surgery (4.2%, 2.8% to 5.5%; $I^2 = 86\%$) and in lower gastrointestinal tract surgery (3.2%, 2.6% to 3.8%; $I^2 = 84\%$); the incidence was lowest after abdominal wall surgery (0.5%, 0.0% to 0.9%; $I^2 = 0\%$), upper gastrointestinal tract surgery (1.2%, 0.8% to 1.6%; $I^2 = 80\%$), and urological surgery (1.5%, 0.1% to 3.0%; $I^2 = 67\%$)^[11].

DIAGNOSIS

Preliminary assessment

The first step in the diagnostic work flow for ASBO is a detailed anamnesis and physical examination, followed by the evaluation of a complete blood count with differential especially white blood cell (WBC) count, electrolytes including blood urea nitrogen and creatinine, C-reactive protein, serum lactate, lactate dehydrogenase (LDH) and creatine kinase (CK). In patients who present with systemic signs (*e.g.*, fever, tachycardia, hypotension, altered mental status), additional laboratory investigation should include arterial blood gas and serum lactate. Although patients with ASBO generally may complain a varied assortment of symptoms, such as discontinuous abdominal pain, nausea and vomiting, associated, in the vast majority of cases, with a history of previous abdominal surgery^[11], these clinical symptoms contribute only to some extent to the diagnosis of ASBO^[12]. Unfortunately, the clinical symptoms of ASBO are even less consistent predictors in differentiating patients with bowel strangulation who

need emergency surgical intervention^[13]. Laboratory tests may be more useful to estimate the grade of systemic illness, than to confirm clinical suspicions. Actually the typical inflammatory markers, like WBC count and CPR levels, cannot discriminate between the inflammation due to ASBO and that caused by other inflammatory conditions^[14,15]. In the case of bowel ischemia due to strangulation, these markers cannot discriminate the patients who benefit from conservative treatment and those who need surgery^[16,17]. Nevertheless, when evolution to ischemia follows, serum lactate, LDH and CK may increase due to bowel hypoperfusion^[16]. However, since LDH and CK increase in any ischemic state, they are consequently quite unspecific. Instead, because serum lactate rises only at a stage when widespread bowel infarction is already well established, lactate increase is highly sensitive, but not specific, for ischemia in patients with ASBO (sensitivity 90%-100%, specificity 42%-87%), being thus a robust sign to proceed to urgent surgery^[18,19]. Recent reports indicate that, although there is no reliable clinical or laboratory marker for intestinal ischemia, an intestinal fatty acid binding protein, which is released by necrotic enterocytes, may become a useful marker for the detection of bowel ischemia^[20]. In conclusion, laboratory tests can simply indicate general disease severity and can be used to support or rule out an emergency surgical choice only in the context of agreement of a number of other clinical findings. Moreover, serum tests are clearly worthwhile in the evaluation of any patient with acute obstruction, because they may indicate needed adjustment of electrolyte abnormalities and fluid resuscitation (Figure 1).

Secondary evaluation

While ASBO may be suspected based only upon



Figure 3 Adhesive small bowel obstruction caused by single band adhesion: Computed tomography scan.

risk factors, symptoms, and physical examination, abdominal imaging is usually required to confirm the diagnosis, eventually detecting the location of obstruction and identifying complications, like ischemia, necrosis, and perforation^[21,22]. Although multiple imaging modalities are available to confirm a suspected diagnosis of ASBO, plain radiography and abdominal CT are those most suitable and useful. Thus, the preliminary assessment for all patients suspected for ASBO should include supine and erect plain abdominal radiography that can display multiple air-fluid levels with distension of small bowel together with the absence of gas in the colon^[23]. However, it must be said that the reason or site of obstruction is usually not clear on plain radiography, since a specific site between the enlarged proximal and undilated distal bowel frequently cannot be recognized with certainty. For the diagnosis of ASBO, the sensitivity, specificity, and accuracy of plain X-ray are from 79% to 83%, from 67% to 83%, and from 64% to 82%, respectively (Figure 2).

Abdominal CT scans (Figure 3), especially with administration of oral or intravenous contrast medium, perform better than plain X-ray in finding the transition point, evaluating the severity of obstruction, identifying the cause of obstruction, and recognizing complications (ischemia, necrosis, and perforation)^[24]. The sensitivity, specificity, and accuracy of CT scans for ASBO diagnosis are, respectively, from 90% to 94%, 96%, and 95%^[25]. CT has been demonstrated to be highly diagnostic in ASBO, especially in all patients with inconclusive plain X-ray^[26]. However, it should not be routinely implemented in the diagnosis-making process except when clinical history, physical examination, and plain film were not convincing for ASBO diagnosis^[27], since these are readily available, less expensive, expose the patient to less radiation, and may highlight the need for abdominal CT in some patients.

Abdominal ultrasound and magnetic resonance enterography may be useful for the diagnosis of ASBO only in selected patients and their use should be restricted to those patients having CT or iodine contrast contraindications^[28].

Although small bowel contrast studies, in general, have a limited role in the initial diagnosis of ASBO and in some circumstances, like in the presence of perforation, some of them, as those with the use of barium, are contraindicated^[24], instead those using water-soluble contrast agents (WSCA), being safer than barium in cases of perforation and peritoneal spread, are extremely valuable in patients undergoing initial non-operative conservative management in order to rule out complete ASBO and predict the need for surgery^[29]. In this sense, small bowel WSCA studies in the presence of ASBO have not only diagnostic, but especially therapeutic value^[26].

TREATMENT -

NON-OPERATIVE MANAGEMENT

Patient selection

For patients presenting with ASBO without signs of strangulation, peritonitis or severe intestinal impairment there is good evidence to support NOM.

Free intraperitoneal fluid, mesenteric edema, lack of the "small bowel feces sign" at CT-scan, history of vomiting, severe abdominal pain (VAS > 4), abdominal guarding, raised white cell count and devascularized bowel at CT-scan predict the need for emergent laparotomy^[30].

Moreover, patients with repeated ASBO episodes, many prior laparotomies for adhesions and prolonged conservative treatment should be cautiously selected to find out only those who may benefit from early surgical interventions^[30].

At present, there is no consensus about when conservative treatment should be considered unsuccessful and the patient should undergo surgery; in fact, the use of surgery to solve ASBO is controversial, as surgery induces the formation of new adhesions^[30].

Level I data have shown that NOM can be successful in up to 90% of patients without peritonitis^[31].

As a counterpart, a delay in operation for ASBO places patients at higher risk for bowel resection. A retrospective analysis showed that in patients with a ≤ 24 h wait time until surgery, only 12% experienced bowel resection and in patients with a ≥ 24 h wait time until surgery, 29% required bowel resection^[32].

Schraufnagel *et al.*^[33] showed that in their huge patient cohort, the rates of complications, resection, prolonged length of stay and death were higher in patients admitted for ASBO and operated on after a time period of ≥ 4 d.

The World Society of Emergency Surgery 2013 guidelines stated that NOM in the absence of signs of strangulation or peritonitis can be prolonged up to 72 h. After 72 h of NOM without resolution, surgery is recommended^[30].

There are no objective criteria that identify those patients who are likely to respond to conservative treatment. Less clear, in fact, is the way to predict

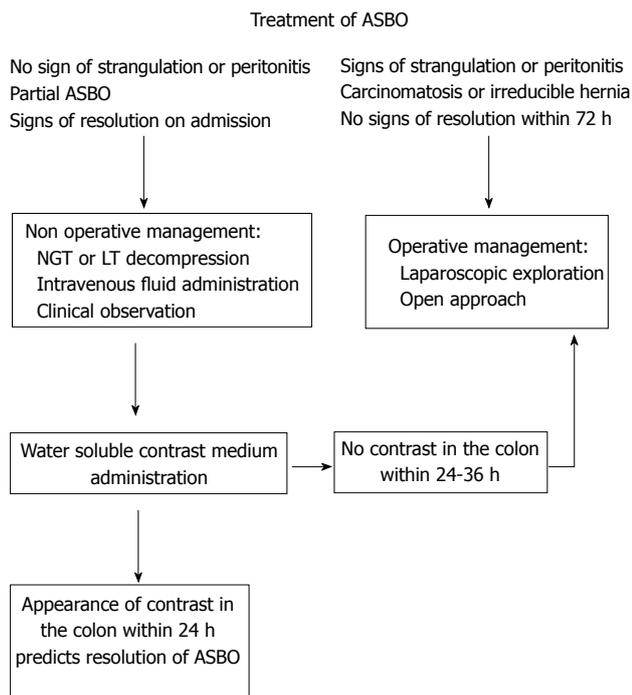


Figure 4 Adhesive small bowel obstruction treatment. ASBO: Adhesive small bowel obstruction; NGT: Naso-gastric tube; LT: Long tube.

between progression to strangulation or resolution of ASBO. Some authors suggested the following as strong predictors of NOM failure: The presence of ascites, complete ASBO (no evidence of air within the large bowel), increased serum creatine phosphokinase and ≥ 500 mL from nasogastric tube on the third NOM day^[30].

However, at any time, if there is an onset of signs of strangulation, peritonitis or severe intestinal impairment, NOM should be discontinued and surgery is recommended.

It is really difficult to predict the risk of operation among those patients with ASBO who initially underwent NOM^[30].

Tube decompression, WSCA and other treatments

Randomized clinical trials showed that there are no differences between the use of nasogastric tubes compared to the use of long tube decompression^[34].

In any case, early tube decompression is beneficial in the initial management, in addition to required attempts of fluid resuscitation and electrolyte imbalance correction. For challenging cases of ASBO, the long tube should be placed as soon as possible, more advisable by endoscopy, rather than by fluoroscopic guide^[35].

Several studies investigated the diagnostic-therapeutic role of WSCA^[36]. Gastrografin is the most commonly utilised contrast medium. It is a mixture of sodium diatrizoate and megluminediatrizoate. Its osmolarity is 2150 mOsm/L. It activates movement of water into the small bowel lumen. Gastrografin also decreases oedema of the small bowel wall and it may also enhance smooth muscle contractile activity that

can generate effective peristalsis and overcome the obstruction^[37].

The administration of WSCA proved to be effective in several randomized studies and meta-analysis. Three recent meta-analyses showed no advantages in waiting longer than 8 h after the administration of WSCA^[26] and demonstrated that the presence of contrast in the colon within 4-24 h is predictive of ASBO resolution. Moreover, for patients undergoing NOM, WSCA decreased the need for surgery and reduced the length of hospital stay^[38,39].

Oral therapy with magnesium oxide, *L. acidophilus* and simethicone may be considered to help the resolution of NOM in partial ASBO with positive results in shortening the hospital stay^[40].

Lastly hyperbaric oxygen therapy may be an option in the management of high anesthesiologic risk patients for whom surgery should be avoided^[41].

No agreement exists about the possibility to predict the recurrence risk. Factors associated with a higher risk of recurrence are age < 40 years, matted adhesion and postoperative surgical complications^[42]. Compared to traditionally conservatively treated patients, Gastrografin use does not affect either the ASBO recurrence rates or recurrences needing surgery (Figure 4)^[29].

SURGERY

Open surgery

Until recently open surgery has been the preferred method for the surgical treatment of ASBO (in case of suspected strangulation or after failed conservative management), and laparoscopy has been suggested only in highly selected group of patients (preferably in case of first episode of ASBO/or anticipated single band adhesion) using an open access technique and the left upper quadrant for entry^[30] (Figure 5).

More recently, the use of laparoscopy is gaining widespread acceptance and is becoming the preferred choice in centers with specific expertise.

A meta-analysis by Li *et al.*^[43] found that there was no statistically significant difference between open vs laparoscopic adhesiolysis in the number of intraoperative bowel injuries, wound infections, or overall mortality. Conversely there was a statistically significant difference in the incidence of overall and pulmonary complications and a considerable reduction of prolonged ileus in the laparoscopic group compared with the open group. The authors concluded that laparoscopic approach is safer than the open procedure, but only in the hands of experienced laparoscopic surgeons and in selected patients^[43].

However, no randomized controlled trial comparing open to laparoscopic adhesiolysis exists to date, and both the precise indications and specific outcomes of laparoscopic adhesiolysis for adhesive SBO remain poorly understood. The only randomized controlled trial aiming to provide level Ib evidence to assess the use of laparoscopy in the treatment of adhesive small bowel



Figure 5 Adhesive small bowel obstruction caused by single band adhesion: Open surgery.



Figure 6 Adhesive small bowel obstruction caused by single band adhesion: Laparoscopic surgery.

obstruction is currently ongoing, having the length of postoperative hospital stay as the primary endpoint and the passage of stools, commencement of enteral nutrition, 30-d mortality, complications, postoperative pain, length of sick leave, rate of ventral hernia and the recurrence of small bowel obstruction during long-term follow-up as secondary and tertiary endpoints^[44].

Laparoscopy

Laparoscopic adhesiolysis (Figure 6) for small bowel obstruction has a number of potential advantages including less postoperative pain, faster return of intestinal function, shorter hospital stay, reduced recovery time, allowing an earlier return to full activity, fewer wound complications, and decreased postoperative adhesion formation^[45].

In a recent large population-based propensity score-matched analysis involving 6762 patients^[46], laparoscopic treatment of ASBO was associated with lower rates of postoperative morbidity, including SSI, intraoperative transfusion, and overall lower resource use compared with laparotomy as well as shorter hospital stay. Laparoscopic treatment of surgical ASBO is not associated with a significant difference in operative time, rates of re-operation within 30 d, or mortality.

Further recent reports confirmed that laparoscopic surgical management of adhesive SBO is associated with quicker gastrointestinal recovery, shorter length of stay (LOS), and reduced overall complications compared to open surgery, without significant differences in operative times^[47]. Furthermore, following exclusion of bowel resections, secondary outcomes continued to favor laparoscopy.

Although laparoscopic adhesiolysis requires a specific skill set and may not be appropriate in all patients, the laparoscopic approach demonstrates a clear benefit in 30-d morbidity and mortality even after controlling for preoperative patient characteristics (lower major complications and incisional complications rate) as well as shorter postoperative LOS and shorter mean operative times. Given these findings in more than 9000

patients and consistent rates of SBO requiring surgical intervention in the United States, increasing the use of laparoscopy could be a feasible way of to decrease costs and improving outcomes in this population^[48].

Patient selection is still a controversial issue. From a recent consensus conference^[49], a panel of experts recommended that the only absolute exclusion criteria for laparoscopic adhesiolysis in SBO are those related to pneumoperitoneum (*e.g.*, hemodynamic instability or cardiopulmonary impairment); all other contraindications are relative and should be judged on a case-to-case basis, depending on the laparoscopic skills of the surgeon.

Nonetheless it is now well known that the immune response correlates with inflammatory markers associated with injury severity and, as a consequence, the magnitude of surgical interventions may influence the clinical outcomes through the production of molecular factors, ultimately inducing systemic inflammatory response and the beneficial effect of minimally invasive surgeries and of avoiding laparotomy is even more relevant in the frail patients^[50].

Laparoscopic adhesiolysis is technically challenging, given the bowel distension and the risk of iatrogenic injuries if the small bowel is not appropriately handled. Key technical steps are to avoid grasping the distended loops and handling only the mesentery or the distal collapsed bowel. It is also mandatory to fully explore the small bowel starting from the cecum and running the small bowel distal to proximal until the transition point is found and the band/transition point identified. After release of the band, the passage into distal bowel is restored and the strangulation mark on the bowel wall is visible and should be carefully inspected.

As a precaution in the absence of advanced laparoscopic skills, a low threshold for open conversion should be maintained when extensive and matted adhesions are found^[51].

Reported predictive factors for a successful laparoscopic adhesiolysis are: Number of previous laparotomies ≤ 2 , non-median previous laparotomy, appendectomy as previous surgical treatment causing adhesions,

unique band adhesion as pathogenetic mechanism of small bowel obstruction, early laparoscopic management within 24 h from the onset of symptoms, no signs of peritonitis on physical examination, and experience of the surgeon^[52].

Because of the consistent risks of inadvertent enterotomies and the subsequent significant morbidity, particularly in elderly patients and those with multiple (three or more) previous laparotomies, the lysis should be limited to the adhesions causing the mechanical obstruction or strangulation or those located at the transition point area; some authors have attempted to design a preoperative nomogram and a score to predict risk of bowel injury during adhesiolysis, and they found that the number of previous laparotomies, anatomical site of the operation, presence of bowel fistula and laparotomy *via* a pre-existing median scar were independent predictors of bowel injury^[53,54].

PREVENTION

Surgical technique

Small bowel obstruction has been the driver of research in adhesion prevention measures, barriers and agents. Recent data from cohort studies and systematic reviews point at major morbidity and socioeconomic burden from adhesiolysis at reoperation, which have broadened the focus of adhesion prevention^[55]. Applying adhesion barriers in two-stage liver surgery and cesarean section, to reduce the incidence of adhesions and adhesiolysis related complications, are examples of the change in paradigm that reducing the incidence of adhesions is clinically more meaningful than only aiming at preventing adhesive small bowel obstruction^[56]. Increasing the number of patients without any peritoneal adhesion should be the general aim of adhesion prevention.

“Good” surgical technique and anti-adhesive barriers are the main current concepts of adhesion prevention. From a recent systematic review and meta-analysis on the impact of different surgical techniques on adhesion formation it was concluded that laparoscopy and not closing the peritoneum lower the incidence of adhesions^[1].

However, the burden of adhesions in laparoscopy is still significant most likely due to the necessity to make specimen extraction incisions in addition to trocar incisions and the unavoidable peritoneal trauma by surgical dissection and the use of CO₂ pneumoperitoneum (intraperitoneal pressure and desiccation). Reduced port laparoscopy and specimen extraction *via* natural orifices may theoretically further reduce peritoneal incision related adhesion formation^[57].

Anti-adhesive barriers

Since all abdominal surgeries involve peritoneal trauma and potential healing with adhesion formation, additional measures are needed to reduce the incidence of adhesions and related clinical manifestations. These measures consist of systemic pharmacological agents,

intraperitoneal pharmaceuticals or adhesion barriers^[58]. Most clinical experience is with intraperitoneal adhesion barriers, applied at the end of surgery with the aim to separate injured peritoneal and serosal surfaces until complete adhesion free healing has occurred. Efficacy of anti-adhesion barriers in open surgery has been well established for reducing the incidence of adhesion formation^[59]. For one type of barrier (Hyaluronate-carboxymethylcellulose, HA-CMC, Seprafilm, Sanofi, Paris, France) the reduction of incidence of adhesive small bowel obstruction after colorectal surgery has also been established (RR = 0.49, 95%CI: 0.28-0.88) without patient harm^[59,60]. Oxidized regenerated cellulose (Interceed, Ethicon, West Somerville, NJ, United States) reduces the incidence of adhesion formation following fertility surgery (RR = 0.51, 95%CI: 0.31-0.86), but the impact on small bowel obstruction after gynecological surgery has not been studied^[59,61]. Drawback of both products is the difficulty to use in laparoscopic surgery, underlining the need to develop gel, spray or fluid barriers that are easy to apply *via* a trocar.

In the Prevention of Postoperative Abdominal Adhesions (P.O.P.A) study, authors randomized 91 patients to have 2000 cc of icodextrin 4% and 90% to have the traditional treatment. The authors noted no significant difference in the incidence of small bowel leakage or anastomotic breakdown; operative times, blood losses, incidence of small bowel resections, return of bowel function, LOS, early and late morbidity and mortality were comparable. After a mean follow-up of 41.4 mo, there have been 2 cases of ASBO recurrence in the icodextrin group and 10 cases in the control group ($P < 0.05$)^[61].

Consistent safety and efficacy evidence has not led to routine application of barriers in open or laparoscopic surgery. Reasons might be the lack of awareness, the question if the “effect size” is large enough for routine application or the belief that adhesion formation even may benefit the patients, *e.g.*, reinforcing intestinal anastomosis or walling off peritoneal infection. However, the most used argument against routine use is the doubt regarding cost-effectiveness of adhesion barriers. The direct hospital costs in the United States in 2005 for adhesive small bowel obstruction alone was estimated at \$3.45 billion. Costs associated with the treatment of an adhesive SBO are estimated to be \$3000 per episode with conservative treatment and \$9000 with operative treatment. The additional costs incurred by operative treatment are partially due to complications of adhesiolysis. The incidence of bowel injuries during adhesiolysis for SBO is estimated to be between 6% and 20%. Inadvertent enterotomy due to adhesiolysis in elective surgery is associated with a mean increase in costs of \$38000^[58,61,62].

In a model, counted for in-hospital costs and savings resulting from adhesive SBO based on United Kingdom price data from 2007, Wilson showed that a low priced barrier at about \$160 with 25% efficacy in preventing SBO would result in healthcare savings. Another

concept with a \$360 priced barrier, would result in a net investment on the long-term unless a higher efficacy of 60% could be achieved. In this model treatment costs for small bowel obstruction were substantially lower than more recent cost calculations. Recent direct healthcare costs associated with treatment of major types of adhesion related complications (small bowel obstruction, adhesiolysis complications and secondary female infertility) within the first 5 years after surgery are \$2350 following open surgery and \$970 after laparoscopy. Application of an anti-adhesion barrier could save between \$678-1030 following open surgery and between \$268-413 following laparoscopic surgery on the direct healthcare costs related to treatment of adhesion related complications (data not published). Benefits from reduction in SBO were \$103 in open surgery and \$32 in laparoscopic surgery, using a high (\$360) priced product and only taken into account reoperations for adhesive small bowel obstruction. From these cost modeling it seems that even routine use of anti-adhesion barriers is cost-effective in both open and laparoscopic surgery^[62-64].

CONCLUSION

Unfortunately, there are not yet devices able to totally prevent the intraperitoneal adhesion formation after abdominal surgery; only the use of correct surgical technique and the avoidance of traumatic intraperitoneal organ maneuvers may help to reduce postoperative adhesion incidence.

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Doppler-guided hemorrhoidal dearterialization/transanal hemorrhoidal dearterialization: Technical evolution and outcomes after 20 years

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Abstract

In the setting of Hemorrhoidal Disease treatment, the

option of conventional hemorrhoidectomy is highly effective, but it is still associated with postoperative pain and discomfort. For this reason, technical alternatives have been developed in order to reduce complications and to provide better postoperative recovery. To accomplish this aim, non-excisional techniques such as stapled hemorrhoidectomy and Doppler-guided hemorrhoidal ligation have been introduced into clinical practice with high expectations. The aim of this article is to revise the literature about transanal hemorrhoidal dearterialization technique in the treatment of hemorrhoidal disease, looking into its evolution, results and possible benefits over other modalities of surgical treatment. The literature review showed that Doppler-guided hemorrhoidal dearterialization is a safe and effective method to treat grades II to IV hemorrhoidal disease. Outcomes in patients presenting prolapse are satisfactory and the association of anopexy is an important aspect of this operation. Anal physiology disturbances are rarely observed and mainly transitory. This technique is an excellent option for every patient, especially in those with previous anal surgeries and in patients with previous alterations of fecal continence, when an additional procedure might represent a risk of definitive incontinence.

Key words: Doppler-guided hemorrhoidal dearterialization; Hemorrhoids; Transanal hemorrhoidal dearterialization

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Core tip: Management of hemorrhoidal disease is a tough task. First of all, because there are some technical alternatives that should be adequately indicated to different patients; secondly, because patients desire a good alternative associated with low morbidity, good long-term results and less postoperative pain. In this setting, the transanal hemorrhoidal dearterialization

(THD) technique is considered a safe and effective choice for internal hemorrhoids of grades II to IV. The present paper reviews technical aspects and literature results of THD in comparison to other operative techniques.

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INTRODUCTION

For over 60 years, since the description of hemorrhoidectomy by Milligan and Morgan *et al.*^[1] and Ferguson *et al.*^[2], conventional hemorrhoidectomy (CH) has been the standard treatment for grades III and IV hemorrhoids. It is also indicated for grade II hemorrhoids refractory to conservative methods (such as rubber band ligation or infrared coagulation) or to those that have recurred. However, CH is still associated with postoperative pain and discomfort. Thus, technical alternatives to manage hemorrhoidal disease have been sought, in order to reduce complications and to provide better postoperative recovery, especially less pain.

In this scenario, stapled hemorrhoidectomy (SH) and Doppler-guided hemorrhoidal ligation have been introduced in our practice since the 90's^[3,4]. Whether called Doppler-guided hemorrhoidal artery ligation (DG-HAL) or transanal hemorrhoidal dearterialization (THD), it is a technique for the treatment of internal hemorrhoids and it was first described by Morinaga *et al.*^[3] in 1995. Few studies have addressed the technique until after the year 2000, with a lot of papers since then.

The aim of this article was to revise the literature about this technique in the treatment of hemorrhoidal disease, looking into its evolution, results and possible benefits over other modalities of surgical treatment.

A literature search was performed in PubMed, looking for "THD", "transanal hemorrhoidal dearterialization", "DG-HAL" and "Doppler guided hemorrhoidal artery ligation". References from the selected articles were also reviewed in order to find additional studies in the subject.

TECHNICAL ASPECTS

Before Morinaga's work for the surgical treatment of hemorrhoids with Doppler-guided ligation, Jaspersen *et al.*^[5] described the successful use of Doppler-guided location of hemorrhoidal vessels for phenol injection for treatment of 1st grade hemorrhoids.

Hemorrhoidal vessels are usually found in the mucosa within 2 cm up from the anorectal junction^[6]

and this is the place where the sutures should be made in this technique (the Dearterialization itself). In the case anopexy is also to be made, this is the position where the first ligation should be made, before the running suture for the anopexy is continued distally.

Different devices were developed to accomplish the location of vessels by Doppler signal as well as to permit the ligation at the same time. Morinaga *et al.*^[3] used a device called the Moricorn to find Doppler signal 2 cm above the dentate line and then ligate arterioles at this point. Afterwards, other proctoscopes were developed and nowadays most studies use THD (THD S.p.A. Correggio, Italy), DG-HAL/DG-RAR (Agency for Medical Innovations GmbH (AMI), Feldkirch, Osterreich, Austria) or HAL-Doppler (AMI Dufour MedicalTM, Maurepas, France).

There does not seem to exist any difference in results according to the type of device used, since they operate in the same way despite the different appearance of each one.

Table 1 refers to difference in rates of success and recurrence for each technique used for the treatment of hemorrhoidal disease: conventional, stapled and dearterialization.

INITIAL RESULTS WITH THD/HAL

When we look at the studies published in the first 12 years following Morinaga's publication, only ligation was performed (without anopexy). It was only in 2007 when a modification of the technique was made, with additional anopexy for patients with prolapse^[7]. Morinaga *et al.*^[3] reported this first series with 112 patients, obtaining satisfactory results in 78% of patients with prolapse, as well as resolution of pain in 96% of patients and of bleeding in 95%.

After 6 years, Sohn *et al.*^[8] published another series of patients treated with hemorrhoidal ligation in 2001. Sixty patients were submitted to a procedure (THD) based on the principles described by Morinaga, and the authors achieved complete success in 92% of patients with prolapse, 88% of those with bleeding and 71% of those with pain. Early postoperative pain, precluding normal activities, was reported in only 8% of patients.

Giordano *et al.*^[9] published the first systematic review concerning THD/DG-HAL in 2009, analyzing 17 papers from 1995 to 2008. In all articles revised no anopexy was performed. The rate of recurrent prolapse varied between 0% and 37%. In the study where this recurrence rate of 37% was found, most patients were lost to follow up, which might have interfered in the results^[10]. The overall rate of prolapse, according to the review, was 9%. Regarding recurrent anal bleeding, the rates ranged between 0% and 21% in those 17 studies, with most papers reporting rates around 4% to 10%. The overall rate of recurrent bleeding, also according with this systematic review, is 7.8%. Early post-operative pain was reported in 18% of patients in

Table 1 Rates of success, post-operative pain and long-term recurrence after different techniques for treatment of hemorrhoidal disease

Technique	Symptom control	Post-operative pain	Recurrence
Conventional hemorrhoidectomy	95%	70%-75%	5%
Stapled hemorrhoidectomy	85%-90%	5%-20%	2%-24%
THD/DG-HAL	80%-95%	2%-20%	8%-10%
THD/DG-HAL + Anopexy	85%-95%	6%-50%	8%

THD: Transanal hemorrhoidal dearterialization; DG-HAL: Doppler-guided hemorrhoidal artery ligation.

the review.

ADDITIONAL ANOPEXY

In 2007, Dal Monte *et al*^[7] were the first to describe a modification of THD/HAL, adding anopexy of the cushions where prolapse was found. They included patients with hemorrhoidal disease grades II to IV, and anopexy was performed in a group of patients with disease grades III and IV. They compared the latter with patients not submitted to anopexy and there was a tendency of worse prolapse relapse without anopexy, although not statistically significant.

Technical aspects of anopexy consist of extending the suture in a continuous manner after the first figure-of-eight stitch, involving mucosa more superficially than the first stitch, until above the pectinate line. The exact point where the suture is to be ended is identified with an audible Doppler signal before the sutures are done. The rationale of this modification was to treat prolapse at the same procedure.

Infantino *et al*^[11] published a multicentric study showing results of the modified technique, treating grades II and III hemorrhoids. Their recurrence rate was 14.3% and patient satisfaction after 15 mo was 87%. Other 4 papers in 2009 and 2010 showed prolapse recurrence in 5%-17%^[12-15].

Several articles on THD/DGHAL with anopexy were published, and the reported prolapse recurrence rates ranged between 3% and 21% and satisfaction rates of 84% to 96%, with follow ups of until 3 to 37 mo^[12-14,16-24]. Scheyer *et al*^[25] reported good results with Dearterialization and anopexy, but in their conclusion results were not good when prolapse was not the main complaint. In one of the most recent papers on the matter, Ratto *et al*^[26] reported a recurrence of prolapse in only 6.3% and a satisfaction rate of 90% after a 11 mo follow up. In this series, 13% of patients suffered pain or tenesmus after surgery.

THD/HAL IN THE TREATMENT OF GRADE IV HEMORRHOIDAL DISEASE

Results of this treatment in patients with high-grade disease (grade IV) seem to be satisfactory in terms of

prolapse resolution.

Two series were published involving only patients with grade IV disease. In both studies anopexy was performed in addition of hemorrhoidal ligation. Giordano *et al*^[19] found an incidence of pain in 70% of patients in the first postoperative day, tenesmus in 10%, but a recurrence of prolapse of only 3% after a follow up of almost 3 years. Faucheron *et al*^[22] reported postoperative pain in only 6% of patients, tenesmus in 1% and recurrence of prolapse in 9% after 34-mo follow up.

COMPARATIVE STUDIES WITH SH

Ramírez *et al*^[27] were the first to publish a randomized trial comparing THD and PPH in 2005. Several other studies compared both techniques from 2009 until 2014. Festen *et al*^[28] published a series comparing 18 patients submitted to stapled hemorrhoidopexy and 23 patients submitted to THD. After a very short follow up of only 3 wk, THD patients had less pain in the first week, with similar results after 3 wk. Symptoms resolution was also similar between groups^[28].

Three studies found that THD patients had an earlier return to normal activities^[29-31]. Tsang *et al*^[31] found similar complication rates and similar satisfaction rates but follow up after procedures was very different (8 mo after THD and 36 mo after SH). Verre *et al*^[32] published a prospective randomized trial in 2013, with 7.9% bleeding rate after SH and none after THD. Postoperative pain was lower in THD group although not statistically significant.

Lucarelli *et al*^[33] reported a randomized trial with long-term follow up, where recurrent prolapse was the primary outcome, after a follow up of 40-43 mo. The technique performed in their study was THD with anopexy vs stapled hemorrhoidopexy. The last follow up was done through a telephone interview, with reports of prolapse recurrence in 25% of patients in the THD group vs 8.2% ($P = 0.021$) in the SH group. In spite of that, patient satisfaction was 73% in THD group vs 86.9% in the SH group. One might argue about detecting recurrence of prolapse by phone interviews, when one study by Ratto *et al*^[13] showed that patients misreported skin tags for prolapse, after a physical examination took place.

As in the study by Infantino *et al*^[34], Lucarelli *et al*^[33] did not find significant difference in levels of post-operative pain. Other studies have found lower pain levels after THD when compared to stapled hemorrhoidopexy^[30,31,35] while in some it was a trend in the group submitted to THD but did not reach statistical significance^[28,29,32].

Giordano *et al*^[29] compared THD vs SH for grades II and III, and reported a recurrence of symptoms recurrence of 14% vs 13%, while satisfaction was also similar between groups (89% vs 87%), respectively. THD technique comprised also anopexy in this study. There were no reports of fecal incontinence in both

groups.

A systematic review included 3 trials comparing these techniques, with a total of 150 patients concluded that both techniques were effective, but THD patients had less immediate postoperative pain^[36].

COMPARISON WITH CH

In our literature search, three studies were found comparing Dearterialization and CH.

In a non-blind randomized study, Elmér *et al.*^[37] compared 20 patients in each group. Although patients presented less postoperative pain after THD, symptoms were effectively controlled in both groups after long-term follow-up.

Bursics *et al.*^[38] randomized 60 patients in 2 groups and also showed similar results after 12 mo of follow up. THD group had an earlier return to normal activities ($P < 0.0005$) and less post-operative pain ($P < 0.005$). Another randomized trial was published recently, with a follow up of 24 mo, showing no difference between groups in terms of postoperative pain in the first month after surgery or regarding resumption of normal activities. Patient satisfaction in the end of follow up was also similar between THD and CH ($P > 0.05$)^[39].

Denoya *et al.*^[40] published the article with the longest follow up, 3 years. Forty patients were randomized in each group, and they also found similar results regarding resolution of symptoms and patient satisfaction.

RESULTS REGARDING ANAL PHYSIOLOGY

According to Walega *et al.*^[41], resting and squeeze pressures following DG-RAR were lower 3 mo after surgery comparing to pre-operative measures ($P < 0.05$) and this result was maintained after 12 mo after surgery.

In their comparative article, Giordano *et al.*^[29], found no complaint of incontinence after THD or SH. Only 2 patients in the SH group ($n = 24$) complained of transient urgency. Tsang *et al.*^[31] described 1 case of incontinence in SH group ($n = 37$) and none in THD group ($P = 0.111$).

In the systematic review by Giordano *et al.*^[9] the overall incontinence rate after THD was 0.4%.

IMPORTANT CONSIDERATIONS

Morinaga *et al.*^[3] described Doppler arterial hemorrhoidal ligation in 1995 as a novel treatment for hemorrhoids. This technique has become more popular and, nowadays, it is used worldwide. It is based on the premise that arterial ligation would lead to a lesser pressure on the vessels on the anal canal, thus relieving the symptoms as bleeding and prolapse. Initial articles reporting this technique showed satisfactory results.

On 2007 Dal Monte *et al.*^[7] were the first to publish a modification on the described technique, including anopexy in order to better treat prolapse for 3rd and 4th grade hemorrhoids. With this, treatment of prolapse associated with 3rd and 4th grade hemorrhoids was guaranteed and recurrence rates were better.

One of the main advantages of the THD/DG-HAL is the low morbidity rate. After CH pain can be an important distress for the patient, influencing return to normal activities. Postoperative pain seems to be lower after THD when compared to CH, as seen in comparative studies^[37,38,40]. In a systematic review concerning THD, 18.5% of patients suffered from pain in the first operative day^[9]. Although this review points out that published data on THD was low quality, thus low significance/power, many studies evaluating this technique showed good results in short-term follow-up, with immediate postoperative bleeding occurring in 0%-8% and recurrence of 3%-20%.

Some works show a high recurrence rate related to grade III or IV hemorrhoids^[10,42,43], but those studies were done before the anopexy was associated with the arterial ligation. The study with the longest follow up showed a trend to higher recurrence rate for grade III hemorrhoids compared to grade II after 5 years, but the difference was not statistically significant^[42]. Two studies involving patients only with grade IV hemorrhoidal disease showed a recurrence of 3%-9% after a follow up of almost 3 years.

SH was first described by Longo^[4] in 1998 and is also a non-excisional technique for the treatment of hemorrhoidal disease. As THD, the goal is to treat hemorrhoids without the risk of sphincter impairment and to reduce postoperative pain. However, serious complications after SH, such as major bleeding, rectovaginal fistulas and perianal sepsis, have been described^[44]. One study prospectively comparing SH and THD for grades II and III hemorrhoidal disease showed no difference regarding recurrent symptoms or patients' satisfaction with their results^[29].

Regarding anal physiology, it seems reasonable to believe that hemorrhoidal dearterialization may contribute with only minor disruption of continence, since there is no risk of anal sphincter damage. On the other hand, the technique affects hemorrhoidal cushions in the anal canal, which play a role in anal continence as well. At the same time, all techniques interfere with the cushions, since it is the goal of the treatment. Maybe due to the fact that THD is a non-excisional technique, the impact after surgery might be reduced compared to excisional techniques.

Incontinence is rarely described, and when it happens it is transitory. More important is the complaint of tenesmus after THD surgery, which is rather common, in about 10% of patients, but also transitory. In a study by Ratto *et al.*^[13], tenesmus was reported by 24% of patients but symptoms disappeared 10 d following surgery. Even though alterations in resting

and squeeze anal pressures might be seen in anorectal manometry after THD, there is no evidence of risk of incontinence with this procedure^[41].

In conclusion, Doppler-guided hemorrhoidal dearterialization is a safe and effective method to treat grades II to IV hemorrhoidal disease. Outcomes in patients presenting prolapse are satisfactory and the association of anopexy has become an important aspect of this operation, contributing to a higher success rate. Anal physiology disturbances are rarely observed and are transitory. This technique is an excellent option for every patient, especially in those with previous anal surgeries and in patients with previous alterations of fecal continence, when an additional procedure might represent a risk of definitive incontinence.

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Retrospective Study

Long-term results after revisions of failed primary vertical banded gastroplasty

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Abstract

AIM: To compare the results after revision of primary vertical banded gastroplasty (Re-VBG) and conversion to sleeve gastrectomy (cSG) or gastric bypass (cRYGB).

METHODS: In this retrospective single-center study, all patients with a failed VBG who underwent revisional surgery were included. Medical charts were reviewed and additional postal questionnaires were sent to update follow-up. Weight loss, postoperative complications and long-term outcome were assessed.

RESULTS: A total 152 patients were included in this study, of which 21 underwent Re-VBG, 16 underwent cSG and 115 patients underwent cRYGB. Sixteen patients necessitated a second revisional procedure. No patients were lost-to-follow-up. Two patients deceased during the follow-up period, 23 patients did not return the questionnaire. Main reasons for revision were dysphagia/vomiting, weight regain and insufficient weight loss. Excess weight loss (%EWL) after Re-VBG, cSG and cRYGB was, respectively, 45%, 57% and 72%. Eighteen patients (11.8%) reported postoperative complications and 27% reported long-term complaints.

CONCLUSION: In terms of additional weight loss, postoperative complaints and reintervention rate, Roux-en-Y gastric bypass seems feasible as a revision for a failed VBG.

Key words: Vertical banded gastroplasty; Conversion; Revision; Gastric bypass; Sleeve gastrectomy; Additional weight loss

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Core tip: This study assesses the long-term outcome after revision of a failed vertical banded gastroplasty (VBG). This manuscript compares three types of revision: revision of the primary VBG, conversion to sleeve gastrectomy and conversion to Roux-en-Y gastric bypass. The main finding in this study is that in terms of additional weight loss, postoperative complaints and reintervention rate, Roux-en-Y gastric bypass seems feasible as a revision for a failed VBG.

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INTRODUCTION

Obesity is a growing global problem, associated with morbidity, health care costs and even an increased mortality rate^[1]. For the treatment of obesity, bariatric surgery is very effective in achieving significantly more long-term weight loss and an improved lifestyle compared with conventional therapy^[2,3]. In 2011, over 340000 bariatric procedures were performed worldwide. Among those procedures, around 2300 procedures were a vertical banded gastroplasty (VBG), first described by Mason *et al*^[4] and later altered by MacLean *et al*^[5] and Buchwald *et al*^[6]. Aim of this procedure was to establish a restriction on food intake with a small stomach pouch, without compromising passage of food through the entire gastro-intestinal tract and thereby avoiding malabsorption of nutrients and medication^[7]. This procedure has shown in earlier reports to have good short-term results in terms of weight loss and reduction in comorbidities^[8-11]. However, there are many studies reporting on the poor long-term results after VBG, showing a tendency for weight regain and other complications resulting in a high revision rate^[12-14]. Various options are available for revisional surgery after VBG, such as revision of the VBG (Re-VBG), conversion to sleeve gastrectomy (cSG) and conversion to Roux-en-Y gastric bypass (cRYGB), in which Re-VBG appears to have the poorest outcome and cRYGB has the best short- and long-term results^[15-19]. However, data on the comparison between the revisional options remains scarce.

Although VBG had been abandoned some years

ago in the Netherlands, still a number of patients can be expected to return with complaints after VBG. In the current series, all three mentioned options for revision have been performed. The aim of this study is to compare the outcome after these revisional procedures.

MATERIALS AND METHODS

Methods

This is a single-center retrospective study. A total of 392 patients underwent primary VBG, between January 1998 and December 2008. Since 2009, VBG was not performed anymore. Only patients undergoing primary VBG at the current center were included to reduce heterogeneity. Medical charts as well as additional postal questionnaires were reviewed. Included parameters were patient's characteristics, operative details of primary and secondary procedures, evolution of weight and comorbidities following both operations, findings at additional imaging, reason for revision, short-term complications and long-term complaints after revisional surgery. The postal questionnaire contained questions on weight and comorbidities, on complaints dysphagia, vitamin deficiencies and incisional hernia. In case of insufficient weight loss, weight regain or complaints and without participation the follow-up program, the patient was invited to the outpatients department. In case of non-response, patients received a phone call and when there was no response at all, the data of the latest visit at the outpatient clinic were used as final outcome.

Excess weight was defined as the difference between the weight before surgery and the highest healthy weight, which is at a body mass index (BMI) of 25 kg/m². Total excess weight loss (%EWL) was defined as a percentage of the amount of excess weight lost after surgery, as described by Deitel *et al*^[20]. The weight before the primary VBG was used as baseline value to calculate %EWL.

Weight loss was categorized according to the criteria described by Reinhold *et al*^[21]. These criteria consider a bariatric procedure successful when an %EWL of at least 50% is achieved. Furthermore, change in BMI and % total body weight loss (TBWL) was calculated. The evolution of any present comorbidities was categorized in stable, improved (reduced amount of medication used and/or a lower setting of a Continuous Positive Airway Pressure-device), resolved (no treatment), worse and *de novo*.

Treatment

Before primary VBG, all patients underwent assessment at our outpatient clinic by a surgeon, a psychologist and a dietitian to consider whether or not they were qualified for a bariatric procedure according to the standard IFSO guidelines for bariatric surgery. There was no specific algorithm for choosing the operative technique if they were approved for a bariatric procedure. There was a tendency for the option of a gastric bypass in case of more comorbidities, otherwise a VBG was chosen at

Table 1 Baseline characteristics (*n* = 152)

	Re-VBG <i>n</i> = 21 (13.8%) Mean ± SD	cSG <i>n</i> = 16 (10.5%) Mean ± SD	cRYGB <i>n</i> = 115 (75.7%) Mean ± SD	<i>P</i> value
Age (yr)	42.3 ± 8.6	41.6 ± 11.4	43.0 ± 8.9	0.828
Male:female	5:16	3:13	19:96	0.674
Body mass index before VBG (kg/m ²)	42.6 ± 5.4	43.6 ± 5.0	44.1 ± 4.9	0.445
Preoperative comorbidities				
Type 2 diabetes mellitus (<i>n</i>)	4	2	13	0.538
Hypertension (<i>n</i>)	4	2	25	0.79
Dyslipidemia (<i>n</i>)	0	3	11	0.111
Sleep apnea (<i>n</i>)	1	1	2	0.249
Osteo-articular disease (<i>n</i>)	5	0	9	0.038
Patients with 1 or more comorbidity	10	5	41	0.512
Operative time (min)	77.0 ± 39.2	100.6 ± 19.6	130.7 ± 47.3	< 0.001
Length of hospital stay (d)	3.1 ± 2.9	3.8 ± 2.2	4.1 ± 5.8	0.761
Interval between VBG and revision (mo)	12.3 ± 10.7	30.7 ± 26.5	47.8 ± 34.8	< 0.001
Average %EWL after VBG (%)	61.7 ± 27.0	38.7 ± 22.9	43.5 ± 25.0	0.007

Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; VBG: Vertical banded gastroplasty; %EWL: Percentage of excess weight loss.

the time. All patients underwent Mason-MacLean VBG, a standard VBG first described by Mason *et al*^[4] with transection of the vertical staple line as described by MacLean *et al*^[5].

Follow-up for these patients consisted of one year guidance by a psychologist, dietician and surgeon. Thereafter, a GP continued care unless weight loss problems or complaints were an issue. In such case patients underwent an analysis by all three disciplines and/or by means of a stomach X-ray and/or a gastroscopy. If considered eligible for revision the options were a re-VBG, cSG or cRYGB.

The Re-VBG technique meant in essence one of the 2 following adjustments. If the pouch was too large, a reshaping of the pouch was performed. The other option was an adjustment of the primarily placed band at the end of the gastric pouch.

A cSG meant a division of the lower part of the stomach 6cm from the pylorus up to the transgastric window to remove the gastric fundus and part of the corpus and antrum^[22]. All sleeve gastrectomies were performed using a 34-Fr intraluminal boogie and stapled by use of the Endo GIATM (Covidien, New Haven, CT, United States).

A cRYGB started with identification of the polytetrafluoroethylene (PTFE) band. Then the stomach was transected horizontally at the proximal side of the band. The band was removed in most cases. The pouch was

resized with use of the endoscopic stapler up to the angle of His. Then, an end-to-side gastro-jejunostomy was constructed by a linear stapler and closed using PolysorbTM sutures before 2009 and V-LocTM sutures after 2009 (Covidien, Mansfield, MA, United States). The alimentary limb, measuring 150-180 cm, was pulled up in an antecolic position. Finally, a side-to-side jejun-jejunostomy was constructed, also using a linear stapler and closing the defect again with either PolysorbTM or V-locTM sutures. Mostly, the procedure was finished by closing the mesenteric defects.

Statistical analysis

All data were collected retrospectively. Management and analysis as performed by using SPSS version 22, for Windows (SPSS Inc, Chicago, IL). Quantitative data are denoted as mean ± SD, whereas rates of complications and evolution on comorbidities are presented as a percentage. The student *t* test, linear regression analysis and logistic regression analysis were used to determine any significance of the observed differences among subgroups. Statistical significance was identified when the *P* value was less than 0.05. An odds ratio (OR) was provided when applicable and considered significant when OR (95%CI) ≠ 1. Summative figures and tables were used when necessary.

No ethical approval was required for this study.

RESULTS

Three hundred and ninety-two patients who underwent primary VBG were identified. According to the medical charts and questionnaires a total of 152 revisional procedures (38.7%) were performed between April 1999 and June 2014, of which six patients underwent revision in another hospital. Necessary data of these patients was retrieved. Furthermore, these six patients did complete the postal questionnaire, so they were included in the analysis, together with the rest of the study population. Baseline characteristics are shown in Table 1.

The initial 392 patients showed an average %EWL of 51.2% ± 27.4% and 54% of all known comorbidities were either improved or resolved. The resolved comorbidities were not taken into account in the current study. The patients necessitating revision showed a lower %EWL of 45.4% ± 25.8%, compared to those not necessitating revision (54.9% ± 27.7%, *P* = 0.001). At last follow-up, 58.4% (*n* = 229) of the total of 392 patients reported long-term complaints, which in 152 patients led to a revisional procedure.

Eighty-two point two percent of the current study population was female. Follow-up of patients necessitating second revision was taken into account until second revision. A total of 127 patients (83.6%) successfully completed last follow-up by either returning the postal questionnaire or answering the questions on the phone. This resulted in a mean follow-up after

Table 2 Complaints before revision (*n* = 152)

	Re-VBG <i>n</i> = 21 (<i>n</i>)	cSG <i>n</i> = 16 (<i>n</i>)	cRYGB <i>n</i> = 115 (<i>n</i>)	Total (%)	<i>P</i> value
Vomiting/ dysphagia/food intolerance	17	8	36	40.2	< 0.001
Weight regain	1	4	42	30.8	0.007
Insufficient weight loss	3	4	25	21.1	0.665
Unknown	0	0	6	3.9	0.792
Severe GERD	0	0	4	2.6	1.000
Decline comorbidities	0	0	1	0.7	1.000
Excessive weight loss	0	0	1	0.7	1.000

Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; GERD: Gastro esophageal reflux disease.

revisional surgery of 56.5 ± 37.9 mo. In total, 25 patients did not return the postal questionnaire and could not be reached despite repeated attempts. Of these 25 patients, two patients deceased during follow-up due to a cause unrelated to bariatric surgery. Of these patients, the unreturned questionnaires were considered as missing data and the data of last known follow-up was used as final outcome so patients could be included in the analysis.

Reasons for revision

Complaints leading to revisional surgery are shown in Table 2. Six patients have had their revisional procedure in another center and therefore the complaints remained unknown. A possible surgically technical cause for failure of the VBG was found in 54.2% of all patients in this study.

Additional tests, in this study a stomach X-ray and/or a gastroscopy, were performed for additional analysis when necessary. The three main technical problems in this study population were a wide outlet, allowing faster passage of food through the pouch (17.1%), pouch dilatation (15.8%) and outlet stenosis (9.9%). Other technical reasons for failure were band erosion (5.3%), band luxation (displacement of the PTFE-band from its original position) (2.0%), staple line dehiscence resulting in a fistula (2.7%), pouch rotation (0.7%) and band dehiscence (0.7%).

Intra- and post-operative complications

126 procedures (82.9%) were performed laparoscopically, 15 procedures (9.9%) had a primary open approach and 11 (7.2%) procedures were converted from a laparoscopic to an open approach. One conversion was due to an intra-operative gastro-intestinal perforation which could not be managed laparoscopically, the other procedures were converted because of an unacceptable laparoscopic overview due to extensive intra-abdominal adhesions. Only 2 intra-

operative complications (1.4%) occurred during surgery, both being an iatrogenic gastro-intestinal perforation.

Complications in the 30-d postoperative period were seen in a combined total of 18 patients (11.8%). No complications were seen after revision of the primary VBG (0/21). After cSG, three complications were objectified (3/16 = 18.8%): One pneumonia, one patient suffering from persistent vomiting after surgery causing dehydration. No evident cause was found for the persistent vomiting. The third patient had an ileus. In the group of patients who underwent cRYGB, 15 complications were registered (15/115 = 13.0%). Reoperation was necessary in two out of three patients with bleeding and in all patients with anastomotic leakage (*n* = 3). All leakages were found at the gastro-jejunoanastomosis. Other complications included intra-abdominal abscesses (*n* = 3), wound infection (*n* = 2), pneumonia (*n* = 1), urinary tract infection (*n* = 1), ileus (*n* = 1) and deep venous thrombosis (*n* = 1). The intra-abdominal abscesses all necessitated re-admission to the hospital for intravenous antibiotic treatment combined with either CT- or ultrasound-guided drainage. In total, eight patients were admitted for appropriate treatment of the complication, three patients did not necessitate readmission and seven complications occurred during primary admission. No significant difference was found in the total number of complications between the groups.

Weight loss and evolution of comorbidities

When not including the follow-up after any secondary revisional procedure, the mean total %EWL at last follow-up after primary revisional surgery was $66.4\% \pm 25.8\%$. In terms of change in BMI, this meant an average reduction of 12.5 ± 5.6 kg/m². Mean TBWL was $28.1\% \pm 11.2\%$. When including the 16 patients that underwent a second revisional procedure, %EWL was $68.2\% \pm 26.4\%$. Change in BMI was 12.7 ± 5.4 kg/m² and TBWL was $28.7\% \pm 11.1\%$.

At baseline, a total of 82 comorbidities were found amongst 56 patients. The separate improvement/resolution percentages for the three different procedures were 71.4%, 77.8% and 67.8% for respectively Re-VBG, cSG and cRYGB when considering each comorbidity as a separate entity. Figure 1 shows the improvement/resolution rates divided between the three groups. Table 3 shows the results after primary revisional surgery, stratified for each procedure.

Long-term complaints

At last follow-up after revisional surgery, 41 patients (27.0%) reported complaints, which in 16 cases necessitated a second revisional procedure. All long-term complaints are displayed in Table 4. In one patient after Re-VBG, complaints were caused by band erosion.

Subgroups based on reason for revision

Since the reason for revision may affect the outcome

Table 3 Results after primary revision at last follow-up (n = 152)

	Re-VBG	cSG	cRYGB	Corrected P value		
	n = 21 Mean ± SD	n = 16 Mean ± SD	n = 115 Mean ± SD	Re-VBG vs cSG	cRYGB vs Re-VBG	cRYGB vs cSG
Follow-up (mo)	39.1 ± 48.7	49.3 ± 17.6	50.0 ± 33.3			
Average %EWL after VBG (%)	61.7 ± 27.0	38.7 ± 22.9	43.5 ± 25.0			
Additional %EWL	-14.6 ± 19.9	17.9 ± 32.7				
Total %EWL (%)	45.4 ± 25.5	56.6 ± 24.4	71.7 ± 23.8	0.614	0.006	0.025
Total body weight loss (%)	18.4 ± 11.1	24.1 ± 11.6	30.4 ± 10.1	0.049	< 0.001	0.016
Change body mass index (kg/m ²)	8.1 ± 5.8	10.8 ± 5.8	13.5 ± 5.1	0.119	< 0.001	0.042
Reinhold (%EWL > 50%) (%)	47.6	56.3	82.6	0.791 ¹ (0.211; 2.972)	0.342 ¹ (0.125; 0.934)	0.271 ¹ (0.090; 0.812)
Long-term complications (%)	61.9	62.5	15.7	0.833 ¹ (0.214; 3.244)	10.105 ¹ (3.600; 28.367)	8.421 ¹ (2.733; 25.950)
2 nd revisional procedure (n, %)	10 (47.6%)	5 (31.3%)	1 (0.9%)	NA	NA	NA
Improvement/resolution in patients with 1 or more comorbidities (%)	80 (8/10)	60 (3/5)	92.7 (38/41)	0.375 ¹ (0.081; 1.738)	1.247 ¹ (0.476; 3.265)	0.468 ¹ (0.126; 1.740)

¹Odds ratio (95%CI). Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; %EWL: Excess weight loss; NA: Not available. P value is corrected for operative time, time between VBG and revision, osteo-articular disease and mean %EWL after VBG. No correction possible in logistic regression analysis due to limited events and group sizes. In case of a second revisional procedure, follow-up until second was taken into account.

of the total weight loss, the evolution of comorbidities and potentially also the early postoperative course, additional analysis was performed. Patients undergoing revision for either weight regain or insufficient weight loss (WR/IWL) were compared to the other reasons given earlier in this manuscript. Results are shown in Table 5.

Second revisional procedures

A total number of 16 patients underwent a second revisional procedure. 10 patients underwent conversion from a revised VBG to RYGB, five patients had their sleeve converted to RYGB. One patient necessitated revision due to persistent vomiting after RYGB. Additional analysis showed a stenosis of the gastro-jejunosotomy. The most common reasons for second revision were weight regain (43.7%) and DVFI (31.3%). Other reasons were insufficient weight loss (18.7%)

Table 4 Long-term complaints after revision (n = 152)

	Re-VBG n = 21 (n)	cSG n = 16 (n)	cRYGB n = 115 (n)	Total (%)
Vomiting/dysphagia/food intolerance	4	4	6	9.2
Weight regain	6	4	4	9.2
Insufficient weight loss	2	1	0	2.0
Petersen's hernia	NA	NA	4	2.6
Incisional hernia	0	0	3	2.0
Recurrent abdominal pain	1	1	1	2.0
None	8	6	97	73.0

Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; NA: Not available.

Table 5 Subgroup analysis (n = 152) (weight regain/insufficient weight loss vs other complaints)

	WR/IWL n = 79 Mean ± SD	Other n = 73 Mean ± SD	P value
Age (yr)	41.6 ± 7.4	43.9 ± 10.7	0.121
Male:female (n)	13:66	14:59	0.661
Body mass index before VBG (kg/m ²)	44.7 ± 5.0	42.8 ± 4.8	0.016
Operative time (min)	128.2 ± 46.3	109.7 ± 48.6	0.02
Length of hospital stay (d)	4.3 ± 6.8	3.4 ± 2.0	0.858
Type of revision			
Re-VBG	4	17	0.004
cSG	8	8	
cRYGB	67	48	
Average %EWL after VBG (%)	31.3 ± 19.0	61.2 ± 23.1	< 0.001
Postoperative complications < 30 d (n, %)	12 (15.2%)	6 (8.2%)	0.184
Total %EWL (%)	67.5 ± 23.7	65.2 ± 28.1	0.583
Reinhold (%EWL > 50%) (%)	79.7	74	0.398
Long-term complications (%)	22.8	28.8	0.399
2 nd revisional procedure (n)	5	11	0.079
Improvement/resolution rate (%), (n)			
Type 2 diabetes mellitus	90 (9/10)	55.6 (5/9)	NA
Hypertension	76.9 (10/13)	44.4 (8/18)	NA
Dyslipidemia	100 (9/9)	100 (5/5)	NA
Sleep apnea	0 (0/1)	66.7 (2/3)	NA
Osteo-articular disease	57.1 (4/7)	57.1 (4/7)	NA

WR: Weight regain; IWL: Insufficient weight loss; Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; %EWL: Excess weight loss; NA: Not available.

and band erosion (6.3%).

DISCUSSION

The absolute number of performed bariatric procedures is still increasing and therefore the number of revisional procedures can be expected to rise as well. Combined with the known poor long-term outcome after VBG, this fact strengthens the belief that more revisional procedures of failed VBG can be expected in the future. This study is the first to report on the comparison

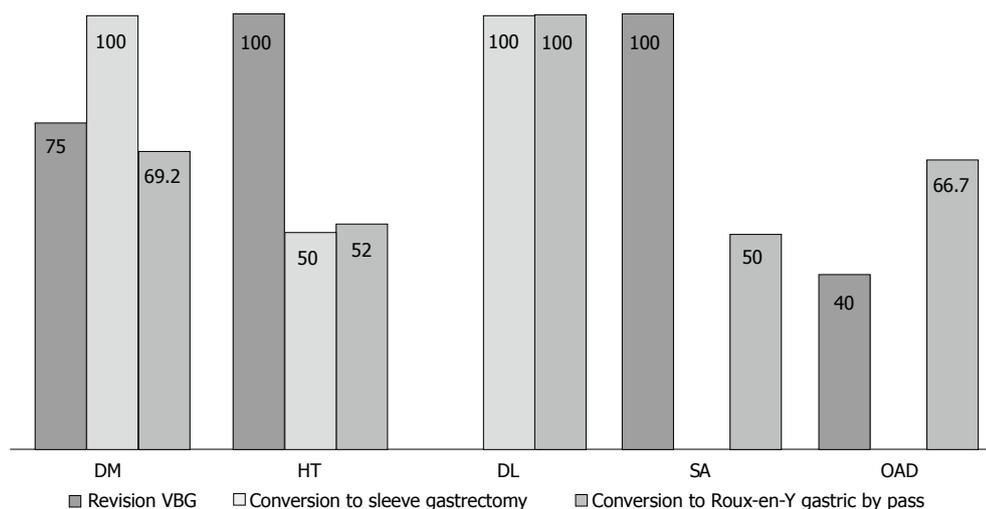


Figure 1 Improvement/resolution rates comorbidities. DM: Type 2 diabetes mellitus; HT: Hypertension; DL: Dyslipidemia; SA: Sleep apnea; OAD: Osteo-articular disease; VBG: Vertical banded gastroplasty.

between Re-VBG, cSG and cRYGB after failed primary VBG.

The revision rate of VBG was almost 39% (152 patients out of a total of 392 primary VBGs). The average %EWL after failed VBG was $45.4\% \pm 25.8\%$ at last follow-up before revision. Patients who underwent Re-VBG had a noticeable better %EWL after VBG at baseline. This can be explained by the much shorter average interval of only 12 mo between the VBG and the revision, making follow-up too short to start noticing weight regain, a common reason for revision^[17].

The main reasons for revision overall were similar to many other studies assessing either the long-term follow-up after VBG or the results after revision of the failed VBG^[12,15,17,19,23]. However, there is a difference in the type of complaints leading to the different revisional procedures in this study. Furthermore, the number of procedures differed between the groups in this study. These facts can be explained by various reasons. First of all, the indication for Re-VBG was limited (mainly band-related problems). In the early years, when a patient had complaints of DVFI, a Re-VBG was performed, especially when the DVFI was caused by band erosion. As more reports became available over the years, showing that cRYGB is a better revisional option than Re-VBG, that latter procedure was abandoned at an early stage and cRYGB has proven to be a better option and has been for quite some years, explaining the low number of VBGs^[15,16,18]. The last Re-VBG was performed in 2006. The second group, representing the cSGs, appears to have a more similar pattern of reasons for revision as seen in the cRYGB group, compared to the Re-VBG group. The size of the cSG group however is small, mainly due to early abandonment of this procedure, because there are very limited reports on the outcome of cSG over the last years and the larger experience with cRYGB, which had already proven to be a reliable procedure^[16,17,22]. The last cSG after VBG was performed in January 2010. Since then, all revisional

procedures after failed VBG were cRYGB.

The results in this study show that, although no early postoperative complications were seen in this group and the improvement/resolution rate of comorbidities is comparable with the other groups, Re-VBG is not the preferred revisional procedure after failed primary VBG. The reasons are a low total %EWL, high long-term complication rate and a high revision rate at long-term follow-up. Considering %EWL, this study actually showed an average decrease after Re-VBG, resulting in patients regaining nearly 15% of their initial excess weight. This result may be biased by the already available experience that cRYGB appeared superior to Re-VBG and the limited indication for Re-VBG^[18].

The second group in this study was the cSGs. The long-term results after cSG are acceptable, with a significant better additional excess weight loss compared to Re-VBG and an improvement/resolution rate of comorbidities comparable with cRYGB. Although cSG appears to give a lower chance on postoperative complications compared to cRYGB, a significant higher long-term complication rate compared to cRYGB and a high second revision rate are showing the limits of this revisional procedure after failed primary VBG.

Although cSG appears to be superior compared to Re-VBG, this study confirms that cRYGB seems to be the best option of these three procedures. At last follow-up, patients showed an average %EWL of almost 72%, improvement or even resolution of comorbidities in 92.8% patients familiar with one or more obesity-related comorbidities. Furthermore, the chance of developing long-term complications after cRYGB is lower compared to the other two revisional procedures. In contrast of these good results, we noticed a high postoperative complication rate of 13.0% after cRYGB. However, this rate is comparable with many previously published results showing postoperative complication rates of 6.5%–25%^[15,23–25]. In terms of %EWL, these results are comparable with previously reported data

after both revisional RYGB for failed VBG as well as after primary RYGB^[24-27]. The current good results may be affected by the used alimentary limb length of 150-180 cm, on the other hand, this seems unlikely, since previous studies have shown that a limb length of 150 cm did not produce a better %EWL compared to a limb length of 75-100 cm^[28,29].

Considering the subgroup analysis performed to differentiate between weight loss related complaints and other complaints, an expected significant difference was found in terms of %EWL. Furthermore, a difference was found in the number of different revisional procedures between the two groups, which can be explained by the earlier reported difference in reason for revision between procedures. This may also explain the difference in operative time, since a Re-VBG takes a significant shorter time than a cRYGB. After revisional surgery, no significant differences were found in terms of %EWL, postoperative complications and number of long-term complications and number of performed 2nd revisional procedures.

The reported high revision rate and previously published unfavorable results underline the limits of this old restrictive procedure^[12,13]. These rates also strengthen the expectation that a number of patients will necessitate revision in the future, since VBG is currently still performed as a primary procedure^[6]. Although revisional surgery seems feasible, the high number of complications after revision should be taken into account.

These results should be interpreted with caution due to a number of limitations in this study. First of all, the unequal distribution of groups, mainly due to a bias caused by the center's greater experience with cRYGB, thereby explaining the small number of Re-VBGs and cSGs. Furthermore, the retrospective design limits the reliability of the reported outcome. Since not all patients responded to our question to update the last known follow-up, a number of long-term complaints might have been missed, as well as potential revisional procedures performed in other hospitals. Not only the distribution between groups is unequal, also total time of follow-up is unequal, since Re-VBGs were performed only in the early and cRYGBs are still performed nowadays. The mean follow-up appears to be similar, but it should be kept in mind that Re-VBG showed a higher second revision rate as opposed to cSG and cRYGB and follow-up of the primary revision was taken into account until second revision. Keeping these limitations in mind, this study still suggests that Roux-en-Y gastric bypass is the superior choice for revisional surgery after failed primary VBG due to a good long-term %EWL, a high improvement rate of comorbidities, a low long-term complication rate and a low percentage of necessitated second revisional procedures.

In conclusion, in terms of additional weight loss, number of postoperative complaints and necessitation of a second revision, the Roux-en-Y gastric bypass seems feasible as a revision for a failed. Furthermore, the high

number of complications after VBG and complications due to revisional procedures underline that VBG should be excluded as a primary option in bariatric surgery and other restrictive should be considered instead.

COMMENTS

Background

Vertical banded gastroplasty (VBG) was a popular restrictive bariatric procedure however, has been abandoned due to a high long-term complications rate in many cases leading to the necessitation of revisional surgery. As a number of these revisions can be expected, this study reports and compares the results after revision of the primary VBG (Re-VBG), conversion to sleeve gastrectomy (cSG) and conversion to Roux-en-Y gastric bypass (cRYGB). As the number of patients with a bariatric procedure rises annually, the number of failed procedures will rise as well, some necessitating surgical treatment (by either revision or conversion). It is good to know what can be expected in both the short term and the long term when it comes to complications, weight loss and other complaints.

Research frontiers

Research on the conversion or revision of failed VBG is limited to mainly results after conversion to Roux-en-Y gastric bypass. These articles show decent results, suggesting that Roux-en-Y gastric is a feasible option as revision of a failed VBG. Results on the comparison of different conversions after failed VBG are limited.

Innovations and breakthroughs

The current article is, by the authors' knowledge, the first to compare different surgical options as treatment of failed VBG.

Applications

When confronted with failed VBG, either due to insufficient weight loss, weight regain or (other) physical complaints, conversion to Roux-en-Y gastric bypass appears to be more feasible compared to revision of the VBG or cSG.

Terminology

Re-VBG: Revision of a primary VBG; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass.

Peer-review

The paper is acceptable and very interesting.

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Retrospective Study

Changes over time in milk test results following pancreatotomy

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Author contributions: Aoki H, Utsumi M, Sui K, Kanaya N and Kunitomo T performed operations; Takeuchi H supervised the research; Aoki H, Takakura N, Shiozaki S and Matsukawa H established milk test; Aoki H wrote this paper.

Institutional review board statement: This study was reviewed and approved by the Iwakuni Clinical Center Institutional Review Board.

Informed consent statement: Patients were not required to give informed consent to this study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The author declares no conflicts of interest.

Data sharing statement: Participants gave informed consent for data sharing.

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Abstract

AIM: To investigate changes over time in, and effects of sealing technology on, milk test results following pancreatotomy.

METHODS: From April 2008 to October 2013, 66 pancreatic resections were performed at the Iwakuni Clinical Center. The milk test has been routinely conducted at the institute whenever possible during pancreatotomy. The milk test comprises the following procedure: A nasogastric tube is inserted until the third portion of the duodenum, followed by injection of 100 mL of milk through the tube. If a chyle leak is present, the patient tests positive in this milk test based on the observation of a white milky discharge. Positive milk test rates, leakage sites, and chylous ascites incidence were examined. LigaSure™ (LS; Covidien, Dublin, Ireland), a vessel-sealing device, is routinely used in pancreatotomy. Positive milk test rates before and after use of LS, as well as drain discharge volume at the 2nd and 3rd postoperative days, were compared retrospectively. Finally, positive milk test rates and chylous ascites incidence were compared with the results of a previous report.

RESULTS: Fifty-nine milk tests were conducted during pancreatectomy. The positive milk test rate for all pancreatectomy cases was 13.6% (8 of 59 cases). One case developed postoperative chylous ascites (2.1% among the pancreatoduodenectomy cases and 1.7% among all pancreatectomies). Positive rates by procedure were 12.8% for pancreatoduodenectomy and 22.2% for distal pancreatectomy. Positive rates by disease were 17.9% for pancreatic and 5.9% for biliary diseases. When comparing results from before and after use of LS, positive milk test rates in pancreatoduodenectomy were 13.0% before and 12.5% after, while those in distal pancreatectomy were 33.3% and 0%. Drainage volume tended to decrease when LS was used on the 3rd postoperative day (volumes were 424 ± 303 mL before LS and 285 ± 185 mL after, $P = 0.056$). Both chylous ascites incidence and positive milk test rates decreased slightly compared with those rates from the previous study.

CONCLUSION: Positive milk test rates and chylous ascites incidence decreased over time. Sealing technology may thus play an important role in preventing postoperative chylous ascites.

Key words: Chylous ascites; Milk test; Pancreatectomy; Surgical energy device; Drain discharge

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Core tip: Chylous ascites is sometimes a severe complication of pancreatectomy. We previously reported that the milk test could serve to prevent chylous ascites following surgery. In this study, changes over time in milk test results, and effects of new energy devices on the test results, were investigated. Compared with the first report results, positive milk test rates and chylous ascites incidence were found to have decreased slightly. Use of the new energy devices also tended to result in decreased drainage volume. These findings suggest that the vessel-sealing technology could play an important role in preventing postoperative chylous ascites.

Aoki H, Utsumi M, Sui K, Kanaya N, Kunitomo T, Takeuchi H, Takakura N, Shiozaki S, Matsukawa H. Changes over time in milk test results following pancreatectomy. *World J Gastrointest Surg* 2016; 8(3): 246-251 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i3/246.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i3.246>

INTRODUCTION

Chylous ascites is a condition defined by the secretion of milky white fluid with high triglyceride content. Generally, it occurs due to traumatic injury or obstruction of the lymphatic system. Although it is a rare condition, there are multiple causes, such as neoplasm,

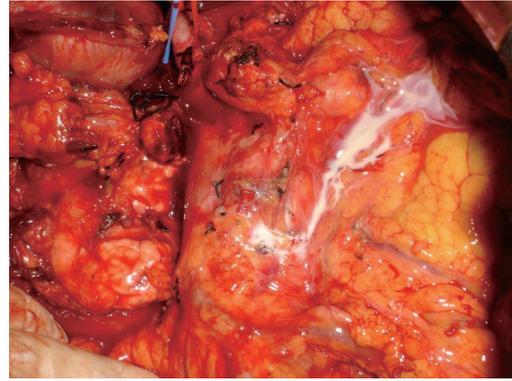


Figure 1 Milk test positive case.

inflammation, infection, surgery, trauma, and so on^[1]. As for postoperative causes, pancreatic surgery is a major cause of chylous ascites^[2-6]. According to reports, rates of chylous ascites incidence after pancreatoduodenectomy ranged from 1.8% to 13%. The cisterna chyli lies anteriorly of the first and second lumbar vertebrae, on the same plane as the pancreas. Injury to the cisterna chyli or its tributaries can occur during pancreatic resection. We experienced several cases of chylous ascites after pancreatectomy, and the condition is often associated with prolonged hospitalization. These are the reasons why we started studying the milk test in 2004 for its potential as a treatment to prevent the development of chylous ascites following pancreatic resection^[5].

On the other hand, remarkable advances have been witnessed in surgical energy technology. Such surgical energy devices as the vessel-sealing system represent a new hemostatic technology based on the combination of pressure and bipolar electrical energy that leads to the denaturation of collagen and elastin in the vessel walls and fusion of these into a hemostatic seal. Besides hemostatic ability, the new surgical energy devices might be used to block lymphatic flow. In terms of technical issues, we cannot ignore the effects of such new surgical energy technologies.

The aim of this study is to investigate changes over time in milk test results following pancreatectomy and the effects of vessel-sealing devices on milk test results.

MATERIALS AND METHODS

From April 2008 to October 2013, 66 pancreatic resections were performed at the Iwakuni Clinical Center, Iwakuni, Japan. Starting in 2004, the milk test has been routinely conducted whenever possible during pancreatectomy. Briefly, the milk test is conducted in the following way: A nasogastric tube is inserted until the third portion of the duodenum, followed by injection of 100 mL of milk through the tube. If a chyle leak is present, the patient tests positive in this milk test based on the observation of a white milky discharge (Figure 1). Seven cases were excluded: 2 laparoscopic surgeries,

Table 1 Positive rate of milk test

Negative	Positive ¹
51	8 (13.6%) leakage site ² SMA 4 SMV 2 LRV 1 Paaorta 1 Mesentery 1

¹Includes one case of postoperative chylous ascites; ²One case showed two leakage sites. SMV: Superior mesenteric vein; LRV: Left renal vein.

Table 2 Positive rate of milk test by operative procedure

Procedure	Positive	Negative
PD (<i>n</i> = 47)	6 (12.8%)	41
DP (<i>n</i> = 9)	2 (22.2%)	7

PD: Pancreatoduodenectomy; DP: Distal pancreatectomy.

as well as 2 emergency and 3 unexpected pancreatic resections. The milk test was used in 59 of these 66 cases [47 pancreatoduodenectomy (PD); 2 total pancreatectomy (TP); 9 distal pancreatectomy (DP); 1 middle pancreatectomy]. Final diagnoses were 21 cases of pancreatic cancer, 12 intraductal papillary mucinous neoplasm, 9 bile duct cancer, 7 ampulla of Vater cancer, 2 each of chronic pancreatitis, gallbladder cancer, and duodenal cancer, and 1 each of metastatic pancreatic cancer and endocrine tumor.

Positive milk test rates, leakage sites, and chylous ascites incidence were examined. Since May 2011 in the Iwakuni Clinical Center, a vessel-sealing system (LigaSure small jaw instrument) is routinely used in pancreatectomy. Positive milk test rates before and after introduction of LigaSure (LS) as well as drain discharge volume were compared retrospectively. Finally, positive milk test rates and chylous ascites incidence were compared with the results of our previous report (conducted from 2004 to 2008)^[5].

Variables were compared using χ^2 test or Student's *t* test. JMP 9 statistical software (SAS Institute, Cary, NC, United States) was used for all analyses. *P* < 0.05 was considered statistically significant. This study was reviewed and approved by the Iwakuni Clinical Center Institutional Review Board.

RESULTS

Positive milk test rate among all pancreatectomy cases was 13.6% (8 of 59 cases). Leakage sites were as follows: Superior mesenteric artery: 4 cases; superior mesenteric vein: 2; left renal vein: 1; paraaorta: 1; and mesentery: 1. One case had two leakage sites. Six of 8 cases presented with leakage sites around superior mesenteric vessels (Table 1). One case demonstrated postoperative chylous ascites. Incidence of chylous

Table 3 Positive rate of milk test by diseases

Disease	Positive	Negative
Biliary disease (<i>n</i> = 17)	1 (5.9%)	16
Pancreatic disease (<i>n</i> = 39)	7 (17.9%)	32
Pancreatic disease with PD (<i>n</i> = 30)	4 (13.3%)	26

PD: Pancreatoduodenectomy.

ascites was 2.1% among the PD cases and 1.7% among all pancreatectomies. This case was milk test positive and treated with a conservative method using octreotide.

Positive rates by procedure were 12.8% for PD and 22.2% for DP (Table 2). No significant differences in positive rates were observed between the different procedures. Positive rates by diseases were 17.9% in pancreatic diseases and 5.9% in biliary diseases. When limited to PD patients in pancreatic diseases, the positive rate reached 13.3%. The positive rates were higher in pancreatic diseases, but this difference did not reach the level of statistical significance (Table 3).

When comparing figures before and after the introduction of LS, positive milk test rates for PD and TP were 13.0% before and 12.5% after, and for DP 33.3% and 0%. There was no statistical significance (Figure 2). As for drain discharge volume, the two groups were compared on the 2nd and 3rd postoperative days (POD) on average. Drain discharge volumes for the 2nd POD cases were 454 ± 237 mL (mean ± SD) before introduction of LS and 383 ± 279 mL after; for the 3rd POD cases, the volumes were 424 ± 303 mL and 285 ± 185 mL, respectively (Figure 3). Although no statistical differences were evident, a tendency for decreased drainage volume was observed when using LS on the 3rd POD cases (*P* = 0.056).

Incidences of chylous ascites were 2.9% in the previous study's period (2004-2008) among all pancreatectomy^[5] cases and 1.7% in this study. Positive milk test rates were 22.1% in the previous study^[5] and 13.6% in this study (Figure 4). Both rates represented a slight decrease compared with the first report, but this difference did not reach the level of statistical significance.

DISCUSSION

Postoperative chylous ascites is a relatively rare condition, but once it occurs the disorder can cause hyponutrition and prolonged hospitalization.

Positive milk test rates by procedure were higher for DP than for PD, but this difference was not significant. In our previous report, the incidences were nearly the same. Some authors report lower rates of chylous ascites in DP^[3], but others do not^[6]. This result might be due to the difference in disease incidence itself, but this aspect is not yet fully understood. According to the positive milk test rates, chylous ascites might

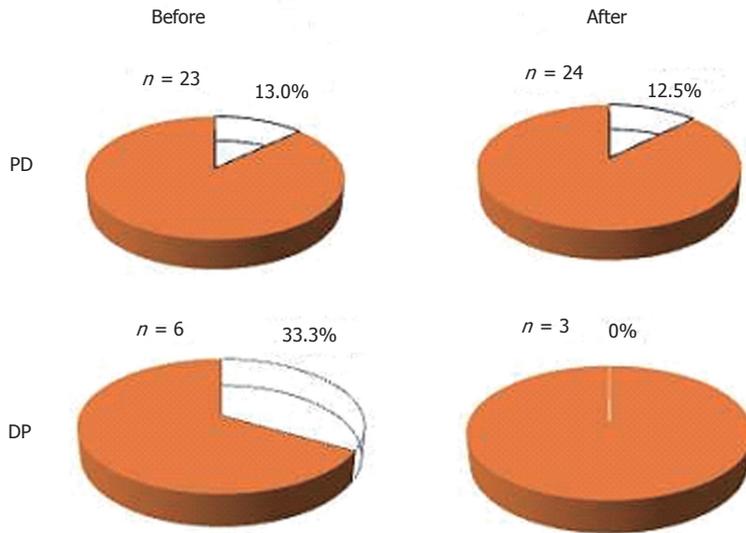


Figure 2 Comparison of milk test positivity: Before and after induction of sealing device. PD: Pancreatoduodenectomy; DP: Distal pancreatectomy.

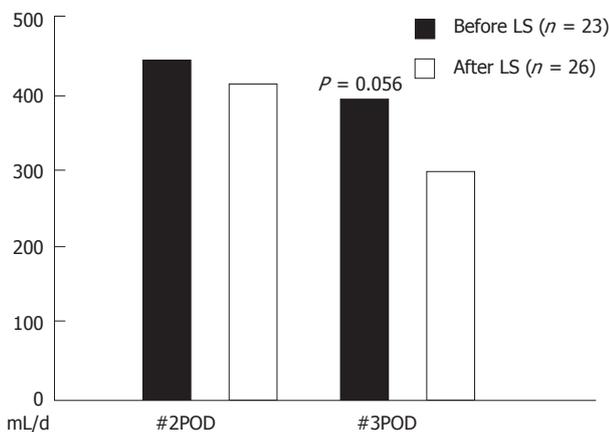


Figure 3 Drain discharge of pancreatoduodenectomy and total pancreatectomy.

occur at least equally in DP. Positive milk test rates by disease were higher in pancreatic than in biliary disease. The existence of concomitant pancreatitis with pancreatic disease might have played a role in this result. In one study, van der Gaag *et al.*^[4] reported that chronic pancreatitis is one of the risk factors for the development of postoperative chylous ascites. Kuboki *et al.*^[6] reported manipulation of the paraaortic area, retroperitoneal invasion, and early enteral feeding to be independent risk factors associated with chylous ascites. The first two of these three factors may have had something to do with the operative procedure itself. As for early enteral feeding, Malik *et al.*^[2] also alerted the medical community about the risk for chyle leak in this treatment. Careful observation of drain discharge is thus necessary before allowing such patients to begin meal intake after pancreatectomy.

The management algorithm used to treat chylous ascites integrates repeat palliative paracentesis, dietary measures, total parenteral nutrition therapy, peritoneovenous shunting, and surgical closure of the lympho-

peritoneal fistula. Somatostatin therapy should be attempted with or without total parenteral nutrition early in the course of treatment of chylous ascites before any invasive steps are taken^[7]. In addition, Kawasaki *et al.*^[8] reported effectiveness of lymphangiography not only for diagnosis but also for treatment of postoperative chylothorax and chylous ascites. In our experience, albeit somewhat limited, none of the cases required surgical treatment for postoperative chylous ascites. Chylous ascites should thus be treated by surgical procedure at the time of the initial operation. We emphasized the importance of steady ligation in our previous report. But now, new surgical energy technologies are gradually replacing that technique.

New surgical energy devices—such as the harmonic scalpel or vessel-sealing system—are reported to be useful in reducing drain discharge in colonic surgery^[9] and in axillary lymphadenectomy^[10], respectively. Nakayama *et al.*^[11] reported the utility of an ultrasonic scalpel in sealing the thoracic duct based on use of a pig model. The burst pressure after sealing by this ultrasonic scalpel was 188–203 mmHg, which is far above the pressure at which lymph vessels are occluded.

The question is what type of surgical energy device should we use to prevent chylous ascites? Seehofer *et al.*^[12] performed a comparison among a new surgical tissue management system that combines ultrasonic vibration and tissue dissection with bipolar coagulation [thunderbeat (TB)], a conventional ultrasonic scissor [Harmonic Ace (HA)], and a bipolar vessel clamp (LS), in terms of safety and efficacy. The burst pressure of the TB technique in the larger-artery category (5–7 mm) was superior to that of the HA technology. The dissection speed of the TB was significantly faster than that of the LS. Although seal width was influenced by the width of the jaw, LS had the widest seal width and the fewest gas pockets. This means that histologically LS is superior in terms of seal reliability and prevention

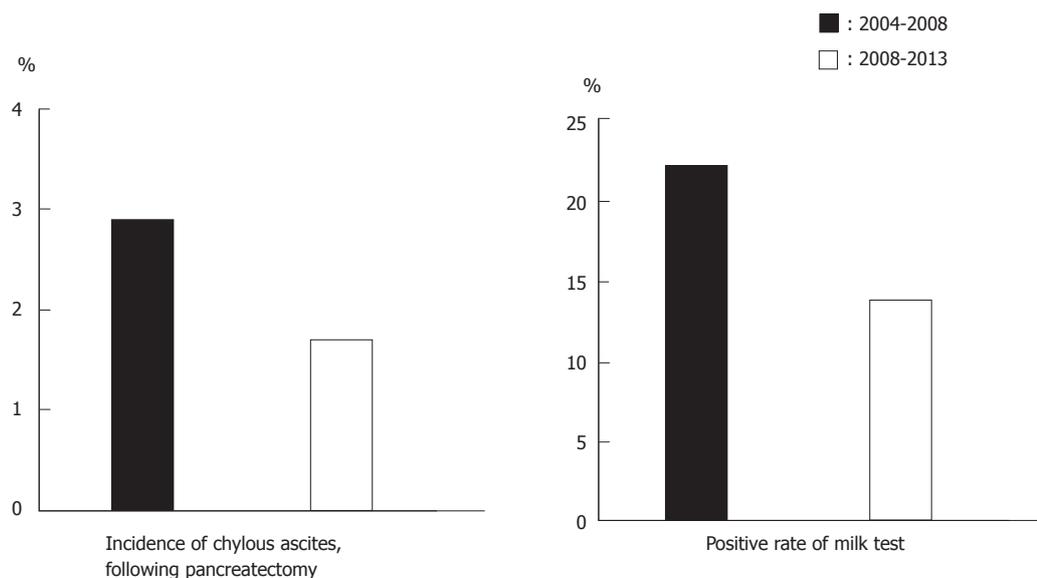


Figure 4 Changes over time in incidence of chylous ascites and milk test positivity.

of thermal injury. Janssen^[13] conducted a systematic search for randomized controlled trials that compared the effectiveness and costs of vessel-sealing devices with those of other electrothermal or ultrasonic devices in abdominal surgical procedures. The researchers involved in the study concluded that vessel-sealing devices may be considered safe and that their use may reduce costs due to reduced blood loss and shorter operating time in some abdominal surgical procedures compared to mono- or bipolar electrothermal devices. Though thermal injury is an issue that needs to be resolved, surgical energy devices can be used as another contributing factor for prevention of chylous ascites.

In our study, although there was no significant difference, both chylous ascites incidence and positive milk test rates decreased over time. The reasons for that are partly because we are more knowledgeable about chylous ascites and because of the technical advances made especially in surgical energy devices. Although we could not prove our results definitively, we think it is a matter of more numbers of cases. We therefore started planning in November 2013 a randomized prospective milk test study. In this study, we will investigate the utility of the milk test and chyle leak sites more comprehensively. We plan for the next study to include comparisons of different surgical energy devices.

In conclusion, positive milk test rates were higher in DP and pancreatic disease. Both chylous ascites incidence and positive milk test rates decreased over time. Based on the study results, surgical energy devices should be used as another contributing factor for the prevention of chylous ascites. Further investigation is needed to confirm the utility of the milk test.

COMMENTS

Background

Postoperative chylous ascites is a rare condition, but once it occurs the disorder can cause hyponutrition and prolonged hospitalization. Although chylous ascites after pancreatectomy has recently become an issue in the field of abdominal surgery, methods for prevention of chylous ascites are not well established. The authors therefore investigated the milk test as a method to resolve this condition starting in 2004. In their previous study, use of the milk test contributed to a decrease in incidence of chylous ascites. In this study, they looked at changes over time in milk test results. In addition, they assessed the effects of energy devices, which first appeared during the study period and now cannot be ignored in cases of abdominal surgery.

Research frontiers

The authors believe that the milk test is a useful method for detecting lymphorrhea during surgery. But to truly prove its utility, a prospective study is necessary. The authors therefore initiated a prospective randomized study in 2013.

Innovations and breakthroughs

To date, many papers have been published about chylous ascites, but most of them are focused on its pathogenesis or treatment. There is no study about prevention, especially in the case of pancreatectomy. The authors emphasize that postoperative chylous ascites should and can be prevented during surgery. The results of this study also suggest that new energy devices may play an important role in decreasing drain discharge.

Applications

A benefit to the milk test is that milk is easy to obtain and inexpensive. When the milk test is used, there is no need for special drugs or instruments. In addition, no complications accompany use of the milk test.

Peer-review

Reviewers mentioned that our paper provided interesting methodology and results. They stated that they are looking forward to the new study results.

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E- Editor: Wu HL



Primary squamous cell carcinoma of the rectum: An update and implications for treatment

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Abstract

AIM: To provide an update on the aetiology, pathogenesis, diagnosis, staging and management of rectal squamous cell carcinoma (SCC).

METHODS: A systematic review was conducted according to the preferred reporting items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search of Ovid MEDLINE was performed with the reference list of selected articles reviewed to ensure all relevant publications were captured. The search strategy was limited to the English language, spanning from 1946 to 2015. A qualitative analysis was undertaken examining patient demographics, clinical presentation, diagnosis, staging, treatment and outcome. The quantitative analysis was limited to data extracted on treatment and outcomes including radiological, clinical and pathological complete response where available. The narrative and quantitative review were synthesised in concert.

RESULTS: The search identified 487 articles in total with 79 included in the qualitative review. The quantitative analysis involved 63 articles, consisting of 43 case reports and 20 case series with a total of 142 individual cases. The underlying pathogenesis of rectal SCC while unclear, continues to be defined, with increasing evidence of a metaplasia-dysplasia-carcinoma sequence and a possible role for human papilloma virus in this progression. The presentation is similar to rectal adenocarcinoma, with a diagnosis confirmed by endoscopic biopsy. Many presumed rectal SCC's are in fact an extension of an anal SCC, and cytokeratin markers are a useful adjunct in this distinction. Staging is most accurately reflected by the tumour-node-metastasis classification for rectal adenocarcinoma. It involves examining locoregional disease by way of magnetic resonance imaging and/or endorectal ultrasound, with systemic spread excluded by way of computed tomography. Positron emission tomography is integral in the workup to exclude an external site

of primary SCC with metastasis to the rectum. While the optimal treatment remains as yet undefined, recent studies have demonstrated a global shift away from surgery towards definitive chemoradiotherapy as primary treatment. Pooled overall survival was calculated to be 86% in patients managed with chemoradiation compared with 48% for those treated traditionally with surgery. Furthermore, local recurrence and metastatic rates were 25% *vs* 10% and 30% *vs* 13% for the chemoradiation *vs* conventional treatment cohorts.

CONCLUSION: The changing paradigm in the treatment of rectal SCC holds great promise for improved outcomes in this rare disease.

Key words: Squamous cell carcinoma; Rectal cancer; Chemoradiotherapy; Surgery; Complete response

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Core tip: Primary squamous cell carcinoma (SCC) of the rectum is a rare entity with a historically poor prognosis. This systematic review provides an in depth summary of the current body of knowledge surrounding the aetiology, pathogenesis, diagnosis, staging and prognosis of this disease. Given the current paradigm shift in the first line treatment of rectal SCC away from traditional surgical management towards definitive chemoradiotherapy, the evidence supporting this change is examined.

Guerra GR, Kong CH, Warriar SK, Lynch AC, Heriot AG, Ngan SY. Primary squamous cell carcinoma of the rectum: An update and implications for treatment. *World J Gastrointest Surg* 2016; 8(3): 252-265 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i3/252.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i3.252>

INTRODUCTION

Rectal squamous cell carcinoma (SCC) is a rare malignancy of the gastrointestinal (GI) tract. Due to the low incidence of this cancer and subsequent lack of literature, the underlying pathogenesis and risk factors are yet to be clearly defined. Furthermore, there is significant heterogeneity in the treatment regimens utilised, with the optimal management yet to be clarified. Nonetheless, certain patterns do emerge on reviewing all published cases by way of a systematic review, to determine where our future research should be directed in order to improve upon treatment and facilitate best patient outcomes.

MATERIALS AND METHODS

A systematic literature review was conducted according to the preferred reporting items for Systematic Reviews

and Meta-Analyses guidelines. A comprehensive search of Ovid Medline was performed with the abstracts screened to determine relevant articles, following which the full texts were obtained. A directed manual review of all embedded references was undertaken of the selected articles to ensure all studies published on primary SCC of the rectum were identified.

The search strategy was based on a combination of medical subject heading terms (carcinoma, squamous cell; rectum) and text words (SCC and rectum), spanning from 1946 to May 2015. The search was limited to English language with the most recent search performed on 8th May 2015.

Inclusion and exclusion criteria

The definition of rectal SCC as stipulated by Williams *et al*⁽¹⁾ which requires three exclusion criteria to be met (detailed in "diagnosis" below) was used to identify relevant studies. Consequently, studies reporting rectal SCC arising in the presence of a fistula, from an anal or gynaecological origin, a distant site *via* metastasis, or where the pathology was mixed (*e.g.*, adenosquamous) were excluded. Additionally, studies where the lesion was premalignant (*e.g.*, metaplasia or SCC *in situ*), of colonic rather than rectal origin or where the data was inadequate were excluded from the quantitative analysis.

Data extraction

Data extracted included the names of the authors, date of publication, demographic information and clinical presentation. Location of the lesion and treatment detailing the primary modality, the use of pre- and/or post-operative modalities and the type of operation where present was also noted. Other collated information included patient outcomes in the form of local recurrence, metastasis, and survival, as well as the length of follow up. Radiological, clinical and pathological complete response (CR) was also recorded where available.

RESULTS

The database and bibliography search identified 487 articles in total. After screening the articles for inclusion and exclusion criteria, 79 were included in the qualitative review and 63 in the quantitative analysis as detailed in Figure 1. This included 43 case reports and 20 case series with a total of 142 individual cases reported. Given the inherent bias in case reports and the inconsistency with reporting important prognostic variables including stage and pathological grade, an in depth individual patient data meta-analysis was not performed.

DISCUSSION

Background

Epidemiology: Rectal SCC is a rare disease with the current literature consisting primarily of case reports, case series and one large population based study.

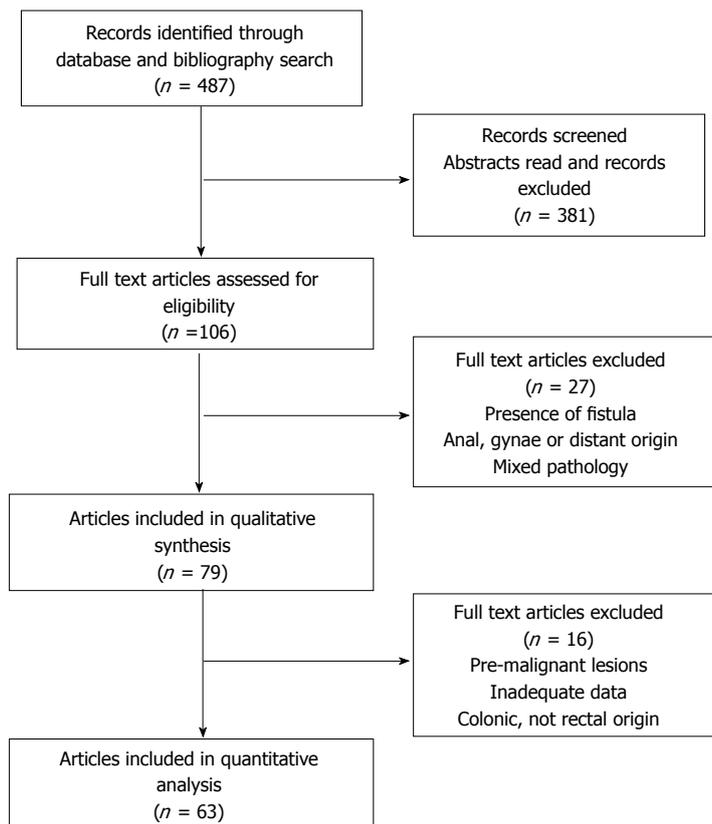


Figure 1 Preferred reporting items for Systematic Reviews and Meta-Analyses flow diagram.

While SCC can occur throughout the GI tract, it most commonly affects the upper aerodigestive tract down to the oesophagogastric junction, and the anal canal. SCC of the rectum however is much less common accounting for 0.3% of all histological subtypes^[2]. While pure SCC is the most frequent histology, cases with a mixed histologic pattern, generally adenosquamous, have been described^[3]. While other rectal cancer subtypes including neuroendocrine, lymphoma and gastrointestinal stromal tumours occur infrequently, rectal SCC remains the most rare with the exception of sarcoma^[2].

Schmidtman^[4] reported the first case of SCC of the colon in 1919, with Raiford^[5] publishing on the first case of rectal SCC in 1933. While SCC can be diagnosed throughout the colorectum, the most common site of predilection is the rectum (93.4%), followed by the right colon (3.4%)^[2]. The true incidence of rectal SCC can be most accurately drawn from the large population based study from the National Cancer Institute (NCI), which estimated it at 1.9 per million population in the year 2000, or 3 per 1000 colorectal cancers. This study also identified a significant rise in the incidence of rectal SCC between 1992 and 2000, estimating it at 5.9% per year. Extrapolating from this figure, the current incidence may be as high as 3.5 per million population^[2].

While strong epidemiological evidence on rectal SCC is absent, patient demographics and risk factors can be gauged from the published retrospective reviews and population study. Patients diagnosed with SCC of the rectum have ranged in age from 39 to 93 years

old, with an average age of 63 years. Female gender predominates, accounting for 57.4% vs 42.6% of cases in the NCI study. Patients most frequently present with early stage localised (stage I/II, 52.8%) or regional (stage III, 29.3%) disease and there is no apparent ethnic or geographic predisposition^[2].

Despite a lack of firm risk factors with a causal link to the development of rectal SCC, loose associations have been identified. The strongest association evident in the literature is that of proctitis, generally secondary to ulcerative colitis. There have been multiple case reports of rectal SCC in this setting, one of which compared the incidence with that of the general population to demonstrate a markedly increased risk in ulcerative colitis patients^[6-15]. Of significance, there has also been a report of rectal SCC in the setting of active Crohn's disease of the rectum^[16], and in the setting of chronic prolapse^[17]. Drawing upon this association with inflammation, the literature also contains three reports of parasitic infections with colorectal SCC, in the form of Schistosomiasis in two cases, and Amoebiasis in one, however, their significance is unclear^[1,18,19].

Other postulated risk factors have included a past history of radiotherapy for other pelvic malignancies, which has been noted in several case reports^[20-23]. Additionally, colorectal adenocarcinoma, both synchronous and metachronous has been identified in patients with SCC of the rectum^[3,24-27]. For colonic SCC, asbestos exposure and colonic duplication have also been associated, but this has not been the case for SCC of rectal origin.

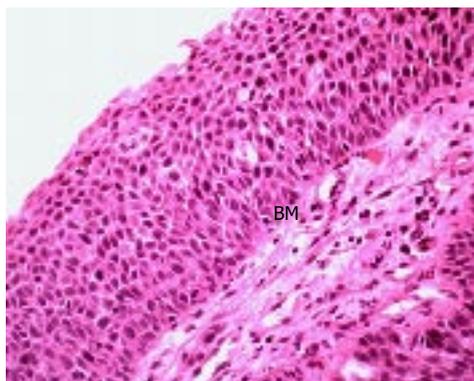


Figure 2 Haematoxylin and eosin stain of rectal squamous cell carcinoma *in situ*. This demonstrates architectural distortion, marked nuclear hyperchromatism and pleomorphism, along with full thickness basal layer expansion and no surface maturation. There is no evidence of invasion through the basement membrane (BM) (Image courtesy of Associate Professor Ken Opeskin, Department of Pathology, St Vincent's Hospital, Melbourne).

Given the strong association of human papilloma virus (HPV) with anal SCC, several studies have investigated its role in rectal SCC. This has produced variable results, with as many studies identifying HPV 16 in colorectal SCC specimens^[12,17,28,29], as those that have failed^[3,16,18]. Given this limited evidence, HPV infection as a risk factor for rectal SCC remains to be proven.

Pathogenesis: Despite reports of rectal SCC since the early 20th century, it's underlying aetiology remains unclear. While multiple theories have been postulated over this time period, its pathogenesis continues to be unravelled by assimilating the current body of evidence.

The theory of chronic inflammation leading to squamous metaplasia and subsequent carcinoma is one of the most prominent. This idea draws upon the fact that irritation and inflammation can lead to a change in the epithelial lining. This is termed metaplasia and is known to occur in the GI tract in response to exposure to various stressors^[30]. Metaplasia is the reversible change of one adult cell type into another and represents an adaptive substitution of stress-sensitive cells by a cell type better able to withstand that particular insult^[31]. The postulated inciting cause for the chronic inflammation leading to metaplasia has included the risk factors mentioned above of ulcerative colitis^[6,32], radiotherapy^[14,20-23] and infection^[18].

Adding support to this theory is firstly the description of squamous metaplasia in the colorectum in numerous instances. This has included sporadically^[33-36], in the regenerating epithelium of chronic ulcerative colitis^[15,32], in a rat by instillation of a chronic irritant (H₂O₂) and in a mouse secondary to chronic rectal prolapse^[37,38]. Secondly and of most significance, is the demonstration of an adjacent histological sequence in the rectum, from squamous metaplasia through dysplasia to carcinoma *in situ* (Figure 2) and invasive squamous carcinoma (Figure 3)^[6,7,12,15,24,35].

Drawing further upon this theory is the idea of

pluripotent mucosal stem cells capable of multidirectional differentiation, first postulated in the 1950's^[17,39-41]. Further work by Nahas *et al*^[16] in 2007 was based on the fact that keratin profiles vary amongst epithelia but remain constant in neoplastic transformation. They demonstrated that rectal SCC and adenocarcinoma stain for cytokeratin CAM5.2, unlike SCC of the anal margin, suggesting a common cell of origin for both rectal cancer subtypes. This lends support to an idea that the mucosal lining of the rectum contains a common pluripotent endodermal stem cell, which under certain conditions (inflammation and epithelial damage) can undergo squamous differentiation to better protect the rectum from the inciting cause. This is visualised as an area of metaplasia, which can subsequently undergo dysplasia and carcinomatous change if the inciting cause is not removed.

HPV has been postulated as a possible factor in inciting the dysplastic change of the squamous metaplasia. However, while there is a strong association between HPV and SCC of multiple sites including the anus, head/neck and cervix, the role in SCC of the rectum has not currently been established. There are more than 100 subtypes of HPV, with the most frequently encountered oncogenic forms being HPV 16 and 18. There are only a limited number of studies that have examined for HPV in rectal SCC, and they have utilised varying techniques for detection with discordant results. Audeau *et al*^[18] used immunohistochemistry to examine 20 squamous lesions (squamous metaplasia, SCC, adenosquamous carcinoma), without evidence of HPV 6, 11, 16 or 18. Frizelle *et al*^[3] and Nahas *et al*^[16] used an *in situ* hybridisation technique on 6 and 5 rectal SCC specimens respectively, again without evidence of HPV deoxyribonucleic acid (DNA). However, studies by Sotlar *et al*^[28] (1 rectal SCC), Kong *et al*^[12] (2 rectal SCC, 1 rectal SCC *in situ*), Matsuda *et al*^[29] (1 rectal SCC) and Jaworski *et al*^[17] (2 rectal SCC *in situ*), all identified HPV 16 in 7 rectal squamous lesions when utilising the PCR method, which is regarded as the gold standard. This may indicate that the sensitivity of the test employed in the detection of HPV has previously masked its presence.

The case presented by Sotlar *et al*^[28] is also of particular interest, given that it reported the findings of adjacent squamous metaplasia, dysplasia, and carcinoma in sequence, with HPV 16 identified in all three components and the surrounding non-tumour affected rectal mucosa. This mirrors the pre-neoplastic to neoplastic progression well documented in HPV driven anogenital cancers. Furthermore, they identified transcriptional activity of the HPV E6/7 oncogenes critical to HPV's role in carcinogenesis. This may suggest that there are two possible pathways to the pathogenesis of colorectal SCC, HPV driven and non-HPV driven. However, while there is currently limited evidence surrounding HPV in rectal SCC, a clear association and a role in causation remains to be

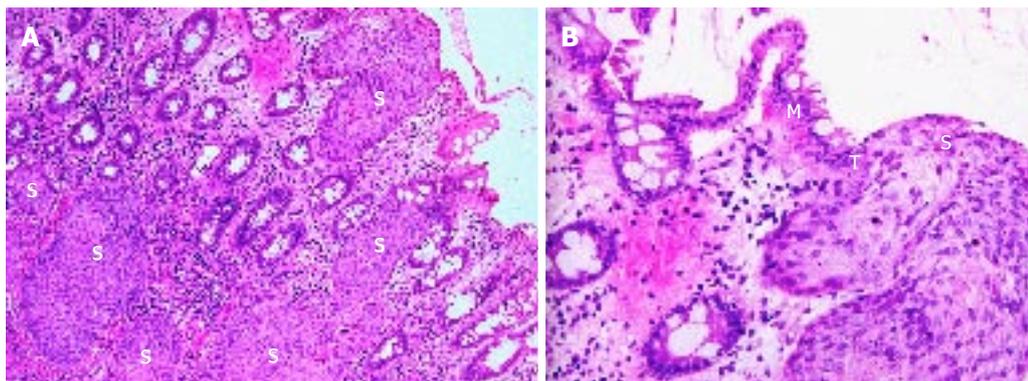


Figure 3 Haematoxylin and eosin stain of rectal squamous cell carcinoma. A: Widespread invasive squamous cell carcinoma (S) throughout the mucosa and submucosa of the rectal wall; B: Demonstration of the clear transition (T) between normal rectal mucosa (M) and invasive squamous cell carcinoma (S).

proven.

Patients with HIV have a higher incidence of HPV infection than the general population and additionally, HIV infection increases susceptibility to virally promoted cancers including Burkitt's lymphoma (Epstein barr virus), Kaposi's sarcoma (human herpes virus 8) and anogenital carcinoma (HPV). Consequently, it could be inferred that the cell mediated immune deficiency associated with HIV would predispose to rectal SCC. However, this is not borne out on review of the literature, with only two case reports of rectal SCC in the setting of HIV infection^[29,42].

Another postulated aetiology, has arisen from the finding of squamous differentiation within colorectal adenomas. Williams *et al*^[1] found this to be present in 3 of 750 adenomas, with a separate villous adenoma containing both invasive squamous and adenocarcinoma. Others have reported squamous metaplasia in adenomatous polyps^[43-46] in addition to a further case of SCC in a villous adenoma^[47]. These findings may again represent the squamous differentiation of a basal colonic cell, with changes inciting development of the adenoma also possibly leading to the metaplastic change.

Diagnosis and staging

Clinical presentation and diagnosis: The pattern of presentation for patients with rectal SCC is similar to those with adenocarcinoma of the rectum. The most frequently reported symptom is per rectal bleeding, followed less commonly by altered bowel habit (constipation, diarrhoea, tenesmus), pain and weight loss^[48]. The duration of symptoms can be variable, but most patients report a symptom history of weeks to months^[49,50].

Many presumed rectal SCCs are in fact an extension of an anal or gynaecological carcinoma, and consequently vigilance in diagnosis is important. Certain exclusion criteria stipulated by Williams *et al*^[1] in 1979, remain relevant for a diagnosis of primary rectal SCC to be established: (1) metastasis to the rectum from SCC of another organ; (2) squamous-lined fistula tract involving the affected region of rectum; and (3) SCC of

anal or gynaecological origin extending into the rectum.

With the above in mind, a detailed history and physical examination should be undertaken, with particular attention to the gynaecological system and anal canal. This often necessitates an examination under anaesthesia of both systems in addition to endoscopy.

The definitive diagnosis of rectal SCC is confirmed by performing a complete colonoscopy with biopsies of any abnormalities. Demonstration of the discontinuity of a lesion from the anal squamous mucosa is of great importance. Rectal SCC has been reported to have a varied endoscopic appearance dependent on the stage of disease. This can range from a small mucosal polyp (Figure 4), plaque or ulceration through to a large obstructing mass (Figure 5)^[51]. Pre-malignant lesions in the form of squamous metaplasia have also been identified by way of narrow band imaging (NBI) in addition to rectal SCC^[32,52]. One report identified an appearance of dark brown dots similar to the intraepithelial papillary capillary loops (IPCL) which herald squamous epithelium in the oesophagus using NBI^[32]. There are classification systems utilising the appearance of IPCL in the oesophagus in order to identify and differentiate squamous lesions along the spectrum towards invasive carcinoma^[53]. Given the possible aetiological sequence of metaplasia through to invasive carcinoma, NBI may find a role in the detection and treatment of pre-malignant lesions for those at high risk, in particular ulcerative colitis patients.

Histologically, if the diagnosis remains unclear, immunohistochemistry can aid in the characterisation of the lesion. This is particularly useful in cases of poorly differentiated tumours where the morphology and architecture provide little clue to the origin. Cytokeratins AE1/AE3, CK 5/6 (34BE12 stains CK5) and p63 stain for cells of squamous origin, assisting in the differentiation from a rectal adenocarcinoma. Cytokeratin CAM5.2 aids in the differentiation of rectal from anal, characteristically staining for rectal squamous cell or adenocarcinoma but not anal SCC. This is particularly useful for squamous carcinomas of the lower rectum^[16].

Squamous cell carcinoma associated antigen is

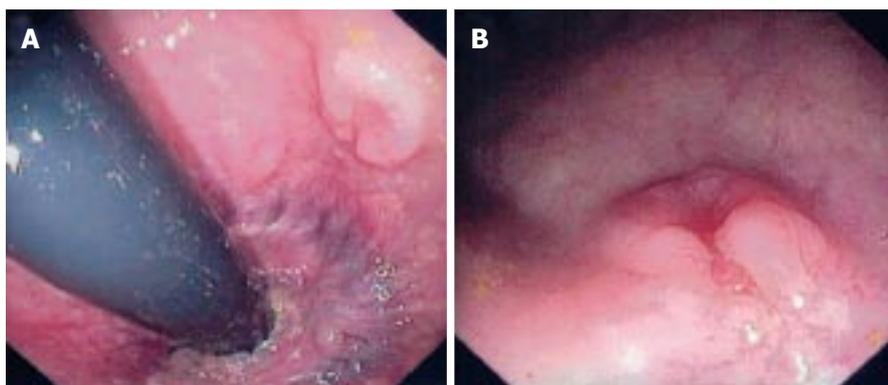


Figure 4 Endoscopic appearance of an early rectal squamous cell carcinoma. Rectal SCC presenting as a flat polypoid lesion with a central ulcerated depression in the distal rectum, 6 cm from the anal verge. A: Endoscopic retroflexed view; B: Endoscopic end-on view. SCC: Squamous cell carcinoma.

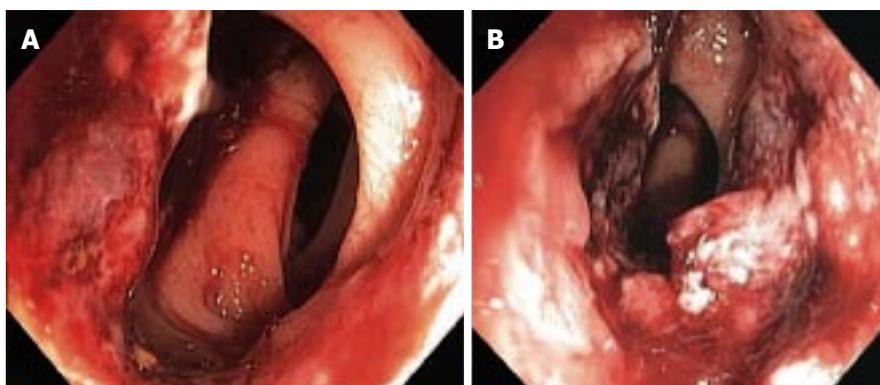


Figure 5 Endoscopic appearance of an advanced rectal squamous cell carcinoma. Large near circumferential rectal SCC with areas of necrosis and friability lying 3 cm above the anorectal ring. A and B: Endoscopic end-on view. SCC: Squamous cell carcinoma.

a serum tumour marker expressed by epidermoid tumours, including squamous carcinomas of the anal canal. Despite studies demonstrating weak evidence it may relate to nodal or relapsed disease in anal SCC, its use in diagnosis and follow-up remains controversial^[54-56]. With very limited data in the setting of rectal SCC, there is currently no clear utility for SCCAg in the diagnosis or management of these patients^[57].

Staging: Accurate staging of rectal SCC is of critical importance, in the same way that it dictates prognosis and management in anal SCC and rectal adenocarcinoma. In the literature, various staging systems have been translated into use for rectal SCC, most commonly the tumour-node-metastasis (TNM) system for rectal adenocarcinoma^[18,49,58-62] or the TNM system for anal SCC^[16,63,64]. While arguments can be made for the use of either staging system, the AJCC staging for rectal carcinoma is likely to have the greatest relevance. Firstly, the tumour stage focuses on the importance of the level of invasion through the rectal wall rather than the maximal dimension of the carcinoma. Secondly, nodal involvement is likely to follow the lymphatic drainage to the mesorectum and higher echelons, in preference to the alternative routes often involved in anal carcinoma such as the inguinal basins.

Staging involves evaluation of the primary tumour, and assessment for regional and metastatic disease. For loco-regional evaluation, as with rectal adenocarcinoma, magnetic resonance imaging (MRI) pelvis and endo-rectal ultrasound (ERUS) both have a role^[65]. A preference for either modality is often dependent on the experience with each technique at individual institutions. In terms of utility, ERUS has advantage in determining the depth of tumour invasion, particularly with differentiating T1/2 lesions. For delineation of more advanced T3/4 tumours and to determine local nodal involvement, pelvic MRI provides improved definition^[65,66]. Recently, there has been growing interest in the use of MRI diffusion weighted imaging (DWI) as a functional modality to assess treatment response in the staging of rectal adenocarcinoma^[67]. With the current shift towards definitive chemoradiotherapy in the treatment of rectal SCC, MRI is likely to find an increasingly useful role, not only for structural pre-treatment staging, but more importantly to determine the functional response of the tumour post-treatment in order to guide the need for operative intervention (Figure 6).

Computed tomography (CT) chest, abdomen and pelvis should be undertaken routinely in order to exclude metastatic disease. Increasingly, Fluorodeoxyglucose -

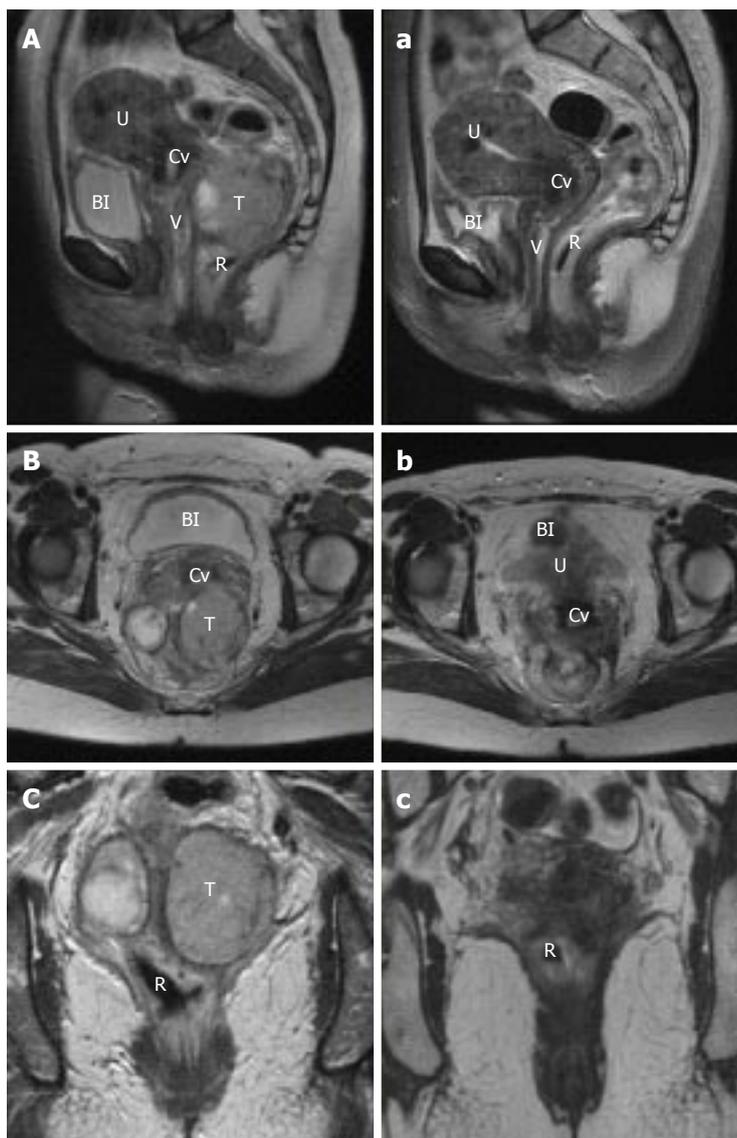


Figure 6 Magnetic resonance imaging appearance of rectal squamous cell carcinoma. Pre (A, B, C) and post (a, b, c) treatment T2 magnetic resonance imaging in sagittal (A, a), axial (B, b) and coronal (C, c) planes of a large rectal SCC, demonstrating an excellent response. T: Tumour; U: Uterus; V: Vagina; Cv: Cervix; BI: Bladder; R: Rectum; SCC: Squamous cell carcinoma.

positron emission tomography fused with simultaneous CT and more recently MRI imaging, is also finding a role in the staging of rectal SCC. Firstly, it allows exclusion of a non-rectal primary SCC that has metastasised to the rectum. Secondly it defines the extent of the primary and nodal disease. Thirdly, it has utility similar to MRI DWI imaging, in assessing the functional response of the tumour by comparing pre and post-treatment scans (Figure 7)^[65,68].

Treatment

The treatment of rectal SCC has traditionally involved surgery, in some cases preceded or followed by adjuvant radiotherapy or chemotherapy (Table 1)^[16,69]. However, in the last decade, there has been increasing interest in the response of rectal SCC to definitive chemoradiotherapy, with very encouraging results (Table 2).

Surgery: Surgery has historically been adopted from the treatment of rectal adenocarcinoma with the operative technique, dependent upon the stage and

location of the tumour. Local excision either trans-anal or endoscopic, has been advocated for selected cases, with several publications reporting short-term survival without recurrence in the setting of trans-anal excision followed by chemoradiotherapy^[12,16,48,70,71]. This included a T3 lesion and another with positive distal and radial margins, suggesting the chemoradiation may have played an important role in reducing local recurrence^[16,70]. With the evolution of endoscopic techniques, in particular endoscopic mucosal resection and submucosal dissection in the treatment of early rectal cancers^[72], these procedures may have a role in managing rectal SCC. Generally, the option of local excision would be limited to low risk T1 lesions, characterised as being well differentiated, without lymphovascular involvement, nodal or metastatic disease.

For most rectal SCC's, anterior resection (AR) or abdominoperineal resection (APR) has classically been performed. The choice and extent of the operation is dependent upon the tumour location and depth of invasion, occasionally requiring exenteration, with

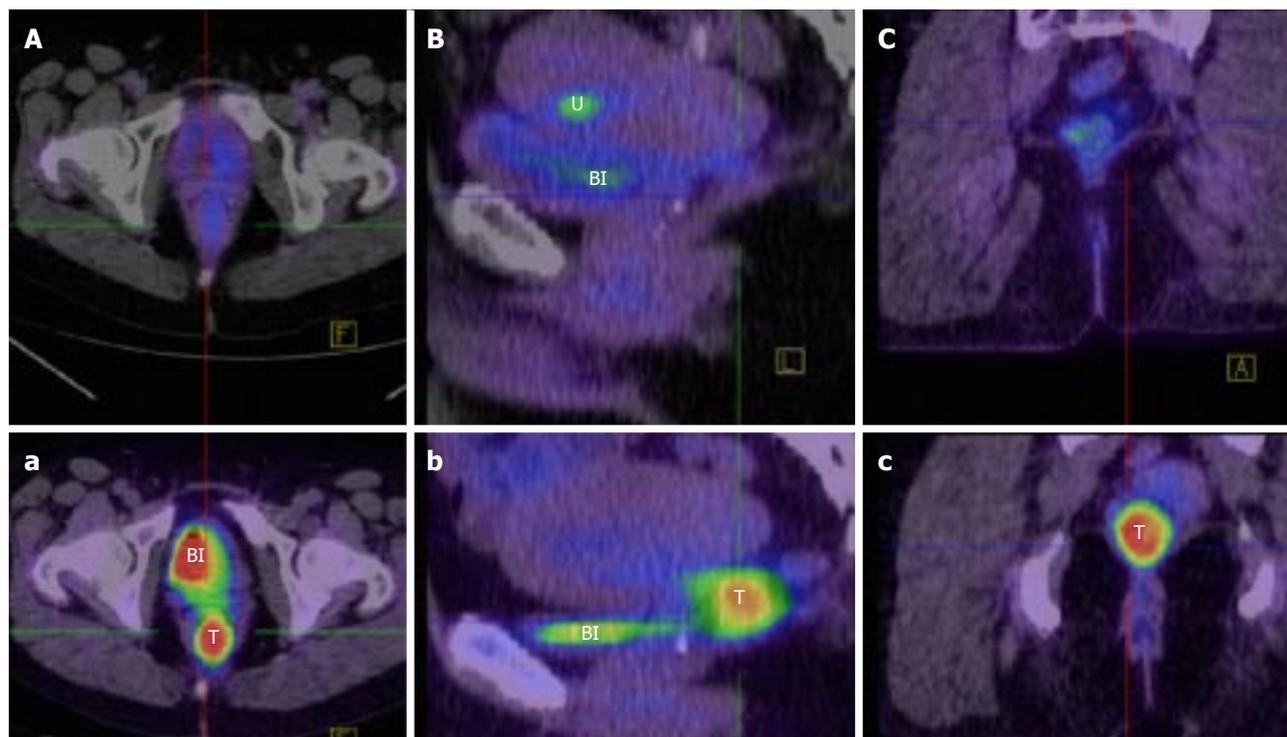


Figure 7 Positron emission tomography/computed tomography appearance of rectal squamous cell carcinoma. Pre (a, b, c) and post (A, B, C) treatment fused FDG-PET/CT imaging in axial (A, a), sagittal (B, b) and coronal (C, c) planes of a rectal SCC (T), demonstrating a complete metabolic response. [FDG is also visibly concentrated anteriorly in the bladder (BI) in images a, B, b, and in the endometrium (U) in image B (menstruation)]. FDG: Fluorodeoxyglucose; CT: Computed tomography; PET: Positron emission tomography; SCC: Squamous cell carcinoma.

removal of involved pelvic structures. On review of the literature, APR was performed much more frequently than AR prior to the year 2000, with an equal split in the frequency of both procedures following the turn of the century (Table 1). This is likely to reflect both the change towards sphincter preservation and avoidance of a permanent stoma in operations for rectal cancer over previous decades, in addition to a down-staging effect of chemoradiation, which is now commonplace. While the incidence of APR and a definitive stoma has been falling, in a similar manner to rectal adenocarcinoma, most patients with a low rectal SCC will require a temporary covering ileostomy given the greater risk of anastomotic leak. Furthermore, for those patients presenting with an obstructing tumour, the use of a defunctioning stoma is an attractive option, providing time to appropriately stage the patient and consider the optimal treatment, including definitive chemoradiotherapy.

Chemoradiotherapy: Following the validation of Nigro's protocol in multiple randomised controlled trials, it has now become the accepted standard treatment for anal SCC. Surgery, previously the preferred management, has subsequently been relegated to a salvage role^[73,74]. In light of this development, a trend of treating rectal SCC in the same manner has emerged.

On review of the literature, which spans from 1933 to the present, it is difficult to compare the treatment of rectal SCC, given the lack of a standardised staging system and treatment protocol. Nonetheless, an

increasing trend in the use of chemoradiation either as definitive treatment or in conjunction with surgery is emerging. There have been several prospective studies evaluating the role of chemoradiation as the primary therapy. The earlier cohorts demonstrated suboptimal outcomes, without a change in mortality or avoidance of surgery^[25,75]. However, with improvements in chemotherapy, radiotherapy and the accuracy of determining stage and response, a multitude of recent studies utilising an anal SCC based treatment regimen have reported promising results (Table 2)^[3,16,49,57,61,63,69].

The 3 most recent case series all published in 2015, comprise 22 patients treated with definitive chemoradiotherapy. Of this grouped cohort, a CR was identified by clinical examination and/or imaging in 14 of the 22 patients^[59,63,76]. The remaining 8 patients who demonstrated either progression of disease, a partial response or discordance between clinical and radiological findings, underwent a salvage operation. Of this group, 5 were noted to have a complete pathological response, equating to 19 of the 22 patients demonstrating a CR. Median follow up was 25 mo, with three patients suffering a recurrence, two of whom underwent a salvage operation, and one who received radiotherapy given the recurrence was outside the original field of treatment. Of these three, one succumbed to their disease at 14 mo post salvage surgery. One patient with an initial partial response and subsequent salvage operation developed metastatic disease without local relapse. The remaining 20 patients

Table 1 Conventional treatment of primary rectal squamous cell carcinoma

Ref.	Pts	Initial Rx	Surgery	Adjuvant Rx	Recurrence	Survival (ANED)	Follow up (mo)
Raiford <i>et al</i> ^[5]	1	-	PP	-	1 - LR	0%	21
Catell <i>et al</i> ^[81]	1	-	APR	-	-	100% (1)	42
LeBlanc <i>et al</i> ^[30]	5	-	1 - APR, PR - 4	-	1 - LR	40% (2)	3-60
O'Brien <i>et al</i> ^[82]	2	-	APR × 2	-	-	100% (2)	12
Kron <i>et al</i> ^[83]	1	-	APR	-	1 - M, 1 - LR	0%	5
² Dixon <i>et al</i> ^[84]	1	-	PR	-	NR	NR	-
Burns <i>et al</i> ^[85]	1	-	APR	-	-	100% (1)	42
Wiener <i>et al</i> ^[86]	1	-	APR	-	M - 1, LR - 1	0%	12
Zirkin <i>et al</i> ^[6]	1	-	TPC/APR	-	-	100% (1)	16
Hohm <i>et al</i> ^[7]	2	-	APR × 2	-	-	100% (1)	156-252
Angelchik <i>et al</i> ^[87]	1	-	AR	-	-	100% (1)	18
Cabrera <i>et al</i> ^[34]	1	-	APR	-	-	100% (1)	10
Minkowitz <i>et al</i> ^[88]	1	-	TPC	-	M - 1	0%	5
² Higton <i>et al</i> ^[11]	1	-	AR	-	NR	NR	-
Comer <i>et al</i> ^[10]	1	-	APR	-	-	100% (1)	156
Williams <i>et al</i> ^[1]	1	-	APR	-	M - 1	0%	9
Vezeridis <i>et al</i> ^[25]	4	CTx - 1	APR - 3	CTx - 1	M - 2, LR - 1	0%	0-15
Lafreniere <i>et al</i> ^[48]	1	-	TAE	CRTx	-	100% (1)	24
Pigott <i>et al</i> ^[89]	1	-	APR	RTx	-	100% (1)	13
Woods <i>et al</i> ^[35]	1	-	APR	-	-	0%	3
Prener <i>et al</i> ^[71]	5	-	APR - 4, TAE - 1	RTx - 1	LR - 3, M - 1	20% (1)	3-36
Schneider <i>et al</i> ^[70]	1	-	TAE	CRTx	-	100% (1)	6
Fazzi <i>et al</i> ^[90]	1	-	Y	RTx	-	100% (1)	72
Copur <i>et al</i> ^[91]	1	-	APR	CRTx	M - 1	NR	-
² Frizelle <i>et al</i> ^[3]	9	-	NR	NR	NR	NR	-
Sotlar <i>et al</i> ^[28]	1	-	AR	-	LR - 1	0%	21
Gelas <i>et al</i> ^[69]	4	RTx - 2	APR × 3	CRTx - 1, RTx - 1	LR - 1, M - 2	25% (1)	4-192
Anagnostopoulos <i>et al</i> ^[92]	1	-	APR	CTx	-	100% (1)	14
Fahim <i>et al</i> ^[93]	1	-	APR	CTx	LR - 1, M - 1	0%	11
² Lam <i>et al</i> ^[94]	1	RTx	AR	-	-	NR	-
² Cheng <i>et al</i> ^[15]	1	-	TPC	CRTx	-	NR	-
Kong <i>et al</i> ^[12]	2	CTx - 1	TAE - 1	CRTx - 1	-	50% (1)	36
Nahas <i>et al</i> ^[16]	3	CTx - 1	APR, TAE	CRTx - 2	-	100% (3)	6-192
¹ Leung <i>et al</i> ^[20]	1	-	S	-	M - 1	0%	-
² Dzeletovic <i>et al</i> ^[52]	1	NR	NR	NR	NR	NR	-
Sameer <i>et al</i> ^[95]	1	-	AR	CTx	-	100% (1)	24
Wang <i>et al</i> ^[60]	2	-	H, TAE	CRTx - 2	M - 1	50% (1)	21, 120
Sanal <i>et al</i> ^[96]	1	CTx	AR	-	-	100% (1)	12
Yeh <i>et al</i> ^[49]	1	-	APR	-	M - 1	0%	7
Faidzal <i>et al</i> ^[97]	1	-	AR	CRTx	-	100% (1)	15
Wang <i>et al</i> ^[98]	1	-	APR	RTx	-	100% (1)	43
Scaringi <i>et al</i> ^[23]	1	-	AR	-	LR - 1, M - 1	0%	4
Ozuner <i>et al</i> ^[14]	7	-	APR - 3 AR - 1 TPC - 1 TAE 1, H - 1	CTx - 4	M - 4, LR - 3	43% (3)	12-96
Péron <i>et al</i> ^[59]	1	RTx	-	-	LR - 1	0%	40
Overall	63 (78 ²)	CTx 4 RTx 4	Resection 53 (PP/PR 6, APR 34, TPC/AR 13) TAE 7, H 2, S 1	CRTx 11 CTx 8 RTx 5	LR 25% (16) M 30% (19)	48% (30)	0-252

¹Not included in analysis as refused treatment; ²Not included in analysis as no relevant information recorded. Pts: Number of patients in study; Rx: Treatment; ANED: Alive, no evidence of disease; AR: Anterior resection; APR: Abdominoperineal resection; PR: Posterior resection; PP: Perineal proctectomy; TPC: Total proctocolectomy; TAE: Trans-anal excision; H: Hartmann's; S: Diverting Stoma; NR: Not recorded; M: Metastasis; LR: Local recurrence.

are alive without evidence of disease^[59,63,76].

Expanding from the above findings, when all cases reported in the literature are examined, it is obvious that patients undergoing definitive chemoradiotherapy have a far superior survival then what has been historically recorded (Table 1 compared with Table 2). The overall survival for the chemoradiation group was 86% compared with 48% for conventional treatment. Likewise, the local recurrence and metastatic rates

were respectively 25% vs 10% and 30% vs 13% for the chemoradiation vs conventional treatment cohorts. These differences are likely due to a combination of factors, including improvements in imaging, tumour staging and perioperative workup and patient care over time. Furthermore, there are significant limitations in the analysis and interpretation of these results, related to the inherent heterogeneity of case reports and the inconsistency in recording important prognostic variables

Table 2 Chemoradiation as primary treatment of rectal squamous cell carcinoma

Ref.	Pts	Chemotherapy		RTx (Gy)	CR	Surgery	Path CR	Recurrence	Survival (ANED)	Follow up (mo)
		5FU/MMC	Other							
Vezeridis <i>et al</i> ^[25]	1	-	1	40	-	-	-	LR - 1	0%	15
¹ Schneider <i>et al</i> ^[70]	1	1	-	30	-	-	-	-	NR	-
Kulayat <i>et al</i> ^[13]	1	1	-	40	-	TPC	100%	-	100% (1)	48
Martinez-Gonzalez <i>et al</i> ^[75]	1	-	1	46	-	AR	0%	-	100% (1)	18
Gelas <i>et al</i> ^[69]	2	-	2	Y	-	AR - 2	0%	-	100% (2)	6-24
Theodosopoulos <i>et al</i> ^[99]	1	1	-	20	-	APR	0%	M - 1	100% (1)	18
Pikarsky <i>et al</i> ^[9]	1	1	-	60	1	-	-	-	100% (1)	84
Nahas <i>et al</i> ^[16]	9	6	3	50.4	2	TAE - 2 APR - 2 AR - 3	86%	-	100% (9)	6-192
Clark <i>et al</i> ^[61]	7	3	4	50.4	7	AR - 1	100%	-	100% (7)	5-31
Matsuda <i>et al</i> ^[29]	1	-	1	59.4	-	APR	0%	LR - 1, M - 1	0%	24
Brammer <i>et al</i> ^[100]	1	1	-	Y	1	-	-	M - 1	100% (1)	24
Rasheed <i>et al</i> ^[57]	6	2	4	45-50.4	4	APR - 2	50%	LR - 1	100% (6)	2-132
Al Hallak <i>et al</i> ^[101]	1	1	-	Y	1	-	-	-	100% (1)	30
Tronconi <i>et al</i> ^[58]	6	1	5	50.4-59.4	4	AR - 1 H - 1	50%	M - 1	83% (5)	24-41
Iannacone <i>et al</i> ^[102]	1	1	-	59.4	1	-	-	-	100% (1)	12
Wang <i>et al</i> ^[60]	5	5	-	45-54	4	AR - 2 APR - 1	100%	M - 2	60% (3)	15-51
Yeh <i>et al</i> ^[49]	5	4	1	30-60	4	AR - 1	100%	LR + M - 1	80% (4)	24-84
Jeong <i>et al</i> ^[62]	4	-	4	50.4-63	4	-	-	-	75% (3)	2-99
Kassir <i>et al</i> ^[103]	1	-	1	Y	-	AR	0%	-	100% (1)	-
Ferreira <i>et al</i> ^[64]	1	1	-	52	1	-	-	-	100% (1)	40
Choi <i>et al</i> ^[42]	1	1	-	Y	1	APR	0%	LR - 1	100% (1)	17
Musio <i>et al</i> ^[63]	8	6	2	45-70.6	4	APR - 4	50%	LR - 1	88% (7)	1-164
Péron <i>et al</i> ^[59]	10	4	6	45-62	6	APR - 2 AR - 2	50%	LR - 1	100% (10)	6-133
Funahashi <i>et al</i> ^[76]	3	-	3	45-59.4	2	PE	100%	M - 1	67% (2)	14-44
Seshadri <i>et al</i> ^[104]	1	1	-	50.4	1	AR	0%	LR + M - 1	0%	36
Ozuner <i>et al</i> ^[14]	1	1	-	Y	-	-	0%	M - 1	0%	12-96
Overall	79 (80 ¹)	42	38	All	60% (48)	44% (35)	57% (20)	LR 10% (8) M 13% (10)	86% (68)	1-192

¹Not included in analysis as no relevant information recorded. Pts: Number of patients in study; RTx: Radiotherapy; CR: Complete response; Path CR: Pathological complete response; ANED: Alive, no evidence of disease; Other: 5FU - 3, 5FU/Cisplatin - 26, Capecitabine/Cisplatin - 3; Capecitabine - 1; Raltitrexed/Oxaliplatin - 2; S1 - 3; Gy: Gray; AR: Anterior resection; H: Hartmann's; PE: Pelvic exenteration; TAE: Trans-anal excision; TPC: Total proctocolectomy; APR: Abdominoperineal resection; NR: Not recorded; M: Metastasis; LR: Local recurrence.

including stage and grade. Despite these limitations, the treatment itself almost certainly accounts for a significant component of the dramatically improved local control and survival.

As with rectal and anal cancer, one of the most pertinent issues with definitive chemoradiation, is determining treatment response, which currently can only be confirmed on histopathology^[73,77]. In the studies to date on rectal SCC, response to chemoradiotherapy has been assessed variably, from 6-8 wk up to 6 mo after the conclusion of treatment. This generally involves a combination of a clinical assessment, by way of a repeat EUA/proctoscopy + biopsy, and an imaging assessment in the form of MRI ± PET/CT ± ERUS^[49,58,60,61]. For patients with a complete clinical and radiological response, follow up and surveillance is performed at regular intervals with reducing frequency out to five years, generally 3 monthly for the first two years, and 6 monthly out to five years. While this is certainly labour and resource intensive with consequent costs, the improved overall and stoma free survival certainly

justifies this approach.

For those cases with clear progression of disease through chemoradiation, salvage surgery should be undertaken as the next line of treatment to ensure optimal outcomes. However, in the setting of a partial response or stable disease, the pathway is less clear. It has been suggested that a more prolonged assessment, with regular EUAs even out to 6 mo, could be required for a better evaluation of tumour response. This is in consideration of the finding that multiple patients with an eventual pathological CR had clinical and radiological findings suggestive of persistent disease in the early post chemoradiation stage^[16]. This is also in keeping with the accepted management of anal SCC, where a delayed tumour response may continue for 6 mo after the completion of chemoradiation^[63]. In the grouped chemoradiation cohort (Table 2), a CR on pathology was identified in 57% of patients, suggesting that time may have played a role in assessing clinical and radiological response. As with rectal and anal cancer, this is likely to remain a contentious area until a more effective means

of determining response is available^[78].

Despite the encouraging results of chemoradiotherapy, currently a set treatment protocol is yet to be established. It appears that 5FU based chemotherapy combined with high dose external beam radiotherapy may be efficacious. However, while these trends are grossly evident from the literature, there is a need for further research in order to determine the most effective regimen to optimise patient outcomes.

It is unlikely that a randomised trial comparing surgery and chemoradiotherapy will ever be conducted for this rare cancer. Given the current knowledge base, it may be reasonable to suggest that primary treatment should be chemoradiotherapy, with surgery reserved as a salvage option. The suggested regimen would be a total dose of 50.4 to 54 Gy external beam radiation in 1.8 Gy per fraction, given concurrently with 5FU and mitomycin C.

Future options: Over recent years, there has been an increasing use of molecular targeted therapies in solid and haematological malignancies^[79]. Furthermore, immunotherapy in the form of tumour vaccines, adoptive T cell therapy and immune checkpoint inhibitors has become a major focus for research in the treatment of cancer, with translated clinical success in specific tumour types^[80]. While there is currently no literature on these modalities in rectal SCC, the early results in other tumours holds promise for a possible role in future treatment, particularly in the cohort of patients with persistent, recurrent or metastatic rectal SCC.

Prognosis

The most important predictor of survival in all cancers is the stage of disease. This is based upon three factors; the size of the primary tumour and depth of invasion (T stage); the location and number of lymph nodes involved (N stage); and the presence or absence of metastasis (M stage). Rectal SCC follows the same route of lymphatic spread for involvement of lymph nodes as rectal adenocarcinoma. Additionally, it has a similar pattern of metastasis with the liver, lung and bones most commonly affected^[66].

While the majority of patients with rectal SCC present with locoregional disease (stage I-III, 82.1%), they are associated with a poorer overall survival when compared stage for stage with adenocarcinoma. From review of the population study by the NCI, the overall 5-year survival for rectal SCC was found to be 48.9% compared with 62.1% for adenocarcinoma. When localised, the 5 years OS was 73.7% (91.8% - adenocarcinoma), with 31.3% (65.8%) for regional and 20.8% (8.8%) for metastatic^[2]. While the above figures and those from older studies report a poor prognosis for patients with rectal SCC, recent studies employing a new treatment paradigm, demonstrate a significantly improved overall survival. The possibility of further

advances in treatment as this disease is better defined, gives hope for improved patient outcomes.

While SCC of the rectum is a rare entity, there is an increasing body of evidence that is improving our understanding of its underlying aetiology. Despite the literature lacking uniformity in the staging and management of rectal SCC, it is hard to ignore the impressive improvements in overall survival and sphincter preservation by way of chemoradiotherapy as the primary modality of treatment. This holds much promise for the future, and certainly lays the foundation for further investigation into determining the optimal treatment regimen.

COMMENTS

Background

A summary of the current body of knowledge surrounding the pathogenesis, presentation, diagnosis, staging and management of rectal squamous cell carcinoma (SCC), with a focus on the changing treatment paradigm and consequent improved patient outcomes.

Research frontiers

While the underlying pathogenesis of rectal SCC is yet to be fully defined, a possible role for human papilloma virus presents an avenue for future investigation. Furthermore, the identification of pre-malignant lesions in the development of rectal SCC raises the possibility of surveillance in high risk patients. The use of magnetic resonance imaging (MRI) and positron emission tomography (PET) has an emerging role not only in diagnosis and staging, but also importantly as a functional modality to determine response to chemoradiotherapy. This role has arisen from the recent shift in the primary treatment of rectal SCC to chemoradiotherapy, accompanied by a dramatic improvement in overall survival.

Innovations and breakthroughs

Assimilation of the current body of evidence lends support to the presence of pre-malignant lesions and a metaplasia-dysplasia-carcinoma sequence in the development of rectal SCC. Staging for rectal SCC fits more appropriately with the tumour-node-metastasis (TNM) criteria for rectal adenocarcinoma than anal SCC. MRI and PET are finding an increasing role in diagnosis, staging and assessment of response to treatment in rectal SCC. Chemoradiotherapy offers improved patient outcomes without the associated morbidity of surgery. Improved markers of complete response will assist in determining the need for salvage treatment in this patient cohort.

Applications

Consideration should be given to screening for premalignant lesions in high risk individuals. Uniform staging utilising the current TNM criteria for rectal adenocarcinoma should be encouraged. PET and MRI should be incorporated into the evaluation of patients, pre and post treatment. Definitive chemoradiotherapy offers improved patient outcomes without the associated morbidity of surgery. While treatment must be individualised and based on patient and tumour factors, chemoradiation should form the basis of primary management.

Terminology

Complete response refers to the resolution of tumour following treatment with chemoradiotherapy. While radiological investigations and clinical examination can act as surrogate markers, a true complete response can currently only be determined post resection and pathological examination.

Peer-review

The review article described the background, diagnosis and staging, treatment,

and prognosis of primary SCC of the rectum. The whole article is well written and characterized.

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Fibrin sealant use in pilonidal sinus: Systematic review

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Abstract

AIM: To review the current data about the success

rates of fibrin sealant use in pilonidal disease.

METHODS: Fibrin sealant can be used for different purposes in pilonidal sinus treatment, such as filling in the sinus tracts, covering the open wound after excision and lay-open treatment, or obliterating the subcutaneous dead space before skin closure. We searched Pubmed, Google-Scholar, Ebsco-Host, clinicaltrials, and Cochrane databases and found nine studies eligible for analysis; these studies included a total of 217 patients (84% male, mean age 24.2 ± 7.8).

RESULTS: In cases where fibrin sealant was used to obliterate the subcutaneous dead space, there was no reduction in wound complication rates (9.8% vs 14.6%, $P = 0.48$). In cases where sealant was used to cover the laid-open area, the wound healing time and patient comfort were reported better than in previous studies (mean 17 d, 88% satisfaction). When fibrin sealant was used to fill the sinus tracts, the recurrence rate was around 20%, despite the highly selected grouping of patients.

CONCLUSION: Consequently, using fibrin sealant to decrease the risk of seroma formation was determined to be an ineffective course of action. It was not advisable to fill the sinus tracts with fibrin sealant because it was not superior to other cost-effective and minimally invasive treatments. New comparative studies can be conducted to confirm the results of sealant use in covering the laid-open area.

Key words: Pilonidal disease; Fibrin sealant; Evidence base medicine; Systematic review

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Core tip: Fibrin sealant use in pilonidal disease treatment may involve filling in the sinus tracts, covering the laid-open area after excision, or obliterating the subcutaneous dead space before skin closure. This systematic review demonstrates that when the fibrin

sealant was used to obliterate the subcutaneous dead space, there was no reduction in wound complications. It was unadvisable to fill the sinus tracts because it was not superior to the other more cost-effective treatments with a 20% recurrence rate. More studies are necessary for sealant use in covering the laid-open area, which has promising results, predicting shorter wound healing time and increased patient satisfaction.

Kayaalp C, Ertugrul I, Tolan K, Sumer F. Fibrin sealant use in pilonidal sinus: Systematic review. *World J Gastrointest Surg* 2016; 8(3): 266-273 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i3/266.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i3.266>

INTRODUCTION

Pilonidal sinus is a benign disease seen more commonly in young males and negatively alters the quality of life. Its prevalence was reported as 26 cases per 100000 people^[1]. The mainstay of pilonidal sinus treatment begins with the surgical excision of the sinus tracts, which is followed by either primary closure after excision or laying open the wound for secondary healing; these are the most commonly preferred surgical methods. However, these traditional techniques prolong the recovery period, cause a delay in returning to daily life, and ultimately interrupt the educational or professional lives of these young and active patients.

Fibrin sealant may be used for different purposes in pilonidal sinus surgery. Filling the sinus tracts with the fibrin sealant instead of surgically removing the sinus tracts has been described in the literature as a minimally invasive technique. Additionally, the open surface of the surgical area may be covered with the fibrin seal in the lay-open technique. A third option requires that the potential dead space that is formed after the total excision and primary closure of the defect may be obliterated by the fibrin sealant. All these methods are used in order to accelerate the recovery period, to decrease morbidity, and to enable a quick return to work. Our aim in this review was to collect all accessible data in the literature on the treatment of pilonidal disease with fibrin sealant and to make a prediction about the promising treatments.

MATERIALS AND METHODS

The databanks of www.ncbi.nlm.nih.gov/pubmed, www.cochrane.org, scholar.google.com and web.a.ebscohost.com were last searched on the 3rd of June, 2015, using the key words [(pilonidal*) and (glue* OR sealant*)]. All varieties of researches, including congressional summaries describing the patient data about the treatment, were analyzed. Two reviewers (IE & CK) determined the selection of the searched articles on www.ncbi.nlm.nih.gov/pubmed and www.cochrane.org

by the key words in all fields. Some studies were excluded due to the nature of their content (editorial letters, reviews, duplicated studies). Later, a search to scholar.google.com and web.a.ebscohost.com were done by the key words in titles of the studies. Lastly, www.clinicaltrials.gov was also searched. We performed an additional reference cross check as well.

As we were scanning the literature for the pilonidal sinus treatment modalities using fibrin glue, publications concerning the use of fibrin glue to fill the tracts without excision, publications concerning covering the defect following surgical excision and publications concerning filling the cavity with fibrin glue before primary closure were all included in this analysis. Treatments of pilonidal sinuses outside of the sacrococcygeal area (interdigital, umbilical, penile, vulvar) were excluded.

We used no limitations to the patient and journal features. All patients were accepted for analysis if there were enough data. There was no restraint with regard to article language, country, or journal. In cases of disagreement during analysis, a consensus of the two researcher authors was necessary for the acceptance of the studies. Data for affiliation, number of patients, age, gender, history of prior pilonidal surgery, method of application, complications, recurrence, time to heal, length of follow-up period, success, clinical findings, inclusion and exclusion criteria, body mass index, intra-operative and postoperative complications, duration of surgery, postoperative pain, postoperative hospital stay, time off work, and overall satisfaction were analyzed.

Data were organized into tables, and column sums were done including percentages, means \pm standard deviations, or the ranges. If the studies reported the median and range, the mean and standard deviation were estimated by Hozo *et al.*^[2] method. Percentages were preferred for the dichotomous parameters and means for the continuous parameters^[3]. The Chi-square test or the Fisher exact test (if expected values were less than 5) and Student's *t* test were used. (SPSS 17.0). $P < 0.05$ was accepted as statistically significant.

RESULTS

A total of nine publications were found that detailed the use of fibrin sealant in pilonidal sinus treatment^[4-12] (Figure 1). These publications included 217 patients that were treated between June 2001 and December 2013 (Table 1). Eighty-four percent of the patients were male, and their mean age was 24.2 ± 7.8 (ranged 12-70). One of the studies was conducted within a pediatric age group; the mean age for participants in this study was 14.5 and their mean body weight was 73 kg^[12]. The inclusion criteria and the surgical techniques used in these studies constituted sufficient heterogeneity (Tables 2 and 3). The studies were gathered into three subgroups depending on the application technique of the fibrin glue (Table 3). Fibrin sealant was used to obliterate the dead space before wound closure in three studies^[4,8,9]. In two other studies, it was used to cover

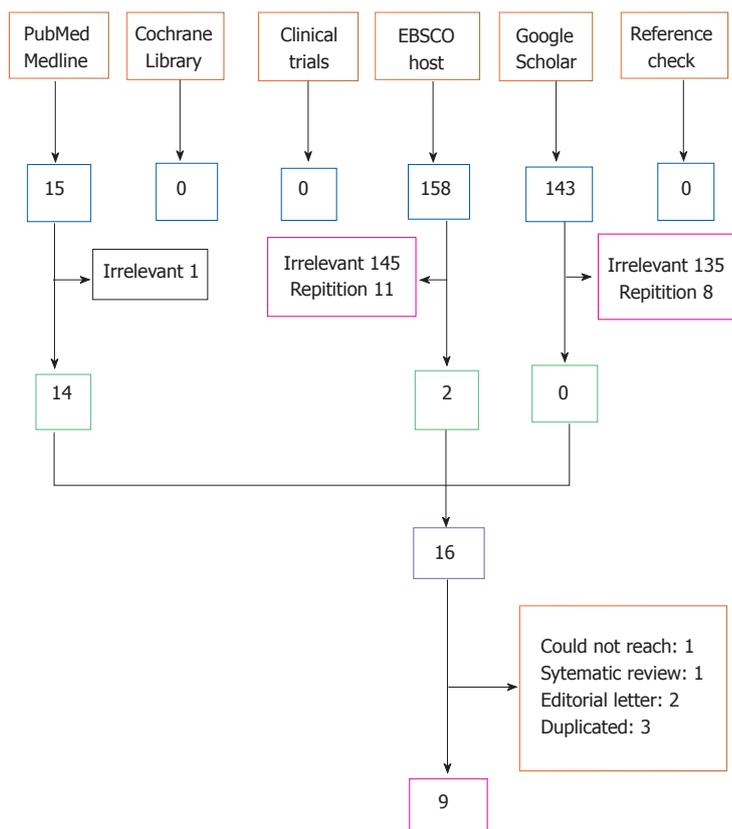


Figure 1 Flowchart of the systematic review.

Table 1 Studies of fibrin sealant at pilonidal sinus: Demographics of the patients

Ref.	Year	Country	Study period	No.	Male	Age	BMI or weight
Greenberg <i>et al</i> ^[4]	2004	Israel	Jun 2001 to Dec 2001	30	22	23.5 ± 2.8 (17-44)	NA
Lund <i>et al</i> ^[5]	2005	United Kingdom	NA	6	6	28.5 ± 5.5 (22-44)	NA
Seleem <i>et al</i> ^[6]	2005	Saudi Arabia	Sep 2001 to Feb 2004	25	23	26.4 ± 8.5 (17-50)	NA
Patti <i>et al</i> ^[7]	2006	Italy	NA	8	8	21.8 ± 6.5	NA
Altinli <i>et al</i> ^[8]	2007	Turkey	Jan 2003 to Jan 2004	16	16	24.5 ± 6.0	25.7 + 4.1 kg/m ²
Sözen <i>et al</i> ^[9]	2011	Turkey	Jan 2008 to Mar 2008	25	25	22.5 ± 4.0 (20-36)	26 kg/m ²
Elsey <i>et al</i> ^[10]	2013	United Kingdom	Mar 2007 to Sep 2011	57	42	26.0 ± 13.3 (17-70)	NA
Isik <i>et al</i> ^[11]	2014	Turkey	Dec 2007 to Dec 2011	40	32	24.0 ± 8.5 (16-50)	NA
Smith <i>et al</i> ^[12]	2014	United Kingdom	Aug 2006 to Dec 2013	10	NA	14.5 ± 1.0 (12-16)	73 kg
Total			Jun 2001 to Dec 2013	217	84%	24.2 ± 7.8 (12-70)	

BMI: Body mass index; NA: Not available.

Table 2 Studies of fibrin sealant at pilonidal sinus: Features of the pilonidal sinuses

Ref.	No.	Inclusion and exclusion criteria	Recurrent
Greenberg <i>et al</i> ^[4]	30	No exclusion criteria	8
Lund <i>et al</i> ^[5]	6	3-4 openings and no large cavity	3
Seleem <i>et al</i> ^[6]	25	1-3 openings, no prior surgery, no infection	0
Patti <i>et al</i> ^[7]	8	3 < openings, no prior surgery, no infection, no large cavity or distant orifice	0
Altinli <i>et al</i> ^[8]	16	No prior surgery	0
Sözen <i>et al</i> ^[9]	25	No prior surgery, no infection, no lateral extension < 3 cm	0
Elsey <i>et al</i> ^[10]	57	No infection, no very scarred cases due to repeated episodes or surgeries	2
Isik <i>et al</i> ^[11]	40	Only 1 opening, no prior surgical or medical treatment, no infection	0
Smith <i>et al</i> ^[12]	10	No exclusion criteria	0
Total	217		13 (6%)

the defect after the excision and lay-open technique^[6,7]. In the remaining four studies, the sinus tracts were

Meta-analysis: Risk difference

Study	Intervention	Controls	Risk Difference	95%CI	Z	P
Altinli	0/16	2/16	-0.125	-0.287-0.0371		
Sözen	6/25	2/25	0.160	-0.0383-0.358		
Total (fixed effects)	6/41	4/41	0.0488	-0.0877-0.185	0.701	0.484
Total (random effects)	6/41	4/41	0.0125	-0.291-0.316	0.0804	0.936

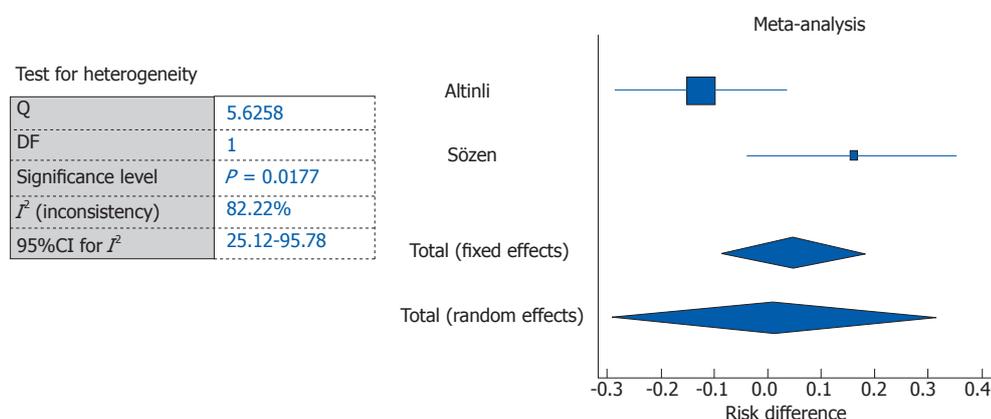


Figure 2 Obliterating the dead space under the closed wound with sealent vs controls: Meta-analysis of the wound complications.

Table 3 Studies of fibrin sealant at pilonidal sinus: Procedures

Ref.	No.	Surgical procedure	Aim of using fibrin sealant
Greenberg <i>et al</i> ^[4]	30	Excision and primary closure	Obliterate the dead space under the wound
Lund <i>et al</i> ^[5]	6	No sinus excision, only cleaning the tracts	Fill the tracts with sealent
Seleem <i>et al</i> ^[6]	25	Excision and lay open	Overlap the open wound with sealent
Patti <i>et al</i> ^[7]	8	Excision and lay open	Overlap the open wound with sealent
Altinli <i>et al</i> ^[8]	16	Excision and closure with Limberg flap	Obliterate the dead space under the wound
Sözen <i>et al</i> ^[9]	25	Excision and closure with Karydakias flap	Obliterate the dead space under the wound
Elsey <i>et al</i> ^[10]	57	No sinus excision, only cleaning the tracts	Fill the tracts with sealent
Isik <i>et al</i> ^[11]	40	No sinus excision, only cleaning the tracts	Fill the tracts with sealent
Smith <i>et al</i> ^[12]	10	No sinus excision, only cleaning the tracts	Fill the tracts with sealent

filled with the fibrin sealant without performing any surgery, which was intended to constitute a definitive treatment^[5,10-12]. Thirty-nine percent of all these interventions were performed under local anesthesia. An average of 3.8 mL (ranged 1-6 mL) of fibrin glue was used; drains were used in only 7.3% of these cases (Table 4).

In three studies, fibrin sealant was applied in order to obliterate the subcutaneous dead space^[4,8,9]. There were no recurrences in any of these cases after a mean follow-up period of 15.2 mo (Table 5). However, wound-related complications were observed in 16.4% of the patients. In one study, the authors declared that postoperative purulent drainage after fibrin sealant application was more frequent in cases requiring recurrent surgeries^[4]. In another study, the amount of drainage decreased within the fibrin sealant group, but instances of wound complications did not decrease significantly^[8]. In another study, fibrin sealant was replaced with a subcutaneous drain; there were no wound-related complications within the no-drain fibrin sealant group^[9]. In the studies with control groups^[8,9],

it was observed that use of the fibrin sealant did not decrease wound complication rates (control groups 9.8% vs sealant groups 14.6%; $P = 0.48$) (Figure 2).

Fibrin sealant was used in two studies in order to shorten the wound's healing period and to mitigate the negative effects associated with an open wound following surgical excision^[6,7] (Table 6). Healing periods for these patients were around 17 d and the morbidity rate was only 6%, which mainly involved early detachment of the fibrin sealant. When the fibrin sealant detached from the wound, either a new sealant was applied to the wound^[7], or it was left open for secondary intention^[6]. Work-off time of those patients was reported to be lower than expected (5.3 + 2.1 d)^[7]. In this group of patients, there were no recurrences reported and the patient satisfaction rate was reported to be 88% (Table 6).

Simply filling the pilonidal sinus tracts with fibrin sealant after curettage was used in four studies conducted with 113 patients as a minimally invasive treatment modality. Work-off time was generally less than 7 d, and the morbidity rates were generally

Study	SD*	Proportion (%)	95%CI
Lund	6	16.667	0.421-64.123
Elsey	57	26.316	15.538-39.663
Isik	40	10.000	2.793-23.664
Smith	10	20.000	2.521-55.610
Total (fixed effects)	113	19.905	13.096-28.296
Total (random effects)	113	19.587	11.255-29.558

Test for heterogeneity

Q	4.1336
DF	3
Significance level	$P = 0.2469$
I^2 (inconsistency)	27.51%
95%CI for I^2	0.00-72.90

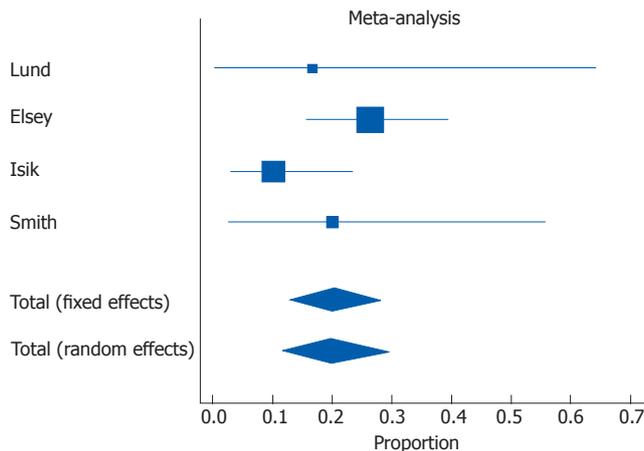


Figure 3 Filling the tracts with fibrin sealant; meta-analysis of the recurrence rates.

Table 4 Surgical details				
Ref.	No.	Anesthesia	Amount of glue	Drain
Greenberg <i>et al</i> ^[4]	30	General or spinal	2-4 mL	None
Lund <i>et al</i> ^[5]	6	General	1-2 mL	None
Seleem <i>et al</i> ^[6]	25	Local (n = 23), general (n = 2)	NA	None
Patti <i>et al</i> ^[7]	8	Local	1.9 ± 0.6 mL	None
Altinli <i>et al</i> ^[8]	16	Spinal	6 mL	Yes
Sözen <i>et al</i> ^[9]	25	NA	6 mL	None
Elsey <i>et al</i> ^[10]	57	General	NA	None
Isik <i>et al</i> ^[11]	40	Local	2-4 mL	None
Smith <i>et al</i> ^[12]	10	General	NA	None
Total	217	Local 39%	3.8 (1-6)	7.3%

NA: Not available.

reported to be less than 1% (Table 7). The success rate for this group of patients was about 80%, after a mean follow up of 21.7 mo. In other words, the recurrence rates were around 20% (Figure 3).

DISCUSSION

The fibrin sealant is composed of two ingredients; human fibrinogen and bovine thrombin. When the two of these are combined, the thrombin converts the fibrinogen into fibrin in less than a minute. This 3 dimensional fibrin plug is used as a haemostatic or a sealing agent. Fibrin was first used as a local haemostatic material in Germany about 100 years ago^[13]. In the 1940s, it was used to repair the peripheral nerves^[14] and to keep skin grafts in place^[15]. Although it has been used commercially in Europe since 1972, it was not approved by the FDA for use in the United States^[16] until around 1998. Nowadays, fibrin sealant has been approved by the FDA for the following uses; hemostasis in surgical interventions, sealing of the colon during colostomy closure, and fixation of skin grafts given to burn patients^[16,17]. The other uses for fibrin sealants that fall outside of the FDA indications include prevention of seroma formation, fixation of mesh, and fistula tract closure^[16].

Recently, there has been a tendency to use minimally invasive surgical techniques in the treatment of pilonidal sinus, as with other surgically-treated diseases^[18]. Ideal treatment of pilonidal sinus should be conducted in outpatient settings under local anesthesia, have less postoperative pain, fast recovery, high success rates, and low costs^[18]. Fibrin sealant can be used for three purposes; (1) to obliterate the dead space under a closed wound; (2) to cover an open wound; (3) for primary treatment of sinus tracts in which they are filled with the sealant.

Obliterating the dead space under the wound

Seroma formation is a commonly observed complication following primary closure or flap closure of a wound. The collection of seroma leads to dehiscence of the wound, prolongation of the healing period, necessitates increased wound dressing changes, and causes a decrease in the patient's overall comfort and satisfaction. Deep sutures or use of drains are the most common techniques for closing the dead space, which prevents seroma formation. However, deep sutures increase pain and invert the natal cleft, which is ought to be flattened. The presence of the drains detracts from patient comfort, increases the workload associated with wound care, and raises the risk of infection. It is suspected that the use of the fibrin sealant may decrease seroma formation and decrease the need for the use of drains. But this analysis did not reveal that the fibrin sealant is effective in decreasing wound complications. Similar seroma problems were reported in mastectomy and axilla dissection cases, and many studies have been conducted with the fibrin sealant as a method of seroma prevention^[19]. Studies on fibrin sealant use in breast cancer surgery laid the groundwork for the use of fibrin sealant in treatment of pilonidal sinus patients. But the evidence-based medicine showed that the fibrin sealant did not influence the incidence of seromas, wound infections, overall complications, and the length of hospital stays for patients undergoing breast cancer surgery^[19]. The fibrin sealant's inability to prevent

Table 5 Obliterating the dead space under the closed wound with sealant

Ref.	No.	Closure method	Return to normal activities	Complications	Mean follow-up (mo)	Recurrence
Greenberg <i>et al</i> ^[4]	30	Primary	11.0 + 6.0 d	Purulent discharge (<i>n</i> = 4)	23.0 ± 3.0	None
Altinli <i>et al</i> ^[8]	16	Limberg	NA	None	8.5	None
Sözen <i>et al</i> ^[9]	25	Karydakis	NA	Fluid collection (<i>n</i> = 6)	10.2	None
Total	61			10 (16.4%)	15.2	None

NA: Not available.

Table 6 Studies on covering the open wound with fibrin sealant after excision

Ref.	No.	Healing time	Morbidity	Satisfaction	Recurrence
Seleem <i>et al</i> ^[6]	25	2 wk	1	84%	None
Patti <i>et al</i> ^[7]	8	25.8 ± 13.2 d	1	100%	None
Total	33	16.9 d	2 (6%)	88%	None

seroma formation can be explained by its tendency to liquefy as it dissolves, and that it causes a tissue reaction^[20]. With the help of this analysis and similar studies conducted in mastectomy patients, we can conclude that the use of the fibrin sealant to obliterate the subcutaneous dead space is not very effective in preventing wound complications. Additionally, it has been observed that the use of the fibrin sealant leads to higher rates of subcutaneous fluid accumulation than treatment with drains^[9].

Covering the open wound by fibrin sealant

To this aim, the fibrin sealant can be used to decrease pain, dressing changes, and healing period. Nevertheless, a control group is needed to confirm that fibrin sealant does indeed achieve these desired ends. The absence of a control group in these studies^[6,7] makes it difficult to objectively evaluate the effectiveness of this technique. Without any comparative studies having been conducted, this technique cannot be proposed as an acceptable application.

Filling the sinus tracts with fibrin sealant

Fibrin sealant may be used as a sole treatment modality in pilonidal sinus treatment. Filling the sinus tracts with fibrin sealant without any other surgery has the advantages of less pain, shorter recovery period and a rapid return to daily life, and fewer dressing changes. Although it is generally recommended that this procedure be performed under local anesthesia, two thirds of all the reported cases were, surprisingly, performed under general anesthesia (Tables 3 and 4). Since even surgical excisions of the pilonidal sinus and flap procedures are performed under local anesthesia^[21], the use of the general anesthesia for a mere tract debridement and fibrin sealant application may be supererogatory. According to us, general or regional anesthesia should be used under special circumstances (pediatric patients, jitters, history of adverse reactions to local anesthesia, etc.). In this meta-analysis, an 80%

Table 7 Studies on filling the tracts with fibrin sealant

Ref.	No.	Work off	Morbidity	Pain	Follow-up
Lund <i>et al</i> ^[5]	6	NA	None	None	18 mo
Elsley <i>et al</i> ^[10]	57	Median 6	None	None	23 mo
Isik <i>et al</i> ^[11]	40	Mean 2.0 ± 1.0	None	32	18 mo
Smith <i>et al</i> ^[12]	10	NA	1 (infection)	1	32 mo
Total	113	Usually < 7	0.9%	33 (29%)	21.7 mo

NA: Not available.

success rate for filling sinus tracts with fibrin sealant is pleasing. However, this result should be approached with caution. In one study, there was a 39% rate of non-responders^[10]. Another study included sinuses only with one orifice and cases without any purulent drainage (may be asymptomatic)^[11]. There was no study that was conducted with a sufficient number of symptomatic patients. Additionally, there was no information about the effect of repetitive applications of the sealant on this success rate. The results of single applications were also unknown. Conditions requiring repeated applications were not identified. Similar analyses were performed previously for phenol application in pilonidal disease; a success rate of 70% in single application and a success rate of 86.7% in repetitive applications were reported^[22,23]. Even if the 80% success rate is to be accepted as accurate, it nevertheless does not constitute an advantage over phenol application. Furthermore, fibrin sealant is much more expensive than phenol. In cases where repeated sealant applications are necessary, the use of phenol may offer an advantage due to the higher cost of fibrin. We may comfortably claim that the treatment of pilonidal tracts with fibrin sealant is not definitively superior to other minimally invasive methods. Additionally, the higher cost of fibrin sealant does not justify its routine use in filling sinus tracts as a primary treatment modality.

A review was published in 2012 about the fibrin sealant use in pilonidal sinus^[24]. In this review, which analyzed only 5 publications with a total number of 85 patients, researchers declared that adjuvant fibrin sealant in the treatment of pilonidal sinus was a promising technique, and they justified more research about it^[24]. In the last four years, new studies have been conducted; our systematic review analyzed 9 publications, which included 217 patients altogether. Analyzing more patients than the previously published review provided us to make some specific comments.

However, it is obvious that more studies are still necessary for clear comments.

The limitations of our study were (1) a low number of randomized controlled trials; (2) heterogeneity of the studies involved; and (3) a lack of subgroup analysis for special groups (pediatric cases, recurrent cases, etc.). Because of these constraints, we used descriptive statistics in general, and sometimes meta-analysis. Despite these limitations, some results of this analysis are able to justify certain conclusions. In our opinion, the use of fibrin sealant in preventing subcutaneous seroma formation is not advantageous. The use of the fibrin sealant in order to fill the sinus tracts is also not advised, as its success rate was not greater than that of more cost-effective minimally invasive methods. New studies must be conducted regarding fibrin sealant use in covering wounds after excision and lay-open.

COMMENTS

Background

Fibrin sealant may be used for different purposes in pilonidal sinus surgery. All the methods are used in order to accelerate the recovery period, to decrease morbidity, and to enable a quick return to work. The aim in this review was to collect all accessible data in the literature on the treatment of pilonidal disease with fibrin sealant and to make a prediction about the promising treatments.

Research frontiers

Fibrin was first used as a local haemostatic material in Germany about 100 years ago. In the 1940s, it was used to repair the peripheral nerves and to keep skin grafts in place. Although it has been used commercially in Europe since 1972, it was not approved by the Food and Drug Administration for use in the United States until around 1998.

Innovations and breakthroughs

Recently, there has been a tendency to use minimally invasive surgical techniques in the treatment of pilonidal sinus, as with other surgically-treated diseases. Ideal treatment of pilonidal sinus should be conducted in outpatient settings under local anesthesia, have less postoperative pain, fast recovery, high success rates, and low costs. Retrieved manuscripts concerning the utility of fibrin sealant in pilonidal disease were reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that fibrin sealant can be used for three purposes; (1) to obliterate the dead space under a closed wound; (2) to cover an open wound; (3) for primary treatment of sinus tracts in which they are filled with the sealant.

Terminology

The fibrin sealant is composed of two ingredients; human fibrinogen and bovine thrombin. When the two of these are combined, the thrombin converts the fibrinogen into fibrin in less than a minute. This 3 dimensional fibrin plug is used as a haemostatic or a sealing agent.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of the utility of fibrin sealant for the treatment of pilonidal disease as a minimally invasive method.

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Post-operative abdominal complications in Crohn's disease in the biological era: Systematic review and meta-analysis

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Abstract

AIM: To perform a systematic review and meta-analysis on post-operative complications after surgery for Crohn's disease (CD) comparing biological with no therapy.

METHODS: PubMed, Medline and Embase databases were searched to identify studies comparing post-operative outcomes in CD patients receiving biological therapy and those who did not. A meta-analysis with a random-effects model was used to calculate pooled odds ratios (OR) and confidence intervals (CI) for each outcome measure of interest.

RESULTS: A total of 14 studies were included for meta-analysis, comprising a total of 5425 patients with CD 1024 (biological treatment, 4401 control group). After biological therapy there was an increased risk of total infectious complications (OR = 1.52; 95%CI: 1.14-2.03, 8 studies) and wound infection (OR = 1.73; 95%CI: 1.12-2.67; $P = 0.01$, 7 studies). There was no increased risk for other complications including anastomotic leak (OR = 1.19; 95%CI: 0.82-1.71; $P = 0.26$), abdominal sepsis (OR = 1.22; 95%CI: 0.87-1.72; $P = 0.25$) and re-operation (OR = 1.12; 95%CI: 0.81-1.54; $P = 0.46$) in patients receiving biological therapy.

CONCLUSION: Pre-operative use of anti-TNF- α therapy may increase risk of post-operative infectious complications after surgery for CD and in particular wound related infections.

Key words: Crohn's; Post-operative complications; Biological; Anti-tumor necrosis factor- α ; Monoclonal antibody; Infliximab; Adulimimab

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Core tip: Pre-operative use of anti-tumor necrosis

factor alpha (TNF- α) therapy increases risks of post-operative infectious complications after surgery for Crohn's disease, particularly wound sepsis. Surgery should be planned carefully and ideally performed after appropriate cessation of anti-TNF- α therapy to mitigate increased post-operative risks.

Waterland P, Athanasiou T, Patel H. Post-operative abdominal complications in Crohn's disease in the biological era: Systematic review and meta-analysis. *World J Gastrointest Surg* 2016; 8(3): 274-283 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i3/274.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i3.274>

INTRODUCTION

The introduction of biological therapy for gastrointestinal Crohn's disease (CD) has been a significant landmark in non-operative management of this chronic relapsing condition. The central role of the cytokine tumor necrosis factor- α (TNF α) in persistence of mucosal inflammation underlies the marked efficacy of monoclonal antibodies such as Infliximab and Adalimumab^[1,2]. Multiple randomised clinical trials including ACCENT and CHARM have shown high clinical response (35%-50%) and maintenance rates for both infliximab and adalimumab in modest to severe CD. Eight-weekly infusion regimes appear to be most effective for patients with an initial response to the induction dose of monoclonal agent. Long term use of such agents is supported up to three years and is extremely effective as a steroid-sparing therapy^[1-3]. Currently monoclonal antibodies are being utilised earlier in the treatment algorithm for moderate to severe inflammatory disease, in addition to more complex intra-abdominal fistulating disease in an attempt to achieve mucosal healing and remission. However, a significant proportion of patients do not achieve mucosal healing and eventually arrive at surgical intervention after step-up therapy (10%-20% per year of use of infliximab)^[4,5]. Other indications for surgery include intolerance of therapy due to complications. Thus, surgical intervention is required in up to 50% of patients with CD within 10 years of diagnosis^[6]. There are concerns as to operative intervention within the context of such potent immunosuppression due to the nature of biological therapy.

Current data reveals a contradictory picture of the adverse effects of pre-operative use of anti-TNF- α agents and postoperative complications following bowel resection. Several studies indicate an increase in septic complications; whether it be abdominal sepsis or superficial wound infections^[7,8]. Other studies report no adverse impact of monoclonal antibodies on post-operative outcome^[9-11]. It would be beneficial to subject study findings in a comprehensive meta-analytical framework to identify any associations. Several meta-analyses have been performed previously and have

examined total or major postoperative complications after abdominal surgery in treatment and control groups^[12-14]. In contrast, our analysis aims to study specific septic complications in the CD patient receiving anti-TNF α therapy to investigate postoperative risk in greater detail.

MATERIALS AND METHODS

Search strategy

PRISMA statement guidelines were followed for conducting and reporting meta-analysis data. We searched Medline and Embase from inception to May 2015 using the search terms "infliximab" or "immunosuppressant" or "monoclonal antibody" or "Humira" or "Adalimumab" or "Remicade" and "Crohn's disease" or "Crohn disease" and "complications" or "outcomes" or "postoperative" or "morbidity". The identical terms were used again in PubMed. The search encompassed titles, abstracts, subject headings and registry words. Articles were limited to those published in the English language, animal studies excluded and duplicates were removed.

Study selection

Studies identified from the differing searches were amalgamated and titles and abstracts were scrutinised to include relevant material only. Full text versions were obtained of eligible articles and were reviewed by both authors (PW and HP) to ensure that appropriate data was selected for analysis. Discrepancies between the authors were resolved by discussion of the particular manuscript. Studies were only included in the analysis if patients had intestinal resection with anastomosis for CD and had been administered infliximab within 90 d preceding abdominal surgery. Postoperative complication rate (30-90 d) including anastomotic leak was a compulsory outcome measure. Studies without the aforementioned data were excluded. Studies on indeterminate colitis, ulcerative colitis (UC) or ileoanal pouch were excluded.

Data extraction

Data were interrogated by both authors (PW and HP) and salient patient, disease and surgery-related factors were noted. The number of patients in the treatment (pre-operative anti-TNF administration) and control group (no use of pre-operative anti-TNF agent) were noted and compared for the outcomes of interest. Both groups comprised of patients with CD. Studies on mixed groups of patients with CD and UC were only included if data pertinent to CD could be extracted with a separation of patients on IFX and those on other therapy. Other conditions such as neoplasia and ileoanal pouch procedures were excluded. An attempt was made to establish severity of CD by noting the presence of pre- or intra- operative abscess and use of steroids pre-operatively. The overall postoperative complication rate was analysed as well as superficial and intra-abdominal sepsis occurrence. Mortality, re-operative and stoma rates were noted if reported and duration of follow-up

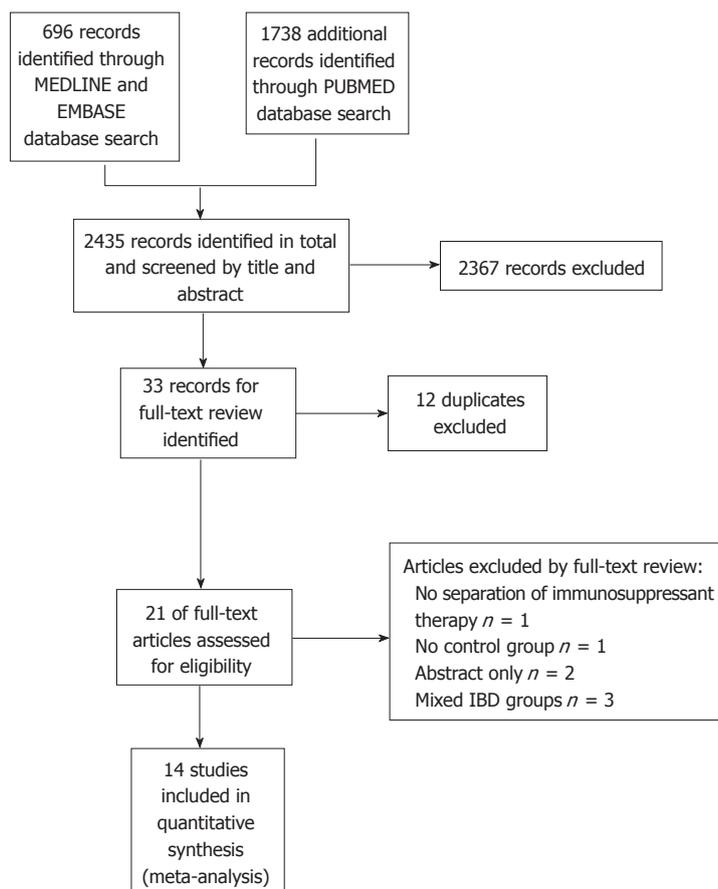


Figure 1 Preferred reporting items for systematic reviews and meta-analyses reporting diagram. IBD: Inflammatory bowel disease.

was recorded. Any intestinal resection with anastomosis and/or strictureplasty was included in analysis.

Risk of bias

The Newcastle-Ottawa score for case-control studies was used to assess the quality of included studies. A maximum of 9 stars was attainable. Publication bias was assessed by funnel plot for each outcome measure. Analysis was repeated without outlier high risk studies as required to reduce bias.

Statistical analysis

Extracted data were entered onto a Microsoft Excel spreadsheet (MS Office 2010, Microsoft, WA, United States) by the lead author (HP) with verification from the co-author (PW). All statistical analyses were performed on Rev Man 5.3 (<http://tech.cochrane.org/revman>; 2014) and SPSS (version 20; IBM). The groups were compared for pre-operative characteristics using χ^2 test without Yates correction and unpaired *t* test for dichotomous and continuous variables respectively. A *P* value of < 0.05 was considered significant.

Outcome measures for meta-analysis were chosen to test the null hypothesis of equivalent post-operative complications in both groups. Primary outcome measures comprised of total infectious complications, abdominal sepsis and anastomotic leak. Secondary outcome measures were wound sepsis, re-operation and mortality rate.

Dichotomous variables were analysed with the Mantel-Haenszel statistical method and random effects model. This particular model was chosen as it does not assume homogeneity between studies in terms of methodology or clinical characteristics and thus allows a more conservative analysis than the fixed effects model. Certain outcome measures were not reported by all studies and hence, the total number of patients in treatment and control groups was variable. No outcome measures were expressed as continuous variables.

Odds ratio, 95%CI, Forest and funnel plots were generated by Rev Man software. Study heterogeneity was assessed by τ^2 and χ^2 testing with a quantitative measure of heterogeneity provided by the I^2 measure. An I^2 value of greater than 50% was considered evidence of substantial heterogeneity.

RESULTS

Search results

The search strategy identified a total of 2434 articles from Medline, Embase and Pubmed databases after application of English language and Human filters. Title and abstract screen eliminated 2367 articles with 33 remaining for analysis. Duplicates were removed at this stage as results from the 3 databases were amalgamated at this point. This left 21 articles for full text review. A total of 14 studies were relevant for meta-analysis after perusal of all 21 articles by both

Table 1 Study characteristics

Ref.	Country	Date	Type	n	NOS (0-9)	Pre-operative infliximab use (w)	Age ¹	Sex (m)	Steroids	Abscess	
Appau <i>et al</i> ^[7]	United States	1998-2007	Retrospective cohort	389	7	12					
							Infliximab	35.8 (11.9)	48.3%	65%	38%
							No infliximab	36.8 (14.4)	45.9%	77%	44%
Canedo <i>et al</i> ^[10]	United States	2000-2008	Retrospective cohort	225	7	12					
							Infliximab	26 (24.9-43.6)	44%	NS	37%
							No infliximab	32 (29.4-41.9)	51%	NS	30%
Colombel <i>et al</i> ^[11]	United States	1998-2001	Retrospective cohort	270	7	8					
							Infliximab	NS	NS	36%	NS
							No infliximab	NS	NS	42%	NS
El Hussuna <i>et al</i> ^[17]	Denmark	2000-2007	Retrospective cohort	369	7	12					
							Infliximab	33 (18-62)	NS	NS	34%
							No infliximab	37 (8-90)	NS	NS	19%
Kasperek <i>et al</i> ^[15]	Munich	2001-2008	Case control match	96	7	12					
							Infliximab	35 (17-66)	43%	94%	NS
							No infliximab	39 (17-68)	50%	94%	NS
Kotze <i>et al</i> ^[23]	Brazil	2007-2010	Retrospective cohort	76	7	4					
							Infliximab	NS	NS	NS	NS
							No infliximab	NS	NS	NS	NS
Marchal <i>et al</i> ^[18]	Netherlands	1998-2002	Case control match	68	8	12					
							Infliximab	36 (16-73)	NS	35%	50%
							No infliximab	38.7 (17-63)	NS	35%	41%
Mascarenhas <i>et al</i> ^[16]	United States	2003-2010	Retrospective cohort	93	6	12					
							Infliximab	35.6 (14.1)	42%	68%	NS
							No infliximab	37 (14.1)	60%	44%	NS
Myrelid <i>et al</i> ^[21]	Europe	1989-2002	Retrospective cohort	298	6	8					
							Infliximab	NS	46%	NS	20%
							No infliximab	NS	36%	NS	20%
Nasir <i>et al</i> ^[20]	United States	2005-2008	Retrospective cohort	370	8	8					
							Infliximab	38.2 (17-66)	43%	31%	NS
							No infliximab	43.3 (17-77)	41%	45%	NS
Nørgård <i>et al</i> ^[9]	Denmark	2000-2010	Retrospective cohort	2293	6	12					
							Infliximab	NS	45%	9%	NS
							No infliximab	NS	41%	14%	NS
Syed <i>et al</i> ^[8]	United States	2004-2011	Retrospective cohort	325	7	8					
							Infliximab	38.2 (13.9)	34%	40%	8%
							No infliximab	40 (14.3)	45%	35%	9%
Tay <i>et al</i> ^[19]	United States	1998-2002	Retrospective cohort	100	7	8					
							Infliximab	NS	NS	0%	NS
							No infliximab	NS	NS	18%	NS
Uchino <i>et al</i> ^[22]	Japan	2008-2011	Retrospective cohort	405	7	12					
							Infliximab	36 (14-72)	73%	37%	NS
							No infliximab	37 (16-78)	69%	34%	NS
Total				5377							

¹Given as SD or range; NS: Not stated.

authors. (Figure 1; PRISMA reporting diagram)^[7-11,15-23].

Study and patient characteristics

The characteristics of the 14 included studies are summarised in Table 1. There was no overlap of study population between included studies. All studies were retrospective case control type including two that reported formal case control matching^[15,18]. A total of 5425 patients with CD were included in the analysis of which 1024 received anti-TNF α agents (treatment group) and 4401 received non-biological therapy (control group). All treatment cases had received anti-TNF agents within the preceding 12 wk before surgery. Infliximab was the only biologic agent used in 8/14 studies (57%). Patients in the remaining 6 studies received either Infliximab, Adalimumab

or another biological agent. Mono or combination therapy with corticosteroids and/or immunomodulators (thiopurines) was used in the majority of the control group. Unsurprisingly, there was a significant difference between steroid use in the treatment and control groups ($P = 0.0012$, χ^2 test). There was no difference between the two groups in terms of age ($P = 0.135$, unpaired t test) and gender distribution ($P = 0.456$, χ^2 test). A subset of patients was eligible for assessment of difference in age as some studies reported age as mean and others as median. Thus, the mean was used and 3 studies could be analysed with no significant difference identified ($n = 629$ in total, unpaired t test $P = 0.135$). There was no difference between the two groups in terms of pre-operative abscess ($P = 0.344$, χ^2 test) or stoma creation during the procedure ($P = 0.66$, χ^2 test).

Table 2 Studies showing primary and secondary outcome measures

Ref.	Follow-up (d)	Anastomotic leak (%)	Abdominal sepsis (%)	Wound sepsis (%)	Total infectious complications (%)	Re-operation (%)	Mortality (%)
Appau <i>et al</i> ^[7]							
Infliximab	30	10	10	0	40	8	1.6
No infliximab		4.2	4.3	0.3	21.5	3	0
Canedo <i>et al</i> ^[10]							
Infliximab	30	5.7	3.1	13.8	21.5	3	NS
No infliximab		4.9	5	8.8	18.8	6	NS
Colombel <i>et al</i> ^[11]							
Infliximab	30	NS	NS	NS	17.3	NS	0
No infliximab		NS	NS	NS	37	NS	0
El Hussuna <i>et al</i> ^[17]							
Infliximab	30	9.4	NS	NS	NS	NS	1.35
No infliximab		12.7	NS	NS	NS	NS	
Kasperek <i>et al</i> ^[15]							
Infliximab	30	8.3	6.2	18.8	56.2	23	2.1
No infliximab		12.5	10.4	14.6	41.6	21	0
Kotze <i>et al</i> ^[23]	30						
Infliximab		NS	10.5	NS	NS	NS	0
No infliximab		NS	15.8	NS	NS	NS	3
Marchal <i>et al</i> ^[18]							
Infliximab	90	0	12.5	5	25	0	0
No infliximab		5.8	10.3	2.5	12.8	0	0
Mascarenhas <i>et al</i> ^[16]							
Infliximab	30	10.5	NS	10.5	NS	NS	0
No infliximab		4.1	NS	4.1	NS	NS	0
Myrelid <i>et al</i> ^[21]							
Infliximab	30	7.2	NS	NS	23.4	8	NS
No infliximab		8	NS	NS	22	7	NS
Nasir <i>et al</i> ^[20]							
Infliximab	30	3.4	NS	NS	NS	NS	0
No infliximab		2	NS	NS	NS	NS	0.79
Nørgård <i>et al</i> ^[9]							
Infliximab	30	3.7	NS	NS	NS	7	0.46
No infliximab		2.7	NS	NS	NS	8	2.59
Syed <i>et al</i> ^[8]							
Infliximab	NS	3.3	18.7	18.7	36	16	1.3
No infliximab		3.4	15.4	11.4	25	13	0.57
Tay <i>et al</i> ^[19]							
Infliximab	30	4.5	9.1	NS	13.6	NS	NS
No infliximab		5.1	5.1	NS	10.2	NS	NS
Uchino <i>et al</i> ^[22]							
Infliximab	30	NS	5.1	1.3	NS	NS	NS
No infliximab		NS	5.2	15.33	NS	NS	NS

NS: Not stated.

Outcome measures

Primary and secondary outcome measures from each study are summarised in Table 2.

Total infectious complications

8 out of 14 studies^[7-11,15,18-21] reported total infectious complications and entered 567 treatment cases and 1291 controls for analysis. Total infectious complications were reported in 4 out of 8 and were derived in 4 studies^[7,10,18,21] by summation of reported site-specific complications. A total of 165 complications were reported in the treatment group as compared to 252 in the control group. There was an increased risk of total infectious complications in the treatment group (OR = 1.52; 95%CI: 1.14-2.03) that reached statistical significance ($Z = 2.87$; $P = 0.005$) (see Figure 2.

Total infectious complications: Study event rate Forest plot). There was a low risk of heterogeneity amongst analysed studies as indicated by the I^2 index (23%) and Tau^2 variable (0.04; Rev Man 5.3). The Cochran Q test revealed some heterogeneity but not to a significant extent ($\chi^2 = 9.06$, $df = 7$; $P = 0.25$).

Postoperative abdominal sepsis

Abdominal sepsis was reported in nine out of fourteen studies^[7-9,10,15,18,19,22,23] and comprised all abdominal septic complications including anastomotic leak, abscess and/or fistula. Septic outcomes were reported in 7 studies and derived in two studies^[9,15]. A total of 60 complications (60/697) were reported in the treatment group and 148 (148/3291) in the control. There was a trend towards increased postoperative abdominal sepsis

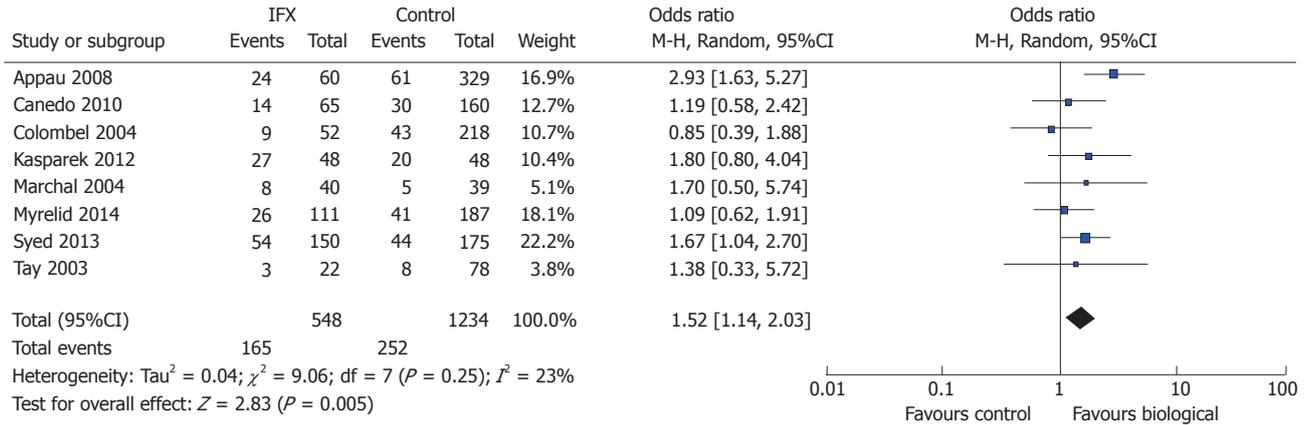


Figure 2 Total infectious complications: Study event rates and forest plot. Forest plot showing significantly higher total infective complications in patients receiving biological therapy - note confidence interval does not overlap one.

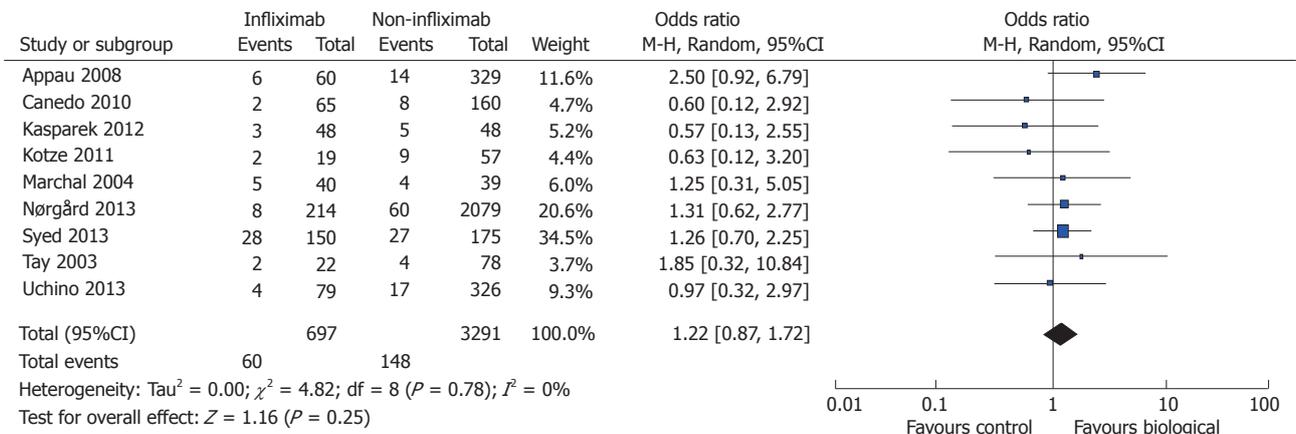


Figure 3 Postoperative abdominal sepsis: Study event rates and forest plot.

in the treatment group (OR = 1.22; 95%CI: 0.87-1.72; $P = 0.25$). (see Figure 3. Postoperative abdominal sepsis: study event rates and forest plot) Heterogeneity amongst studies was minimal with I^2 index of 0% and Tau^2 variable of zero again. Cochran Q test supported lack of heterogeneity with a P value of 0.78.

Anastomotic leak

A total of eleven studies reported on anastomotic leak rates in the two study groups which enabled 812 cases and 3356 controls to be entered for analysis^[7-10,15-21]. There were 43 and 166 anastomotic complications reported in the case and control group respectively. There was a trend towards increased rate of anastomotic leak in the case/treatment group (OR = 1.19; 95%CI: 0.82-1.71; $P = 0.26$) (see Figure 4. Anastomotic leak: Study event rates and forest plot). Minimal heterogeneity was noted in the group ($I^2 = 0\%$; $\text{Tau}^2 = 0$) as further confirmed by a low Cochran Q score ($Q = 6.16$; $P = 0.72$).

Wound infection

A total of seven studies reported data on postoperative wound infection in 461 cases and 1151 controls^[7,8,10,15,16,18,22]. There were 51 and 96 wound

complications reported in the case and control group respectively. There was a trend towards increased rate of wound sepsis in the treatment group (OR = 1.29; 95%CI: 0.62-2.68; $P = 0.49$) (see Figure 5. Wound infection: study event rates and forest plot). Substantial heterogeneity existed in the analysed studies with an I^2 value of 50% and Tau^2 value of 0.42. The Cochran Q test also revealed significant heterogeneity ($P = 0.06$). An outlier study^[22] was identified on the funnel plot and exclusion from meta-analysis revealed an increased risk of postoperative wound infection in the treatment group (OR = 1.73; 95%CI: 1.12-2.67; $P = 0.01$) (see Figure 6. Wound infection: Funnel plot with outlier and Figure 7. Wound infection: Modified study event rates and forest plot). Heterogeneity also became minimal with the second analysis ($\text{Tau}^2 = 0$; $I^2 = 0\%$).

Re-operation and mortality rates

The rate of re-operation was not reported widely and only six studies were eligible for analysis^[7-10,15,21]. Thus, a total of 648 cases and 2978 controls were analysed with a predictable low re-operation rate (67 vs 240). There was a potential trend for increased re-operation in the treatment group (OR = 1.12; 95%CI: 0.81-1.54; $P = 0.54$) with a minimal element of heterogeneity (Tau^2

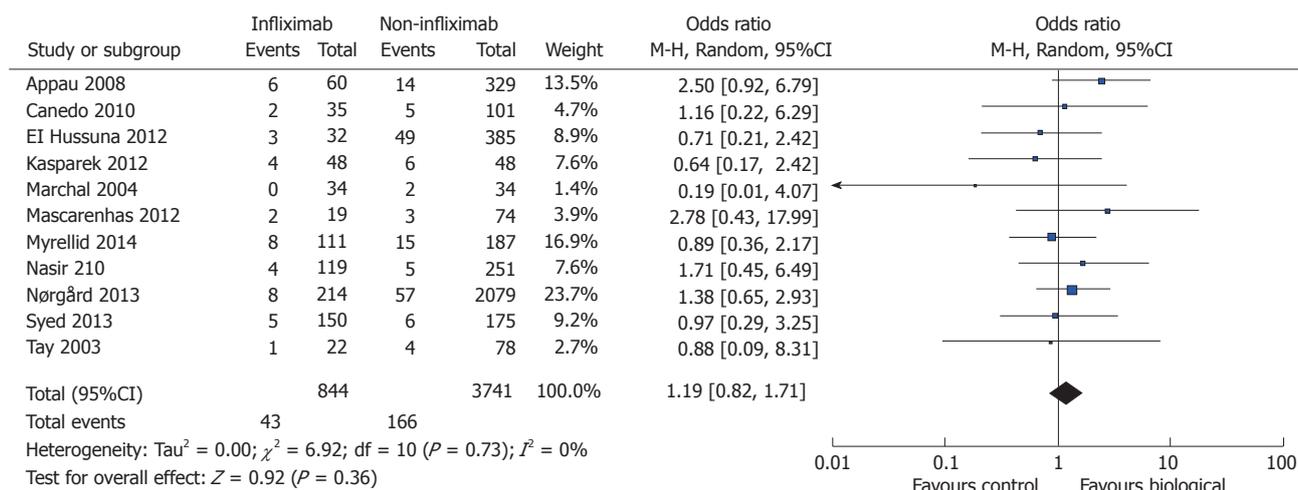


Figure 4 Anastomotic leak: Study event rates and forest plot.

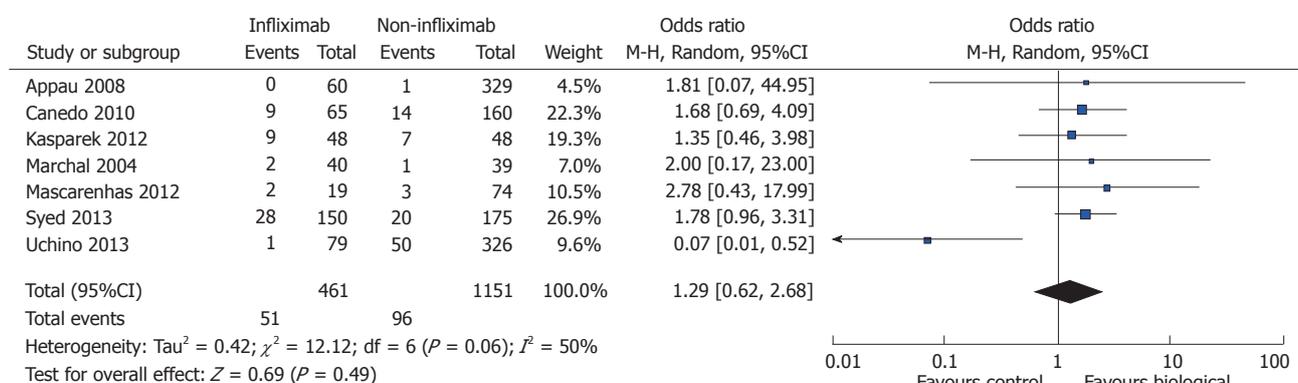


Figure 5 Wound infection: Study event rates and forest plot. Lone outlier study (Uchino 2013) visible on forest plot.

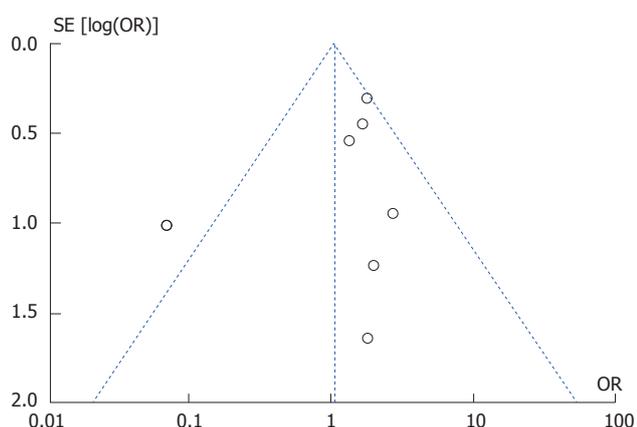


Figure 6 Wound infection: Funnel plot with outlier. A single statistical outlier visible outside the funnel plot suggestive of possible publication bias.

= 0.00; $I^2 = 0\%$; Cochran $Q = 4.65$) (see Figure 8. Re-operation: Study event rates and forest plot).

Thirty-day mortality rates were reported in ten out of 14 studies and were low as expected from sample size (ranging from 0 to 3 actual events per study). There was only one large-scale study and thus further statistical analysis was not attempted^[9].

DISCUSSION

Surgery for abdominal CD presents unique challenges to the surgeon and gastroenterologist. There are substantial risk factors pertaining to patient physiology, operative anatomy and co-existing medication. Anti-TNF agents have shown remarkable therapeutic efficacy in CD but concerns over increased rate of opportunistic infections and re-activation of latent TB remain^[24,25]. Our meta-analysis demonstrates an increased risk of total infectious complications after abdominal surgery in patients receiving anti-TNF α therapy. Furthermore, after adjusting for publication bias a significant increase in wound sepsis was also identified. There was no increase in risk of intra-abdominal outcomes of anastomotic leak or abdominal sepsis for the same patient group. Re-operation rate was also not increased in the treatment group receiving anti-TNF α agents. Mortality rate was not compared between treatment and control groups as event numbers were too small for meaningful statistical analysis.

We defined total infectious complications to include abdominal, wound, urinary and respiratory sepsis and data was available in 8 out of 14 studies for analysis.

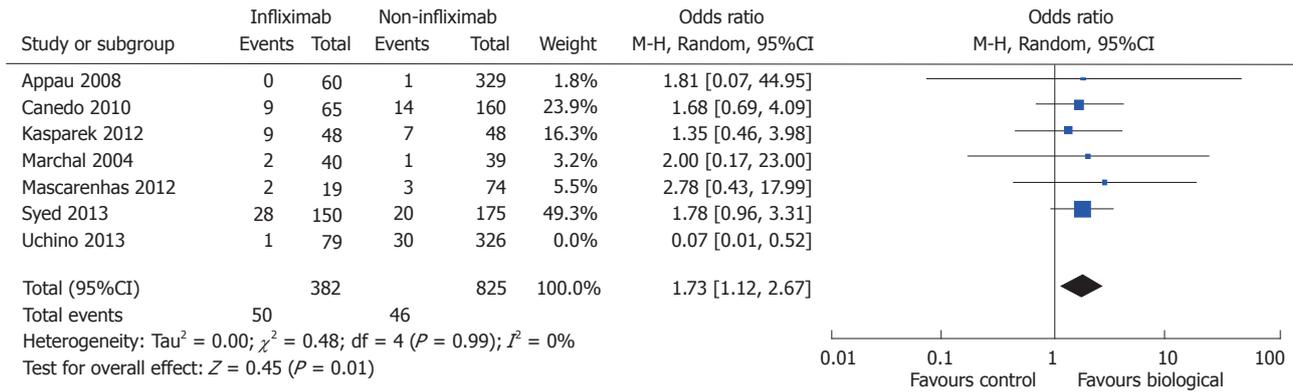


Figure 7 Wound infection: Modified study event rates and forest plot.

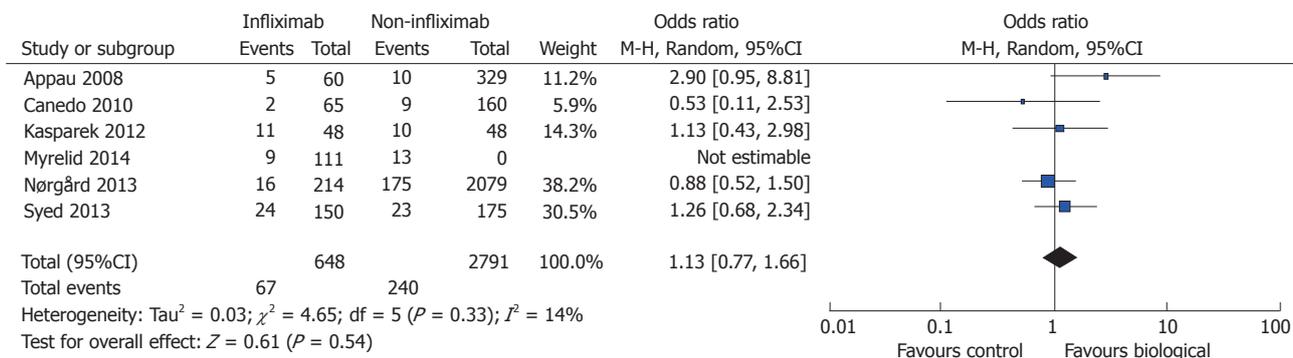


Figure 8 Re-operation: Study event rates and forest plot.

Half of the included studies reported on the full spectrum of septic complications as described previously and data was derived in the remainder. There was some minor heterogeneity noted, which may be expected with such data given variability between studies in the criteria used to define infections arising from surgical wounds, or the urinary and respiratory tracts. Use of derivative data may also lead to a degree of inaccuracy as multiple septic complications could have occurred in the same patient and as a consequence result in over or underestimation of the true absolute event rate. Reassuringly, in spite of such confounders heterogeneity was slight with no major outliers seen on funnel plot.

The outcome measures of anastomotic leak, abdominal sepsis and wound infection were analysed separately in an attempt to define the relative contribution of each outcome to the increased risk for total infectious complications. A tendency was noted towards increased complications with biological therapy for anastomotic leak and abdominal sepsis though this was not significant for either measure. In addition, heterogeneity was minimal for both analyses. The more objective nature of abdominal sepsis and anastomotic leak in terms of diagnosis and data recording may explain homogeneity in the meta-analysis. Thus, the demonstrated increase in total infectious complications in the anti-TNF α group may be inferred to be “non-abdominal” in origin. A significant increase in wound infection rates were noted in patients treated with anti-

TNF α agents.

Prior meta-analyses have revealed similar findings^[12,14,26,27] apart from one analysis with equivalent outcomes across both groups^[13]. An increased risk was found for major postoperative infection in 4 out of 5 meta-analyses that addressed this issue^[12,14,26,27]. The meta-analysis that showed no difference between treatment and control groups divided postoperative complications into major and minor categories^[13]. Postoperative sepsis was allocated to either category depending on type and thus it is difficult to extrapolate the true risk of sepsis in this analysis. Our meta-analysis differs from previous efforts in that we concentrated solely on infectious postoperative complications. Analyses were also conducted separately for site specific sepsis. This was performed to assess the excess burden of each outcome in patients on anti-TNF α therapy and has not been performed previously. It is also noted that heterogeneity was markedly reduced in our analysis as compared to previous efforts and could reflect more stringent inclusion criteria.

There are several limitations to our meta-analysis. Firstly, the severity of CD is likely to be disparate between the treatment and control groups. Anti-TNF α therapy is usually prescribed for disease that is refractory to steroids and/or immunomodulators. Thus, patients would be expected to possess a greater risk for postoperative complications as operative pathology may be more complex. We attempted to analyse this by

comparing the presence of preoperative abscess or use of stoma as part of the operative procedure between the treatment and control groups. There was no significant difference identified in either of these parameters and that could indicate a degree of equivalence in disease severity between the treatment groups. However, it seems more likely that these parameters may not be sensitive enough to differentiate usefully between either group. A more objective comparison of CD severity between groups could be performed using quantitative measures such as the Crohn's Disease Activity Index (or Harvey-Bradshaw index). Unfortunately, no attempts at comparative disease severity stratification were performed within the included studies.

Patients in the control group received differing medications which again suggests that disease severity is not consistent across the control group. As previously mentioned postoperative complications are not defined or diagnosed in a standardised manner across the included studies. Thus, there may be over- or under- representation of the true extent of particular postoperative complications.

A significant limitation of this meta-analysis relates to the retrospective nature of all the included studies and the fact that only two studies attempted to match case and control groups albeit in a limited fashion^[15,18]. This accurately reflects the existing literature and randomised controlled trials to address this issue are not feasible or ethical, so data is likely to be restricted to cohort studies in the future.

In conclusion, our meta-analysis may provide further support to the hypothesis of an increase in postoperative infectious complications in patients receiving anti-TNF α therapy. Our results are similar to other analyses on this subject and we have attempted to extract the specific infectious complications that are increased in this group of patients. A significant increase in both total infectious complications and wound infection rates in patients receiving anti-TNF α therapy were identified.

Our meta-analysis does not support the use of a protective stoma in patients receiving anti-TNF α therapy as a single risk factor, as there was no increase in abdominal sepsis, leak or re-operation rate. Our recommendation is to consider operative risk for patients with CD on an individual basis, incorporating recognised risk factors such as steroid use, hypoalbuminaemia, presence of fistula or abscess, in addition to preoperative anti-TNF α therapy alone. Furthermore, it seems sensible to attempt to mitigate risk of postoperative infection by planning surgery after cessation of anti-TNF α therapy where possible.

COMMENTS

Background

Current data reveals a contradictory picture of the adverse effects of pre-operative use of anti-TNF α agents and postoperative complications following bowel resection. It would be valuable to perform a comprehensive meta-analysis to identify any associations. The authors' analysis aims to study specific septic

complications in the Crohn's disease patient receiving anti-tumor necrosis factor alpha (TNF- α) therapy to investigate postoperative risk in greater detail.

Research frontiers

Not applicable as this is a meta-analysis from synthesised data from previous original studies.

Innovations and breakthroughs

Their meta-analysis demonstrates an increased risk of total infectious complications after abdominal surgery in patients receiving anti-TNF α therapy. This is the first meta-analysis to show a site-specific increase in septic complications, in particular wound sepsis.

Applications

The authors recommend risk assessment on an individual basis for patients with Crohn's disease taking into account use of anti-TNF α therapy in combination with other known risk factors for post-operative septic complications. Discontinuation of anti-TNF α should be considered 6-8 wk prior to planned surgery.

Terminology

Anti-TNF α therapy: Anti-tumour necrosis factor alpha therapies are mostly monoclonal antibodies to tumour necrosis factor, a chemokine which is implicated in the abnormal inflammatory response associated with active inflammatory bowel disease. CD: Crohn's disease; UC: Ulcerative colitis; Fistulating disease: Enterocutaneous or inflammatory mass with entero-entero fistulae and/or fistula-ano.

Peer-review

This is a well-written review about the role of the pre-operative use of anti-TNF α therapy that may increase risk of post-operative infectious complications after surgery for CD and in particular wound related infections.

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***NOD2* mutations and colorectal cancer - Where do we stand?**

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Abstract

Due to the overwhelming burden of colorectal cancer (CRC), great effort has been placed on identifying genetic mutations that contribute to disease development and progression. One of the most studied polymorphisms that could potentially increase susceptibility to CRC involves the nucleotide-binding and oligomerization-domain containing 2 (*NOD2*) gene. There is growing evidence that the biological activity of *NOD2* is far greater than previously thought and a link with intestinal microbiota and mucosal immunity is increasingly sought after. In fact, microbial composition may be an important contributor not only to inflammatory bowel diseases (IBD) but also to CRC. Recent studies have showed that deficient *NOD2* function confers a communicable risk of colitis and CRC. Despite the evidence from experimental models, population-based studies that tried to link certain *NOD2* polymorphisms and an increase in CRC risk have been described as conflicting. Significant geographic discrepancies in the frequency of such polymorphisms and different interpretations of the results may have limited the conclusions of those studies. Since being first associated to IBD and CRC, our understanding of the role of this gene has come a long way, and it is tempting to postulate that it may contribute to identify individuals with susceptible genetic background that may benefit from early CRC screening programs or in predicting response to current therapeutic tools. The aim of this review is to clarify the status quo of *NOD2* mutations as genetic risk factors to chronic inflammation and ultimately to CRC. The use of *NOD2* as a predictor of certain phenotypic characteristics of the disease will be analyzed as well.

Key words: Colorectal cancer; Fecal microbiota; Cancer susceptibility; Intestinal inflammation; Nucleotide-binding and oligomerization-domain containing 2 mutations

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Core tip: Recently, data from animal models showed that nucleotide-binding and oligomerization-domain containing 2 (*NOD2*) deficiency leads to dysbiosis and to an increased risk of colitis and colitis-associated colorectal cancer (CRC). Furthermore, it is now known that this receptor has a much more expanded role than previously thought. Concerning population-based studies, and despite initial inconsistencies, recent data points to an important role for *NOD2* mutations in CRC susceptibility. Identifying carriers of such polymorphisms may allow them to be included in stricter CRC surveillance programs. A link between *NOD2* mutation carriage and response to different chemotherapy regimens is also a promising field of research.

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INTRODUCTION

Despite several advances in the diagnosis and treatment of colorectal cancer (CRC), it continues to be one of the most significant causes of morbidity and cancer-related deaths^[1]. Apart from familial syndromes that account for 5%-10% of CRC cases^[2], this disease is considered to have a multifactorial etiology and therefore predicting individual risk has been problematic, as there are many genetic polymorphisms with probably modest individual effect^[3]. Due to its proven role as a genetic predisposing factor for chronic inflammation, most notably in Crohn's disease (CD)^[4], nucleotide-binding and oligomerization-domain containing 2 (*NOD2*) mutations have been suggested to have a similar role in CRC. This assumption derives from the fact that several gastrointestinal cancers are strongly linked to chronic inflammatory conditions. The risk for malignancy may even increase according to the degree of underlying inflammation, as is the case for long-standing ulcerative colitis^[5] and *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis. One plausible hypothesis is that pro-inflammatory stimulus may lead to continuous cell proliferation, angiogenesis and eventually DNA damage^[6]. If the association between chronic inflammation and cancer is based on solid experimental and epidemiological data, what remains to be fully understood is how do *NOD2* mutations lead to chronic inflammation?

The *NOD2* protein plays an important role in innate immunity by recognizing bacterial lipopolysaccharides and activating the nuclear factor-kappaB. The mutant alleles for *NOD2* gene are thought to cause loss of function - deficient recognition, impaired clearance and proliferation of bacterial pathogens that lead to increased pro-inflammatory cytokines and subsequently to chronic inflammation^[7]. Recently, the role of *NOD2* has been analyzed under a different light, as it seems to take a central place in the intricate balance between protection

of the intestinal mucosa under physiological settings and the production of pro-inflammatory cytokines in chronic inflammatory conditions. Any shift, either gain or loss of function for *NOD2*, elicits a disturbance in the immune system that may lead to inflammation^[8].

Another promising approach to understanding the pathogenesis of these diseases is the modulation of intestinal microbiota. Formerly considered a passive element in the homeostasis of the intestinal mucosa, the microbiota is nowadays considered as essential for epithelial differentiation and in maintaining a protective environment^[9]. To that end, commensal bacteria and *NOD2* interact in a feedback-like mechanism - *NOD2* keeps bacterial proliferation in a steady, controlled state and the microbiota intervene in controlling *NOD2* expression^[10]. Animal models with high risk genotype for colitis and CRC show less severe or even absent inflammation and fewer cases of adenomas if raised in selected bacterial or germ-free conditions^[11], suggesting that changes in microbial species affect colitis and CRC development.

From 2004 to 2010, several population-based studies tried to find an increased risk for CRC in *NOD2* polymorphism carriers. The most studied mutations have been two missense mutations - R702W (rs2066844 C/T) and G908R (rs2066845 C/G), and a frameshift mutation - 3020insC (rs2066847 insC). The frequency of these polymorphisms differs greatly between populations, being much less common in Asian cohorts^[12]. Even among Caucasian populations, there is significant genetic heterogeneity that may have limited the findings of such studies. Furthermore, the source of controls and the type of methodology used are also potential bias. Another relevant finding is that individual polymorphisms may increase the risk of CRC only in selected groups (*e.g.*, German individuals under 45-year-old carrying R702W polymorphism^[13]). These promising studies may ultimately lead to identifying individuals with susceptible genetic background, other than those with well-known familial syndromes, therefore benefitting from early diagnostic screening.

In order to find recent publications (2004 to present) on *NOD2* mutations and CRC susceptibility, an extensive literature search was performed using PubMed and MEDLINE. The key search terms used were *NOD2*/caspase recruitment domain 15 (CARD15) mutations, CRC genetics, microbiota, mucosal immunity and chronic inflammation, either alone or in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

THE EXPANDING *NOD2* ROLE

In order to protect the epithelium of the gastrointestinal tract, the largest surface in our body exposed to external environment, a number of obstacles within the mucosa are disposed to prevent the spread of pathogenic organisms. Besides mechanical barriers

such as the mucus layers, the innate immune system is probably the first mechanism to act against deleterious microorganisms, and once triggered it becomes activated within minutes^[14]. This almost immediate response is due to pathogen recognition receptors (PRRs). One of the most prominent families of PRR includes Nod-like receptors (NLRs) that recognize bacterial wall component peptidoglycan. Certainly the most researched member of this family is *NOD2*, expressed in dendritic cells, leukocytes and epithelial cells of the gastrointestinal tract, especially after inflammatory stimuli^[15]. Paneth cells are secretory epithelial cells found in small bowel crypts that express significant levels of *NOD2*. The structural features of NLRs include a central nucleotide-binding oligomerization domain, a variable N-terminal protein-protein interaction domain, defined by the CARD, and a C-terminal leucine-rich repeat that senses pathogen-associated molecular patterns^[8]. After activation, recruitment of a serine threonine kinase called RIP2 occurs, which leads to the enrollment of the NF- κ B signaling pathway, leading to the transcription of immune response genes^[16].

Along with this traditional role, *NOD2* plays a part in the induction of autophagy as well. This process leads to the destruction of damaged proteins and organelles which has paramount importance not only in recycling biomolecules but also in eliciting anti-microbial properties^[17]. Growing evidence has shown that *NOD2* may be also a relevant player in CD4⁺ T cell function and in generating a Th1 response. This leads to the production of IFN- γ by T cells. In addition to detecting bacterial pathogens, *NOD2* has shown a different role in host defense. According to *in vitro* studies, *NOD2*-deficient animals showed an increased susceptibility to several viral infections^[18]. The response to certain parasite infections may be compromised as well, due to a reduced production of IFN- γ ^[16,19]. In *NOD2*^{-/-} animals, through stimulation of Th1-associated cytokines, an increase in mucosal permeability and low-grade chronic inflammation occurs^[20].

The aforementioned evidence places *NOD2* in the center of the immune system, quite distant from its first described role as a "simple" pathogen sensor. But the essential question remains: How do *NOD2* mutations predispose to CD and do they have a role in cancer development?

Although our understanding of these complex interactions has improved in recent years, we still have no solid evidence to prove that polymorphisms in *NOD2* actually lead to the production of a stable protein. Currently, there are at least two possible ways in which *NOD2* mutations can lead to chronic inflammation and CD. The first is related with the basic function of *NOD2* as a positive regulator for innate response. We can assume that if there is no efficient *NOD2* activation during early phases of pathogen exposure, bacteria will proliferate and ultimately lead to chronic inflammation. An alternative explanation involves the deficient activation of *NOD2* as well, but in a later stage, during an ongoing inflammatory

process. A continuous stimulus of pro-inflammatory pathways will take place, triggering toll-like receptors (TLR) (*NOD2* is a negative regulator of TLR signaling) and favoring Th1 response and the release of cytokines. Animal models have shown that *NOD2* has a paramount importance in the bactericidal activity of ileal crypts and the regulation of ileal microbiota. This allows us to hypothesize that ileal CD caused by *NOD2* mutations is due to the dysfunction of Paneth cells^[8,10,21]. This diverse function of *NOD2* may explain the heterogeneity of CD^[16].

In what concerns CRC, there are several factors that could explain its link to *NOD2* mutations. It is a well-known fact that the risk for CRC increases with duration and severity of the inflammatory process, while it decreases when anti-inflammatory drugs such as mesalazine and immunomodulators such as azathioprine are used in ulcerative colitis, consistent with a causative role for inflammation in colon carcinogenesis. The chemopreventive activity of aspirin and other nonsteroidal anti-inflammatory drugs in CRC supports this concept as well.

If these mutations play a consistent part in the pathogenesis of inflammatory bowel diseases (IBD), most notably in CD, then the hypothesis that such mutations are potential risk factors for cancer may have solid grounds. The study by Couturier-Maillard^[9] shed some light in the role of *NOD2* in colitis-associated cancer: *NOD2*^{-/-} mice showed increased tumor load in the distal colon than wild-type animals. Furthermore, this risk was shown to be transmittable if both animals were cohoused. An acceptable rationale to explain these findings may involve an unbalance between pro- and anti-inflammatory cytokines and lead to the loss of autophagy and apoptosis stimuli. This could eventually lead to increased risk of infection, chronic inflammation and cancer^[22].

The most promising body of evidence that supports the role of *NOD2* in colorectal carcinogenesis involves its capacity to shape a protective assembly of gut bacterial communities. The deregulation of intestinal microbiota seems to be the essential element in the complex interaction between *NOD2* mutations and CRC.

LINKING MICROBIOTA TO MUCOSAL IMMUNITY AND CRC

Recently, a significant effort has been made to identify the components and the role of intestinal microbiota in colonic health and homeostasis. The microbiota has been increasingly recognized as a major player in normal metabolic and physiologic processes. This community of 10¹³-10¹⁴ microorganisms represents a perfect example of symbiotic relationship. It exerts several essential functions like the synthesis of essential compounds for the normal growth of colonic mucosa, regulation of its lymphoid tissue and synthesis of amino acids that inhibit the growth of pathogenic microorganisms. The latter is

of paramount importance, as a delicate equilibrium has to be achieved between commensal bacterial load and the innate immune system. The commensal bacteria must be contained in their capacity to proliferate and should be maintained in adequate amounts. Conversely, any change in the composition of luminal bacterial flora may favor the production of toxins and metabolites associated with carcinogenesis and induce dysregulation of the immune response, allowing pathogenic agents to replicate, therefore promoting and sustaining inflammation and carcinogenesis^[23]. A well balanced gut microbiota leads to healthy colocytes through the production of important compounds and the correct modulation of the immune system. It is now believed that *NOD2* mutations may result in altered host-microbial interactions in the intestinal mucosa.

COMPOSITION OF THE MICROBIOTA

It is known that the human intestine is sterile in utero, but progressively over 36000 bacterial species colonize the gastrointestinal tract and develop a symbiotic relation with their host. The human distal intestinal microbiota includes two predominant phyla, the Firmicutes and Bacteroidetes, with less significant contributions from Proteobacteria and Actinobacteria, and minor contributions from Fusobacteria, Verrucomicrobia, and Cyanobacteria^[24]. The production of propionate and butyrate from the degradation of indigestible polysaccharides is one of its main roles. Despite being outnumbered by other species, Actinobacteria, Proteobacteria (including *Escherichia coli*) and Verrucomicrobia, showed potential to influence health outcomes^[25]. A significant effort is being made to characterize the diverse genetic material of these numerous microorganisms (also known as microbiome). Ultimately, the goal is to understand the link between variations in the composition of these communities and common diseases, such as IBD and CRC. The hypothesis formulated by several investigators lies on the ability of these variations of the microbiota to cause a breakdown of the balance between bacterial communities and the epithelial barrier may lead to chronic inflammation. It is thought that some species may not be able to maintain a quiet state of protective immunity in dysbiotic conditions. For example, *Bacteroides thetaiotaomicron* was found to be not only a commensal but also an opportunistic microorganism in predisposed individuals^[26].

A special attention has been devoted to factors that may influence the composition of the microbiota. Aging, place of birth and mode of delivery are quite relevant determinants. Antibiotics are also important and modifiable factors, especially with larger antimicrobial spectrums, as their effect on the microbiota varies from drastic to only temporary. After the end of the antibiotic treatment, certain species may recover in about a month while others may not recover at all, most often in children^[27]. Besides antibiotics, different dietary habits may modify significantly the microbiota as well. Quite interestingly, even a short-term increase in fat

and carbohydrate consumption may influence not only the relative abundance of each bacterial species, but also the functionality of the microbiota^[28]. Obesity has also been proposed as a major factor in this equation, as it may alter the composition of the microbiota and increase its metabolic potential to harvest energy from the host diet. The capacity of the microbiota to confer host traits was revealed by studies where fecal content was transplanted from obese mice into lean germ-free recipients. The recipients showed significant weight gain and increased adiposity^[29]. This surprising discovery opened the door for further investigation on genetic and microbiota manipulation and its ability to cause disease in animal models. Another interesting concept was revealed by Couturier-Maillard *et al.*^[9]. The absence of *NOD2* confers a transmissible risk for colitis and CRC, even to immunocompetent hosts. In other words, after sharing the same environment with *NOD2*^{-/-} mice, wild-type animals treated with dextran sodium sulfate revealed an increased risk for colitis, probably due to an altered commensal flora acquired from knockout mice. This dysbiotic microbiota is then passed to the next generation. Growing evidence now shows us that the risk for colitis and CRC is influenced by specific members of the commensal microbiota. In fact, in *IL10*-deficient mice treated with colon-specific carcinogen azoxymethane (AOM) showed high levels of mucosal inflammation and adenoma development when raised in conventional conditions, but when *Bacteroides vulgatus* is the only commensal, the carcinogenicity of AOM is somewhat attenuated. Even more surprising is the fact that these mice show almost no inflammation or adenomas if created in a germ-free environment^[11]. This is consistent with the notion that treating *NOD2*-deficient mice with broad spectrum antibiotics may mitigate its disease risk^[9]. In the opposite direction, a recent study suggests that antibiotics promote inflammation through translocation of commensal colonic bacteria and it is suggested that this may explain the association between increasing antibiotic use and the growing incidence of inflammatory disorders^[30].

The importance of *NOD2* as a regulator of microbiota and consequently as a risk factor for injury of the colonic mucosa was reinforced by studies using reciprocal fecal microbiota transplantation. Such interventions led to profound changes in the microbiota. The end result was that *NOD2*-deficient mice that received fecal transplantation from wild-type animals showed decreased mucosal injury and inflammation. On the contrary, there was an increased risk of colonic disease in wild-type hosts that received dysbiotic fecal microbiota from *NOD2*-deficient mice^[9]. A crucial role in this equilibrium is played by Paneth cells, specialized secretory epithelial cells of the small intestinal crypts that express *NOD2* at high levels. Recent studies demonstrated that *NOD2*-deficient mice had a significant rise in the amount of commensal bacteria in the terminal ileum, probably due to impaired cryptal activity^[31]. This is a potential mechanism by which *NOD2* mutations may disturb intestinal homeostasis and

lead to CD and colitis-associated CRC. But the intestinal microbiota role in this equilibrium is not passive at all. On the contrary, it is now known that it plays a part in controlling the expression of *NOD2* as well.

The influence of *NOD2* in microbial communities and its consequences on disease risk have solid basis. But how exactly does an altered microbiota lead to colonic inflammation? One possible explanation is the production of bioproducts with anticancer properties by the metabolic machinery of the microbiota. Butyrate and other small-chain fatty acids are nutrients formed by the fermentation of indigestible carbohydrate and are known to have an interesting paradoxical activity. In colon carcinoma cells, it leads to apoptosis, inhibits cell proliferation and angiogenesis, therefore showing a protective effect. On the other hand, in normal colonic cells it shows opposite effects as it prevents apoptosis^[32]. Another potential role for the microbiota and especially for butyrate is maintaining inhibition of the histone deacetylase, therefore maintaining histones in an acetylated state, thus facilitating the transcription of anti-oncogenes^[33]. This is an objective of anticancer drugs such as Vorinostat, an approved agent for the treatment of cutaneous T cell lymphoma. Detrimental influences are provided by the accumulation of toxic compounds in the gut that can exert a mutagenic action. Poli-heterocyclic amines, deoxycholic acid and calibactin are examples of compounds directly or indirectly produced by commensal bacteria that harbor potential to damage colonocytes' DNA^[34]. This conflicting evidence supports the idea that the role of the microbiota shouldn't be considered univocal, but rather be regarded as a complex set of influences that may have a protective or deleterious effect on mucosal immunity, depending on its specific components. It is reasonable to postulate that the same bacterial agents will elicit different effects according to each individual genetic background and environmental exposure.

CASE-CONTROL STUDIES ON *NOD2* POLYMORPHISMS

Conflicting

This is a common word found in the introduction of most studies on *NOD2* mutations as a risk factor for CRC. However, for an adequate analysis of the published results, several factors should be taken into consideration.

First, the most studied polymorphisms of *NOD2* have significantly different prevalence in different populations. Three of the most common polymorphisms were not found in 342 patients included in a Malaysian study^[12]. On the contrary, in a Danish study that included more than 40000 individuals, about 13% were carriers of at least one of the polymorphisms^[35]. An obvious conclusion is that we should analyze these results according to the geographic region where they were conducted. Even in European studies, where these polymorphisms are thought to be more common, the number of carriers

is often low. For example, in a study from Finland, there was only one homozygote for the R702W mutation in a universe of 1400 subjects^[36]. Achieving solid conclusions with such low numbers is extremely difficult. Another limiting aspect that may hinder the conclusions of such studies is the source of controls. The results differ according to the source of controls. According to a meta-analysis that included 30 case-control studies about *NOD2* polymorphisms and cancer risk^[37], there was only an increased risk in the subgroup with hospital-based controls, while no significant risk was observed in population-based studies. A factor worth looking at as well is that the great majority of studies about *NOD2* polymorphisms described so far analyzed only DNA extracted from nonneoplastic tissue (searching only germline mutations). For a complete understanding of the role of these mutations in the pathogenesis of CRC, an investigation of the neoplastic tissue should be undertaken as well (somatic mutations). To our knowledge, there is only one study that tried to determine if these mutations were of germline or somatic nature^[38]. A total genotypic agreement between blood and neoplastic samples was observed, therefore suggesting that CRC susceptibility associated with these variants is linked to germline mutations, apparently without the participation of somatic mutations.

Most studies addressing *NOD2* polymorphisms and CRC are essentially linkage studies concerning a specific country or region. Nowadays, genome-wide association studies (GWAS) have a significant impact on medical research. As they search for differences in allele frequencies or genotypes in a large number of patients, through the identification of thousands of single-nucleotide polymorphisms, GWAS have stronger statistical power than linkage studies. However, as it was already mentioned, the frequency of *NOD2* polymorphisms shows a significant geographic variability. As GWAS often recur to samples from a quite diverse set of countries, the effect of these polymorphisms in a certain population may go unnoticed.

When analyzing the results from these studies, it is important to consider each polymorphism separately as well. It seems plausible to admit that each polymorphism will have different effects on *NOD2* function and therefore its effect on cancer risk will probably be different as well. The most studied polymorphisms are two missense mutations - rs2066845 C/G (G908R) and rs2066844 C/T (R702W), and one frameshift mutation - rs2066847 insC (3020insC). For the first missense mutation, G908R, results are equivocal (Table 1). Case-control studies failed to identify an increased susceptibility to CRC for G908R mutation carriers in German, Portuguese and Hungarian populations^[13,38,39]. On the other hand, a Greek study was able to find an association between this mutation and CRC susceptibility^[40]. In what concerns meta-analysis, the results are conflicting. In the meta-analysis by Tian *et al.*^[41], there is evidence for an increased risk, but more recently, in 2014, a new meta-analysis showed no association between CRC and the G908R mutation^[37]. For the last of the missense mutations,

Table 1 Genotype frequencies of the nucleotide-binding and oligomerization-domain containing 2 polymorphisms

Country		Finland ^[36]	Greece ^[40]	Hungary ^[39]	New Zealand ^[43]	Portugal ^[38]
	CRC (n)	953/960/926 ¹	104	194	133	112
	Controls (n)	508/508/348 ¹	100	200	201	152
R702W						
CRC	% Allele frequency	2.2	4.8	1.8	7.1	12.5
Control	% Allele frequency	2.1	1.0	1.5	3.0	5.3
	P value	0.88	0.02	0.78	0.03	0.03
G908R						
CRC	% Allele frequency	0.3	8.65	1.8	2.2	2.73
Control	% Allele frequency	0.2	3.5	1.8	0.8	3.29
	P value	0.57	0.025	0.95	0.09	0.77
3020insC						
CRC	% Allele frequency	1.9	12.5	3.6	2.2	0.89
Control	% Allele frequency	1.9	6	2.5	1.0	1.3
	P value	0.96	0.017	0.40	0.19	0.75
At least one mutation						
CRC	% Genotype frequency	-	51.9	14.4	21.8	16.1
Control	% Genotype frequency	-	21.0	11.5	8.9	9.9
	P value	-	< 0.0001	0.45	0.001	0.132

¹CRC cases and controls for each mutation, respectively (R702W, G908R, 3020insC). CRC: Colorectal cancer.

R702W, there is strong evidence for an important role in CRC susceptibility. Several population-based studies and two meta-analyses revealed a significantly increased prevalence of this mutation in CRC patients (Table 1). For the frameshift mutation 3020insC, most studies support a relevant role for an increased risk of disease (Table 1)^[40,42]. Both meta-analysis published on this subject revealed that carrying the 3020insC mutation was associated with a higher risk for CRC development^[37,41].

If our objective is to assess the risk for CRC in *NOD2* polymorphism carriers, we should analyze the combined effect of the three main mutations. Several studies tried to determine if there was an increased risk for an individual carrying at least one of these polymorphisms. According to at least three population-based studies^[13,38,40], there was evidence of an increased CRC risk if one or more of the described polymorphisms were identified.

Besides searching for a potential role for *NOD2* mutations and a hypothetic increased susceptibility for CRC, several groups searched for genotype-phenotype correlations in these patients. One of the main concerns for investigators and clinicians working in the field of CRC are young patients suffering from this disease. Finding a marker of increased risk that could identify patients under 50 that should enter an early surveillance program is obviously a sought-after goal. In a German cohort of patients under 50, a significant association between *NOD2* mutations and CRC susceptibility was described^[13]. In a Portuguese study^[38], the R702W variant was associated with an increased risk for CRC only in female patients under 60. In the opposite direction, the groundbreaking work by Kurzawski *et al.*^[42], the first group that tried to find a correlation between these polymorphisms and CRC, revealed a bigger propensity of 3020insC mutation carriers to develop CRC at a later age. An association with certain phenotypic characteristics was researched as well. Tumor location

and size, vascular or lymphatic invasion, differentiation and distance to margins in resected specimens showed no relation with the presence of *NOD2* polymorphisms in most studies^[38,39,43]. This lack of genotype-phenotype agreement may be due to the genetic heterogeneity of the disease or it can be explained by the small number of mutation carriers diagnosed with CRC, therefore limiting the ability to reach such a conclusion. Only a Greek study was able to show a relevant association between tumor stage (TNM classification) and the occurrence of these mutations^[40].

Currently, new therapies for cancer are designed for a specific set of patients that are expected to respond, according to certain clinical and biological features. For example, Cetuximab is only prescribed to patients with advanced CRC and no mutation in the *KRAS* gene (wild type at codons 12 and 13 of *KRAS*). For *NOD2* mutations, a potential role for predicting response to treatment was researched as well. In 2014, Omrane *et al.*^[44] described an association between CRC patients carrying 3020insC polymorphism and the need for neoadjuvant chemotherapy. The presence of this polymorphism was able to predict failure of neoadjuvant chemotherapy. Conversely, the presence of 3020insC mutation was predictive of successful adjuvant chemotherapy^[44]. Despite the relatively small size of the sample, this may be a promising role for *NOD2* mutations, needing confirmation by large-scale studies.

Routine detection of *NOD2* mutations is still not being offered in the management of CRC patients. However, there is a new simple and cost-effective tool for the genetic screening of CRC^[45]. Besides well-known mutations in *MLH1*, *MSH2* and *MSH6* genes, the DNA microarray assay also searches the 3020insC polymorphisms in the *NOD2* gene. This may be a useful tool in clinical practice in CRC screening programs.

Due to the already described conflicting nature of the results from studies on *NOD2* mutations and CRC risk,

Table 2 Nucleotide-binding and oligomerization-domain containing 2 polymorphisms and cancer risk: Results of meta-analysis

Meta-analysis		Liu <i>et al</i> ^[37] (2014)	Tian <i>et al</i> ^[41] (2010)
R702W			
Variant genotypes <i>vs</i> homozygous wild-type	OR	1.32	1.59
	95%CI	1.01-1.72	1.09-2.32
	<i>P</i> value	0.04	0.02
G908R			
Variant genotypes <i>vs</i> homozygous wild-type	OR	1.32	1.98
	95%CI	1.01-1.72	1.14-3.44
	<i>P</i> value	0.04	0.01
3020insC			
Variant genotypes <i>vs</i> homozygous wild-type	OR	1.23	1.44
	95%CI	1.10-1.38	1.13-1.84
	<i>P</i> value	< 0.001	0.003
R702W/G908R/3020insC			
Variant genotypes <i>vs</i> homozygous wild-type	OR	-	1.58
	95%CI	-	1.03-2.42
	<i>P</i> value	-	0.03

OR: Odds ratio.

two meta-analyses on this subject were conducted (Table 2)^[37,41]. The first was published in 2010 and remains, to our knowledge, the only meta-analysis that studied *NOD2* mutations and CRC exclusively. A total of 85 papers were screened, but only 8 were considered appropriate to be included (all from Caucasian populations), totaling 3524 CRC cases and 2364 controls (Table 2). The most significant risk for CRC was found in patients carrying the G908R mutation (5 studies; OR = 1.98; 95%CI: 1.14-3.44). Increased risk was also found for the R702W mutation (5 studies; OR = 1.59; 95%CI: 1.09-2.32) and the missense mutation 3020insC (7 studies; OR = 1.44; 95%CI: 1.13-1.84). For an individual carrying at least one of these high-risk alleles, there is also an increased probability of developing CRC (5 studies; OR = 1.58; 95%CI: 1.03-2.42). The most recent meta-analysis on this subject studied the effect of *NOD2* mutations in the susceptibility for several types of cancer (melanoma, breast cancer, non-Hodgkin lymphoma and different gastrointestinal tumors). A total of 30 articles were included, 11 of which exclusively with CRC patients, published from 2004 to 2010. The results were similar to the ones described by Tian *et al*^[41], as it was demonstrated that both R702W and 3020insC were risk factors for CRC (Table 2). The only discrepancy was the effect of carrying G908R polymorphism. This allele was found to contribute to the overall risk of cancer, but not specifically to CRC. The studies included in this meta-analysis showed no obvious heterogeneity ($I^2 < 50\%$). Excluding any of the included studies would not change significantly the outcome, therefore suggesting that these results are statistically robust^[41].

***NOD2* MUTATIONS AND OTHER MALIGNANT AND NON-MALIGNANT CONDITIONS**

Since the publication in 2001 by Ogura *et al*^[41] of the first study about *NOD2* mutations and increased susceptibility

to CD, several investigators tried to understand the intricate mechanism behind this association and to find a link between these polymorphisms and other inflammatory and malignant conditions.

In fact, a role for *NOD2* mutations has been postulated for several malignant diseases other than CRC. In common digestive tract tumors, a significant number of published studies have addressed this putative relation. The 3020insC missense mutation was shown to be a risk factor for intestinal type gastric cancer in a Portuguese population^[46]. The same was demonstrated by an Italian study for the R702W and 1007fs polymorphisms^[47]. According to the meta-analysis by Liu *et al*^[37], there was an increased risk for gastric cancer for carriers of the G908R and 3020insC mutations, but the same was not observed for the R702W polymorphism. In a recent population-based Chinese study, an increased risk for gastric cancer was found for individuals carrying the rs718226 AG or GG genotype. Interestingly, this single-nucleotide polymorphism revealed significant joint effects with *H. pylori* in dysplasia and gastric cancer risk. On the contrary, both the rs2111235 C allele and the rs7205423 G allele showed a protective effect, as they were associated with a decreased risk of progression to dysplasia and gastric cancer in *H. pylori*-infected subjects^[48].

In what concerns pancreatic cancer, there was no evidence of increased risk neither in the familial nor the sporadic form of the disease^[37,49]. The same meta-analysis revealed an increased risk for MALT lymphoma, breast, lung and laryngeal cancer for the carriers of the 3020insC mutation. On the other hand, none of the *NOD2* mutations were found to be risk factors for melanoma or non-Hodgkin lymphoma^[37].

These discrepancies found between different studies may be attributed to a variety of factors, especially those that influence the expression of these polymorphisms, as well as differences in sample size, geographic variation or genotyping methods^[22].

The effect of *NOD2* as a risk factor for disease is best established in CD. After an etiologic role was consolidated for these mutations in CD, further investigation was undertaken to find out if these mutations influenced the behavior, prognosis and response to treatment as well. The presence of one mutation increased the risk for structuring or penetrating disease by 8% and this effect was largely increased if two *NOD2* mutations were present (41% risk increase)^[38]. An Australian study revealed as well that carriers have a more aggressive disease, needing more frequent and more precocious surgery^[50]. A recent European multicenter cohort study recently revealed that *NOD2* mutations and early use of immunomodulatory drugs are the most relevant predictors of the course of disease^[51].

It was speculated as well that certain disease phenotypes and their response to treatment could be influenced by *NOD2* mutations. The development of perianal fistulas is thought to depend on the proliferation of luminal bacteria. As such a possible connection between *NOD2*, a regulator of host response to microbial agents, and perianal fistulas was evaluated in recent literature. These fistulas showed significantly worse response to antibiotics in *NOD2* mutation carriers^[52], probably due to impaired recognition of intestinal bacteria and a decreased ability to mount an effective innate immune response. This kind of studies emphasizes the importance of gene mapping and corresponding phenotypic correlations in order to predict disease severity and optimize treatment strategies.

CONCLUSION

In the last fifteen years, the proposed role of *NOD2* and its mutations in disease has grown significantly. From only a susceptibility gene to an important predictor of prognosis and response to treatment in CD, these mutations have been postulated as a risk factor in several conditions such as mycobacterial infections, common gastroenterological disorders and malignant diseases like gastric and colorectal cancer. The expanding role of this receptor as a major coordinator of several inflammatory pathways and a modulator of microbiota is increasingly accepted, mainly due to evidence arising from *NOD2*-deficient animal models. In fact, it was shown that losing *NOD2* activity leads to more severe colitis and higher propensity to adenomas and CRC. It seems likely that *NOD2* may be the key element of the intricate puzzle that links the disturbance of mucosal immune defense, dysbiotic bacterial communities and conditions such as CD and colitis-associated CRC.

Furthermore, *NOD2* polymorphisms such as 3020insC and R702W seem to increase susceptibility to CRC. The search of these mutations is still not offered routinely in clinical practice. However, the identification of its carriers would allow such patients to be included in a more intense CRC surveillance program, contributing to early diagnosis of a disease that carries such a heavy burden. Predicting response to different chemotherapy regimens

according to the presence of *NOD2* polymorphisms could become a useful tool for clinicians. More large-scale studies should be conducted to confirm this association. The development of new therapeutic targets based on research about *NOD2* protein function and interactions could ultimately lead to a tailored approach to the treatment of CRC.

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Lymphadenectomy in gastric cancer: Contentious issues

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Abstract

The stomach is the sixth most common cause of cancer

worldwide. Surgery is an important component of the multi-modality treatment of the gastric cancer. The extent of lymphadenectomy has been a controversial issue in the surgical management of gastric cancer. The East-Asian surgeons believe that quality-controlled extended lymphadenectomy resulting in better loco-regional control leads to survival benefit in the gastric cancer; contrary to that, many western surgeons believe that extended lymphadenectomy adds to only postoperative morbidity and mortality without significantly enhancing the overall survival. We present a comprehensive review of the lymphadenectomy in the gastric cancer based on the previously published randomized controlled trials.

Key words: Gastric neoplasms; Lymphadenectomy; Gastrectomy; Survival; Disease recurrence

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Core tip: The only potentially curative option for the gastric cancer is surgery which may promise complete resection. Presently, D2 lymphadenectomy is the standard of care in an operable gastric cancer. Routine excision of spleen and pancreatic tail should not be undertaken as it increases the postoperative morbidity without adding significantly to overall survival.

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INTRODUCTION

As per GLOBOCAN 2012 data, the stomach is the sixth most common cause of cancer worldwide with an age-standardized incidence and mortality of 12.1/100000 and 8.9/100000 population^[1]. Though the multimodality

management of the gastric cancer has gradually become the standard of care, surgery continues to be at the forefront of it^[2]. Needless to say, complete surgical excision is the only potentially curable treatment available for an operable non-metastatic gastric cancer. In the last three decades, there has been a considerable debate related to the extent of lymphadenectomy in gastric cancer surgery at various surgical forums. The East Asian surgeons believe that the quality-controlled extended lymphadenectomy results in better locoregional control and leads to survival benefit in the gastric cancer; on the contrary, many western surgeons believe that the extended lymphadenectomy only adds to postoperative morbidity and mortality without significantly enhancing the overall survival. The present mini-review is an attempt to address this contentious surgical issue based on the information available from the published randomized controlled trials in this area.

Classification of lymphnode stations and types of lymphadenectomy

The lymph nodes stations of the stomach are categorized anatomically and identified numerically by the Japanese Gastric Cancer Association (JGCA) as published in the Japanese classification of gastric carcinoma: 3rd edition in 2011^[3]. Table 1 displays the various lymph nodes stations and their anatomical definitions. Previously, in its description of 2nd edition of Japanese classification of gastric carcinoma, JGCA classified regional lymph nodes into three groups based on the location of primary gastric tumor^[4]. These three groups of lymph node basins were used to describe the extent of lymph nodes dissection in a gastrectomy: D0 dissection - no dissection or incomplete dissection of the group 1 nodes; D1 - dissection of all the group 1 nodes; D2 - dissection of all the group 1 and group 2 nodes; and D3 - dissection of all the group 1, 2 and 3 nodes. This needs to be understood that each lymph nodal station would carry a different meaning for a particular primary tumor location - suprapyloric (station 5) falls under group 1 for an antral primary tumor while it would come under group 3 for proximal third gastric cancer. As expected, this classification was perceived to be quite complicated in the surgical fraternity, especially among western surgeons; and rightly so, it failed to garner widespread acceptance^[5]. In order to bring uniformity in the extent of lymphadenectomy, JGCA remarkably simplified the definition of lymphadenectomy in its recent classification^[6]. The lymph node stations 1-12 and 14v have been categorized as regional gastric lymph nodes while metastasis to any other node station classified as M1. The Japanese Gastric Cancer Guidelines 2010 (version 3) state that the extent of systematic lymphadenectomy is defined according to the type of gastrectomy indicated with the D level criteria.

For a total gastrectomy - D0 lymphadenectomy includes anything less than D1; D1 includes dissection of level 1 to 7; D1 + includes D1 lymph nodal dissection and stations 8a, 9 and 11p; D2 incorporates D1 lymph nodal dissection and stations 8a, 9, 10, 11p, 11d and

12a. For tumors involving the distal esophagus, D1+ includes dissection of 110 while D2 includes dissection of 19, 20 and 111. For a distal gastrectomy - D0 lymphadenectomy includes anything less than D1; D1 includes dissection of level 1, 3, 4sb, 4d, 5, 6 and 7; D1 + includes D1 lymph nodal dissection and stations 8a and 9; D2 incorporates D1 lymph nodal dissection and stations 8a, 9, 11p, and 12a.

RATIONAL AND EXTENT OF LYMPHADENECTOMY

The key point of debate related to the extent of lymphadenectomy has been to balance the oncological benefit vis-à-vis postoperative morbidity and mortality^[7,8]. The oncological scenarios where survival is thought to be increased by the extended lymphadenectomy are few; moreover, there is paucity of level I evidence confirming the survival benefit^[8]. There is a widely held view among the western surgeons that malignant lymph nodes are indicators and not governors of survival^[9,10]. Contrary to this view, Japanese surgeons have demonstrated that better loco-regional control through quality-controlled radical resections with extensive lymphadenectomy, leads to improvement in survival by preventing the loco-regional recurrences and thereby reducing the distant metastasis. There have been a few randomized controlled trials (RCTs), published in the last two decades, which compared various extents of lymphadenectomy in the gastric cancer surgery to assess the associated postoperative morbidity and mortality, and their impact on survival (Table 2).

D1 vs D2 lymphadenectomy

The contentious issue of the extent of lymphadenectomy was a real dividing line between the Japanese surgeons and western surgeons in the 1990s. There are three published RCTs which have compared the D1 and D2 lymphadenectomy in the gastric cancer surgery.

The landmark Dutch trial was conducted by Dutch Gastric Cancer Group from August 1989 till July 1993^[11]. They randomized 711 patients into two groups: One group had D1 dissection while the other group had D2 dissection. The D1 dissection included clearance of 1st tier lymph nodal echelons (stations 1-6) while D2 dissection incorporated additional clearance of 2nd tier lymph nodal echelons (stations 7-11). Distal pancreatectomy with splenectomy was done in all patients who had a D2 dissection in order to achieve adequate lymphadenectomy, while it was done selectively in a D1 dissection, when they were involved by the tumor. The eligibility criterion of the patients for inclusion in the trial was the presence of histologically confirmed gastric cancer without evidence of distant metastasis. The quality control was undertaken with the histopathological confirmation of lymph nodes and their number at a particular station. They coined two terms: "Contamination" and "non-compliance" to describe violation of the protocol. The "contamination"

Table 1 Anatomical definition of lymph node stations

Lymph node station	Label	Anatomical description
1	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery
2	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery
3	Lesser curvature	3a: Along the branches of the left gastric artery 3b: Along the 2 nd branch and distal part of the right gastric artery
4	Left gastric curvature	4sa: Left greater curvature LNs along the short gastric arteries (perigastric area) 4sb: Left greater curvature LNs along the left gastroepiploic artery (perigastric area)
	Right greater curvature	4d: Rt. greater curvature LNs along the 2 nd branch and distal part of the right gastroepiploic artery
5	Suprapyloric	Along the 1 st branch and proximal part of the right gastric artery
6	Infrapyloric	Along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreaticoduodenal vein
7	Left gastric artery	Along the trunk of left gastric artery between its root and the origin of its ascending branch
8	Common hepatic artery	8a: Anterosuperior LNs along the common hepatic artery 8p: Posterior LNs along the common hepatic artery
9	Celiac	Along the coeliac artery
10	Splenic hilum	Lymph nodes in the splenic hilum including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1 st gastric branch
11	Splenic artery	11p: Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end 11d: Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail
12	Hepatoduodenal ligament	12a: Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas 12b: Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas 12p: Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
13	Posterior pancreatic head	On the posterior surface of the pancreatic head cranial to the duodenal papilla
14v	Superior mesenteric vein	Along the superior mesenteric vein
15	Middle colic vessels	Along the middle colic vessels
16	Para-aortic	16a1: Paraaortic lymph nodes in the diaphragmatic aortic hiatus 16a2: Paraaortic lymph nodes between the upper margin of the origin of the celiac artery and the lower border of the left renal vein 16b1: Paraaortic lymph nodes between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery 16b2: Paraaortic lymph nodes between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	Anterior surface of pancreatic head	On the anterior surface of the pancreatic head beneath the pancreatic sheath
18	Inferior border of the pancreatic body	Along the inferior border of the pancreatic body
19	Infradiaphragmatic	Infradiaphragmatic, predominantly along the subphrenic artery
20	Paraesophageal, esophageal hiatus	In the diaphragmatic esophageal hiatus
110	Paraesophageal, lower thoracic	In the lower thorax
111	Supradiaphragmatic	Supradiaphragmatic lymph nodes separate from the esophagus
112	Posterior mediastinal	Posterior mediastinal lymph nodes separate from the esophagus and the esophageal hiatus

LNs: Lymph nodes.

was considered when a surgeon dissected two or more lymph node stations which should not have been dissected; the "non-compliance" was considered when a surgeon did not dissect two or more lymph node stations which should, otherwise, have been dissected. It was thought that a high contamination in D1 dissection and a high noncompliance in D2 dissection would blur the distinction between operative procedures in the two groups and it would affect the conclusions. They reported a significantly high postoperative morbidity (43% vs 4%, $P < 0.001$) and mortality (10% vs 4%, $P < 0.004$) in the D2 dissection group as compared to the other group. Moreover, they reported no difference in 5-year survival

in between the two groups (34% in D1 vs 33% in D2). Based on these results, they concluded that their data did not support routine D2 lymphadenectomy in gastric cancer patients. However, this trial drew a lot of criticism in view of a number of flaws. The participating surgeons had no previous experience of D2 lymphadenectomy; they were trained with the help of videotapes and booklets. There were a number of centres which were low volume centres for gastric resection, performing only a few in a year. The non compliance was very high in the D2 lymphadenectomy group, to the tune of 51%. The 11-year follow-up data of this trial (published in 2004) indicated similar survival in between the two groups

Table 2 Previously published randomized clinical trials addressing the extent of lymphadenectomy in gastric cancer

Ref.	Study period	Study groups	Median follow-up	Result	Conclusion
Cuschieri <i>et al</i> ^[14]	1986-1993	D1 = 200, D2 = 200	6.5 yr, overall	5-yr OS in D1 vs D2 - 35% vs 33%, (HR = 1.10, 95%CI: 0.87-1.39)	Classical Japanese D2 resection offers no survival advantage over D1 surgery
Songun <i>et al</i> ^[13]	1989-1993	D1 = 380, D2 = 331	15.2 yr, overall	5-yr OS D1 vs D2 - 21% vs 29%, (log-rank $P = 0.34$), subgroup analysis of patients without pancreatico-splenectomy, 15-yr OS in D1 vs D2 = 22% vs 35% (HR = 1.34, 95%CI: 1.09-1.65; log-rank $P = 0.006$)	Spleen preserving D2 resection should be recommended as the standard surgical approach to resectable gastric cancer
Degiuli <i>et al</i> ^[17]	1998-2006	D1 = 133, D2 = 134	6.7 yr, overall	5-yr OS in two arms D1 vs D2 - 66.5% vs 64.2%, (difference -2.3, 95%CI: -14.0 to 9.3; $P = 0.695$), 5-yr disease-specific survival in pathological tumour pT2-4 in two arms D1 vs D2 - 38% vs 59%; $P = 0.055$	No difference in overall 5-yr survival between D1 and D2 resection; D2 lymphadenectomy may be a better choice in patients with advanced disease and lymph node metastases
Wu <i>et al</i> ^[19]	1993-1999	D1 = 110, D3 = 111	94.5 mo, for survivors	5-yr OS in D1 vs D3 - 53.6% vs 59.5% difference between groups 5.9% (95%CI: -7.3 to 19.1), log-rank $P = 0.041$)	D3 dissection offers a survival benefit for patients with gastric cancer compared with D1 dissection
Sasako <i>et al</i> ^[21]	1995-2001	D2 = 260, D2 + PAND = 263	5.6 yr for D2 lymphadenectomy alone and 5.7 yr for D2 lymphadenectomy plus PAND 94.5 mo, for survivors	5-yr overall survival rate for D2 vs D2 + PAND -69.2% vs 70.3% HR for death 1.03 (95%CI: 0.77-1.37; $P = 0.85$)	No survival benefit with D2 lymphadenectomy plus PAND in curable gastric cancer as compared with D2 lymphadenectomy alone
Yonemura <i>et al</i> ^[22]	1995-2002	D2 = 135, D2 + PAND = 134	NS	5-yr overall survival rate for D2 vs D2 + PAND -52.6% vs 55.0% ($\chi^2 = 0.064$; $P = 0.801$)	Prophylactic D4 dissection is not recommended for patients with potentially curable advanced gastric cancer
Kulig <i>et al</i> ^[20]	1999-2003	D2 = 141, D2 + PAND = 134	Results awaited	Results awaited	Results awaited

D1: D1 lymphadenectomy; D2: D2 lymphadenectomy; OS: Overall survival; HR: Hazard ratio; PAND: Para-aortic node dissection.

(30% for D1 vs 35% for D2, $P = 0.53$); risk of relapse in two groups was also shown to be similar (78% for D1 vs 65% for D2, $P = 0.43$)^[12]. The 15-year survival data for the Dutch trial (published in 2010), however, swayed the evidence towards the D2 dissection; gastric-cancer-related deaths were significantly higher in the D1 group compared with the D2 group (HR = 0.74 for D2 vs D1, 95%CI: 0.59-0.93, $P = 0.01$), whereas death due to other causes was not different between the two groups (HR = 1.22 for D2 vs D1, 0.95-1.58, $P = 0.12$). Loco-regional recurrences were higher in D1 group compared to D2 group (40.7%, 155/380 vs 21.8%, 83/330). The 15-year overall survival for patients who had curative resections was 21% (95%CI: 17-26) for D1 and 29% (98 of 331, 24-34) for D2 (log-rank P value, 0.34); however, the difference in survival (25% for D1 vs 35% for D2, log-rank P value 0.08) in two groups became more evident if the postoperative deaths in two groups were excluded (4% in D1 and 10% in D2). Subgroup analysis showed that pancreatectomy and splenectomy, which were routinely done in D2 group as per the protocol, significantly lowered the overall survival. These findings led the authors to recommend spleen preserving D2 dissection in the patients with resectable gastric cancer^[13].

Another landmark trial published in 1999 was MRC trial conducted by Cuschieri *et al*^[14]. This was a large multicentric trial (patients recruited by 32 surgeons) which randomized 400 patients into two arms: 200 patients in one arm underwent D1 dissection which was defined as removal of lymph nodes within 3.0 cm of the tumor while another 200 patients in other arm had D2 dissection which incorporated additional removal of omental bursa, the hepatoduodenal and retroduodenal nodes (antral lesions), and the splenic artery/splenic hilar nodes and retropancreatic nodes by distal hemipancreatectomy for middle and upper third lesions. The authors reported that D2 lymphadenectomy was associated with significantly higher postoperative complications (D2 vs D1, 46% vs 28%, $P < 0.001$); the postoperative mortality was also significantly higher in the D2 group (13%) than in the D1 group (6.5%; $P = 0.04$)^[15]. The authors showed that the 5-year survival rates were 35% for D1 resection and 33% for D2 resection and there was no statistically significant difference in overall 5-year survival between these two arms (HR = 1.10, 95%CI: 0.87-1.39, where HR > 1 implies a survival benefit to D1 surgery) after a median follow-up of 6.5 years. Gastric cancer-specific survival was also similar in the D1 and D2 groups (HR = 1.05,

95%CI: 0.79-1.39) as was recurrence-free survival (HR = 1.03, 95%CI: 0.82-1.29). Based the findings of the trial, the authors suggested that the classical Japanese D2 resection offered no survival advantage over D1 resection. However, they did not refute the possibility that the D2 resection without pancreatoco-splenectomy might be better than standard the D1 resection as there was a significant survival disadvantage in the group undergoing splenectomy with distal pancreatectomy ($P = 0.01$). This fact may also be responsible for confounding the results as 57% of the D2 group underwent distal pancreatectomy and splenectomy vs 4% in the D1 group. Though the D2 lymphadenectomy included more extensive lymph nodes dissection than the D1, there was a little difference in the median number of nodes examined with a mean of 13 in the D1 group vs 17 nodes in the D2 group.

The Italian gastric cancer study group (IGCSG) conducted another trial to compare the D1 and D2 lymphadenectomy in the gastric cancer^[16,17]. The previous trials, MRC and Dutch trial, reported higher postoperative morbidity and mortality in the D2 lymphadenectomy. In order to address the safety concerns and survival benefits of D2 lymphadenectomy, IGCSG initiated multicentric RCT in 1998; they randomized 267 patients into two arms - D1 and D2 lymphadenectomy. The promising part of the trial was its strict quality controlled surgery - only those surgeons who had participated in their previous trial were asked to participate in the present trial in order to avoid bias related to surgical inexperience in D2 gastrectomy technique. However, the trial still had high contamination (17.3%) and non-compliance (33.6%) among the operated patients. In their initial publication of short term results of trial, the authors reported that the overall morbidity rate following D1 and D2 dissections was comparable (12.0% vs 17.9%, P value 0.178) as per intention to treat analysis; there was also no difference in the 30-d postoperative mortality rates (D1 vs D2, 3.0% vs 2.2%, $P = 0.72$). They concluded that the postoperative complications following D2 lymphadenectomy are not as high as they have been reported in previous randomized western trials in the specialized centers, and it should be considered a safe option for the radical management of gastric cancer in Western patients in an appropriate setting^[17]. The authors published their long term results in 2014^[16]. The median follow-up was 8.8 (range 4.5-13.1) years for surviving patients and 2.4 (0.2-11.9) years for those who died, and was not different in the two treatment arms. The overall 5-year survival was similar in two groups (D1 vs D2, 66.5% vs 64.2%, P value = 0.69). Subgroup analyses showed a 5-year disease-specific survival benefit for patients with pathological tumour 1 (pT1) disease in the D1 as compared to D2 (98% vs 83 %, $P = 0.015$), and for patients with pT2-4 status and positive lymph nodes in the D2 as compared to D1 (59% vs 38%, $P = 0.055$). The authors concluded that D2 lymphadenectomy might be a better choice in patients with advanced disease (pT2-4) and lymph node metastases. Though the overall 5-year survival

rate of approximately 65% in the whole patient cohort is impressive, it seems to be related to the unexpectedly high proportion (33%) of patients with pT category 1 tumors, who have a good prognosis and probably would not benefit from a D2 procedure^[18]. The Italian study contributes to the view that D2 lymphadenectomy can be performed safely and adequately, producing 5-year survival results that help to close the gap between survival results reported from Asia and those from Europe.

D1 vs D3 lymphadenectomy

Wu *et al.*^[19] reported a randomized controlled trial of nodal dissection for patients with the gastric cancer from Taiwan; they randomly allocated 221 patients with the advanced gastric cancer at the Taipei Veterans General Hospital, Taiwan, to either D1 lymphadenectomy or D3 lymphadenectomy during the study period 1993-1999. At a median follow-up of 94.5 mo, the authors reported that the 5-year overall survival was 59.5% (95%CI: 50.3-68.7) for the D3 group and 53.6% (95%CI: 44.2-63.0) for the D1 group (difference between groups 5.9%, 95%CI: -7.3 to 19.1, log-rank $P = 0.041$) as per the intention to treat analysis. Among patients who had R0 resection, D3 dissection group had fewer disease recurrences than D1 (42% vs 52%), though it did not attain statistical significance (P value = 0.117, χ^2 test). However, among this R0 resection group, D3 group had significantly higher 5-year overall survival than D1 group (61.1%, 95%CI: 51.9-70.3 vs 54.2%, 95%CI: 44.8-63.6; difference between groups 6.9%, 95%CI: -6.3-20.7, log-rank $P = 0.026$). The authors concluded that D3 nodal dissection performed by well trained and experienced surgeons offers survival advantage compared with D1 in gastric cancer. This trial had its own limitations. The preoperative work up of the patients was not stringent as sizeable number of patients ($n = 114$, 34%) met exclusion criteria. More troublesome is those 64 patients who were found to have not met the protocol after randomization in view of early cancer, oesophageal invasion, or positive resection margin following histopathological examination. This highlights the growing role of high resolution computed tomography and endoscopic ultrasonography for accurate disease staging. The authors did not mention anatomical mapping of late nodal recurrences; this detailed anatomic information would have highlighted whether extensive lymphadenectomy helped avoiding the nodal recurrence in the dissected lymph node basins.

D2 vs extended D2 lymphadenectomy

Three published RCTs have addressed this issue of D2 vs extended D2 (including Paraaortic lymph node dissection). Significant postoperative morbidity and mortality following extensive lymphadenectomy has always been a matter of grave concern especially among the western surgeons. In order to address the safety concerns of extensive D2 dissection, Polish Gastric Cancer Study Group published the interim analysis of their multicentre, randomized clinical trial which was

initiated to evaluate the possible benefits of extended D2 (D2+) lymphadenectomy after potentially curative resection of gastric cancer^[20]. They defined standard D2 lymphadenectomy according to the JGCA classification; D2+ lymphadenectomy included additional removal of para-aortic nodes. They randomized 275 patients into two groups: 141 to standard D2 and 134 to D2+ lymphadenectomy. The overall morbidity rates were comparable in two groups: D2 and D2+ (27.7%, 95%CI 20.3-35.1 vs 21.6%, 95%CI: 13.7-29.5, P value = 0.248). The postoperative mortality rates were also similar in two groups (D2 vs D2+, 4.9% vs 2.2%, P value = 0.376). They concluded that the interim safety analysis suggested similar surgical outcome in two groups. Long term survival data from the POLAND trial is still awaited.

Though the POLAND trial established the safety of extended D2 dissection, the JCOG 9501 trial failed to establish oncological benefit of D2 extended dissection^[21]. The JCOG 9501 trial addressed the surgical issue if addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival. They conducted a multi-centric (24 hospitals in Japan) randomized controlled trial to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND in patients undergoing gastrectomy for curable gastric cancer. They randomized 523 patients with curable stage T2b, T3, or T4 gastric cancer to D2 lymphadenectomy alone ($n = 263$ patients) or to D2 lymphadenectomy plus PAND ($n = 260$ patients). No adjuvant treatment was prescribed to any patient following surgery. The rates of surgery-related complications (anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia) in two groups were similar (D2 vs D2+, 20.9% vs 28.1%, P value = 0.07), Death rates from any cause within 30 d after surgery in two groups were also similar. There was also no difference in 5-year overall survival rate in two groups (D2 vs D2+, 69.2% vs 70.3%, HR = 1.03, $P = 0.85$). There were no significant differences in recurrence-free survival between the two groups (HR for recurrence 1.08, $P = 0.56$). The authors concluded that D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer in comparison to D2 lymphadenectomy alone.

The third RCT was conducted by the East Asia Surgical Oncology (EASO) group to evaluate the survival benefit of para-aortic dissection in addition to the D2 lymphadenectomy in potentially curable gastric adenocarcinoma^[22]. They randomized 269 patients into two groups 135 patients were allocated to the D2 group and 134 to the D2 + para-aortic lymphadenectomy (D2+, also designated as D4 by the authors) group. There was no statistically significant difference in survival between the two groups (52.6% for D2 vs 55.0% for D2+, $\chi^2 = 0.064$; $P = 0.80$). The authors concluded that prophylactic para-aortic dissection is not recommended for patients with potentially curable advanced gastric

cancer. It is worth mentioning here that out of 12 patients who had pathologically positive station 16 nodes, three of them survived for more than 5 years (median survival 2.8 years).

What do we learn from these trials?

Though the MRC^[15] and Dutch trial^[11] suggested that D2 dissection is associated with significantly higher postoperative morbidity in terms of anastomotic leakage, pancreatic leakage, reoperation rates, wound infection and pulmonary complications, it seems that higher postoperative risk reported with D2 dissection in these trials can be contributed largely to splenectomy and pancreatectomy and not to D2 itself. Secondly, inadequate surgical training in the D2 dissection and sub-optimal quality control would further explain the higher postoperative morbidity and mortality in earlier trials. IGCSG trial showed that D2 dissection could be performed safely without splenectomy and distal pancreatectomy, with comparable mortality and morbidity to those for D1 dissection^[17]. Splenectomy or distal pancreatectomy might be considered beneficial only when the primary tumour or metastatic lymph nodes directly invade these organs. Routine resection of spleen and pancreatic tail is no longer recommended as a necessary component of modern D2 dissection^[23].

Though the initial results of the Dutch trial and the MRC trial did not show survival benefit of D2 lymphadenectomy, 15-year follow-up data of Dutch trial clearly swayed the evidence in favour of spleen preserving D2 lymphadenectomy. This was despite the significant problem of contamination and non-compliance. This further reiterated the notion that long term follow-up is needed to document the survival benefit of good loco-regional control. It must be remembered that adjuvant treatment is not the replacement of inadequate surgery; subgroup analysis of Intergroup 116 trial showed that while adjuvant chemoradiotherapy is required after D0/1 dissection, it had no added value after D2 dissection^[24-26].

Prophylactic dissection of station 16 does not provide any significant benefit over standard D2 lymphadenectomy, though 25% 5-year survival among patients with pathologically positive para-aortic nodes in EASO group trial^[22] gives a hope for this patient cohort.

When will there be reconciliation in Eastern and Western surgeons is not the issue; the basic question remains what is the optimum lymphadenectomy for a given patient to improve survival without adding significant postoperative complications. A personalized surgical approach may be beneficial in a given patient to select D1 or D2 lymphadenectomy - a D2 lymphadenectomy may not benefit a patient with early gastric cancer and may indeed lead to increased complications; on the contrary, patients with more advanced disease may benefit from an extensive lymphadenectomy^[27].

CONCLUSION

Presently, the D2 lymphadenectomy is the standard of

care in an operable gastric cancer. Routine excision of spleen and pancreatic tail should not be undertaken as it increases the postoperative complications without adding significantly to overall survival.

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Basic Study

Effect of Roux-en-Y gastric bypass surgery on intestinal *Akkermansia muciniphila*

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Abstract

AIM: To investigate changes in intestinal *Akkermansia muciniphila* (*A. muciniphila*) and explore the mechanism underlying the therapeutic effects of Roux-en-Y gastric bypass (RYGB) surgery on type 2 diabetes in diabetic Goto-Kakizaki (GK) rats.

METHODS: Male diabetic GK rats ($n = 12$) aged 8 wk were randomly assigned to the surgery group (GK-RYGB) or sham surgery group (GK-Sham) ($n = 6$ per group), and another 6 male Wistar rats aged 8 wk served as controls (WS-Sham). In the surgery group, RYGB surgery was conducted, and a sham operation was performed in both sham groups. Fasting blood glucose (FBG) levels before and after surgery, fasting levels of serum insulin and serum glucagon-like peptide-1 (GLP-1) and levels 30 min after intragastric injection of glucose, and the amount of *A. muciniphila* in the stool were determined. Insulin and GLP-1 were measured by enzyme-linked immunosorbent assay, and *A. muciniphila* were detected by fluorescence-based quantitative polymerase chain reaction.

RESULTS: The FBG was improved, and serum GLP-1 and insulin increased significantly ($P < 0.05$) in the GK-RYGB group after surgery compared to levels before surgery and to levels in the GK-Sham group. Before surgery, the amounts of *A. muciniphila* in the GK-RYGB and GK-Sham groups were significantly lower than in the WS-Sham group ($P < 0.05$). After surgery, the amount of *A. muciniphila* in the GK-RYGB group increased markedly compared to that before surgery and to that in the GK-Sham and WS-Sham groups ($P < 0.05$). In addition, the *A.*

muciniphila amount was positively related to GLP-1 ($r = 0.86, P < 0.05$).

CONCLUSION: Our results demonstrated RYGB surgery may increase GLP-1 secretion, elevate serum insulin after intragastric injection of glucose, and improve insulin resistance in diabetic GK rats, thereby contributing to a significant reduction in blood glucose. The increased amount of *A. muciniphila* after RYGB surgery may be related to elevated GLP-1 secretion.

Key words: Roux-en-Y gastric bypass surgery; Type 2 diabetes; Glucagon-like peptide-1; Glucose-dependent insulinotropic peptide; *Akkermansia muciniphila*

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Core tip: Roux-en-Y gastric bypass (RYGB) surgery can improve blood glucose with definite efficacy in obese patients with type 2 diabetes mellitus and that this effect is also long lasting. But the mechanism of RYGB is not clear. Our study demonstrated RYGB surgery may increase glucagon-like peptide-1 (GLP-1) secretion, elevate serum insulin after intragastric injection of glucose, and improve insulin resistance in diabetic Goto-Kakizaki rats, thereby contributing to a significant reduction in blood glucose. The increased amount of *Akkermansia muciniphila* after RYGB surgery may be related to elevated GLP-1 secretion.

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INTRODUCTION

According to the International Diabetes Federation^[1], diabetes mellitus (DM) affected about 370 million people in 2011, and an estimated 550 million people will develop DM. Of DM patients, 90% are diagnosed with type 2 DM (T2DM)^[2]. The specific etiology of T2DM is still unclear, but it is widely accepted that T2DM develops as a result of genetic and environmental factors^[3]. Intestinal microorganisms have been regarded as environmental factors^[4] and are closely related to the occurrence and development of metabolic diseases, including DM^[5-8].

In recent years, increasing numbers of studies have reported that Roux-en-Y gastric bypass (RYGB) surgery may alter the intestinal flora. Animal experiments^[9,10] and clinical trials^[11,12] have revealed that the intestinal flora change significantly after RYGB surgery. However, a majority of studies focused on the bacterial genus, and a specific type of bacterium has never been investigated in depth. Studies in the field of internal medicine typically emphasize *Akkermansia muciniphila* (*A. muciniphila*),

and findings demonstrate that *A. muciniphila* is closely related to the occurrence and development of obesity and DM^[13-18]. In the present study, RYGB surgery was performed in diabetic Goto-Kakizaki (GK) rats, and blood glucose, glucagon-like peptide-1 (GLP-1), and the amount of *A. muciniphila* in the stool were measured before and after surgery to evaluate the association of postoperative blood glucose and GLP-1 with the amount of *A. muciniphila* and to explore the potential mechanisms underlying the therapeutic effects of RYGB surgery on T2DM.

MATERIALS AND METHODS

Animals

GK rats aged 8 wk (specific pathogen free; $n = 12$) and Wistar rats ($n = 6$) were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. China. GK rats were randomly assigned to 1 of 2 groups ($n = 6$ per group): The GK-RYGB group and GK-sham group. Wistar rats served as controls (WS-Sham group). This study was approved by the Ethics Committee of the Beijing Tiantan Hospital Affiliated to Capital Medical University, and all the procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals.

Surgical procedures and postoperative treatments

Before surgery, rats were fasted for 12 h and then were intraperitoneally anesthetized with 10% chloral hydrate at 0.35 mL/100 g, followed by RYGB surgery. A 4-cm incision was made in the upper abdomen, and laparotomy was performed: First, the stomach was divided just below the gastroesophageal junction from the greater to the lesser curve, taking care to preserve the vagus nerve in this region. A gastric pouch of approximately 20% of the total stomach volume was preserved. Second, the jejunum was divided 8 cm below the ligament of Treitz, and the distal cut end was anastomosed on the anterior surface of the gastric pouch with 5-0 suture. The anastomosis was 4-6 cm in length. Third, a 1-cm enterotomy was made on the antimesenteric aspect of the jejunum 10 cm distal to the gastrojejunostomy and was anastomosed to the proximal cut end of the jejunum as an end-to-side anastomosis that was 4-6 cm in length.

Sham surgery was performed in the following manner: A midline 4-cm incision was made in the upper abdomen, and laparotomy was performed. The gastrointestinal tract was explored, straightened out, and placed back into the abdominal cavity. Food was withheld for 24 h after surgery, but animals were given *ad libitum* access to water. Beginning 2 d after surgery, fluid (10% glucose) was administered for 2 d, and normal diet was resumed at 4 d after surgery. None of the animals in the 3 groups died during the experiment.

Fasting blood glucose

Fasting blood glucose (FBG) was measured at 1 wk before surgery and at 1, 2, 3, and 4 wk after surgery.

Table 1 Fasting blood glucose in different groups before and after surgery ($\bar{x} \pm s$, mmol/L)

Time point	GK-RYGB	GK-Sham	WS-Sham
1 wk presurgery	6.98 ± 0.32 ^a	7.07 ± 0.57 ^a	4.57 ± 0.26
1 wk postsurgery	6.42 ± 0.25 ^c	6.82 ± 0.49 ^a	4.25 ± 0.23
2 wk postsurgery	6.01 ± 0.20 ^{a,c,e}	6.88 ± 0.52 ^a	4.37 ± 0.22
3 wk postsurgery	5.60 ± 0.26 ^{a,c,e}	6.93 ± 0.52 ^a	4.37 ± 0.23
4 wk postsurgery	5.72 ± 0.25 ^{a,c,e}	7.03 ± 0.52 ^a	4.50 ± 0.24

^a*P* < 0.05 vs WS-Sham group; ^c*P* < 0.05 vs GK-Sham group; ^e*P* < 0.05 vs presurgery value. GK: Goto-Kakizaki; RYGB: Roux-en-Y gastric bypass; WS: Wistar.

Rats were fasted overnight, blood was collected from the tail vein, and glucose was measured with a glucose meter (Beijing Yicheng Company) at 8:00 AM.

Serum insulin and GLP-1

Serum insulin and GLP-1 were measured 1 wk before surgery and 4 wk after surgery. Rats were fasted overnight, and blood was collected from the tail vein at fasting status and at 30 min after intragastric administration of 1 g/kg glucose. Blood was transferred into an EDTA-pretreated tube and centrifuged at 3000 rpm for 12 min at 4 °C. The serum was collected and stored at -80 °C for further analysis. Rat radioimmunoassay kits (IBL, Germany) were used for the detection of serum insulin and GLP-1 according to the manufacturer's instructions.

Homeostasis model assessment-insulin resistance

Homeostasis model assessment-insulin resistance (HOMA-IR) was measured before surgery and 4 wk after surgery as follows: HOMA-IR = fasting plasma glucose (mmol/L) × fasting insulin (pmol/L)/22.5. HOMA-IR was used to evaluate the insulin resistance.

A. muciniphila in the stool. Extraction of bacterial DNA took place as follows: Stool was collected 1 wk before and 4 wk after surgery and was stored at -80 °C. The standard Muc^T (ATCC BAA-835^T) was thawed, cultured, and then stored at 4 °C. DNA was extracted with the QIAamp bacterial genomic DNA extraction kit (Qiagen, Germany) according to the manufacturer's instructions and then was stored at -20 °C for use. Next, primers for polymerase chain reaction (PCR) were designed: On the basis of the V1 and V6 variable regions of 16S RNA of *A. muciniphila*^[17], forward and reverse primers were designed with Primer Premier 5.0 (Premier Biosoft, Palo Alto, CA, United States) and were synthesized as follows:

Forward: 5' CAGCACGTGAAGGTGGGGAC 3'

Reverse: 5' CCTTGCGGTTGGCTTCAGAT 3'

Product length: 214 bp.

Routine PCR was conducted as follows: Genomic DNA extracted from the bacteria in rat stool, and standard bacteria served as templates for routine PCR. The purity and integrity of genomic DNA were determined by 1.0% agarose gel electrophoresis. After PCR, the amplified DNA was harvested with a DNA retrieval kit (Company,

Country). The retrieved DNA of standard bacteria served as standards for fluorescence-based quantitative PCR, and a standard curve was delineated.

A 10-fold dilution series of standard DNA template and DNA template from stool bacteria were independently prepared and used for real-time quantitative PCR. Product specificity was determined according to the melt curve, and the Ct value and the standard curve were employed to calculate the amount of measured bacteria (copies per g stool).

Statistical analysis

Statistical analysis was performed with SPSS version 19.0 (Chicago, IL, United States), and data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Comparisons of means among groups were done with one-way analysis of variance. A value of *P* < 0.05 was considered statistically significant. Correlations between *A. muciniphila* amount and serum GLP-1 were evaluated with Pearson correlation analyses and univariate regression analyses.

RESULTS

Blood glucose and insulin

Before surgery, FBG in GK rats was significantly higher than that in Wistar rats (*P* < 0.05). At 1 wk after surgery, FBG was reduced in the 3 groups, but a significant difference was found only in the GK-RYGB group (*P* < 0.05). FBG increased gradually in the GK-Sham group and the WS-Sham group within 2 wk after surgery. At 2, 3, and 4 wk after surgery, FBG in the GK-RYGB group was lower than that in the GK-Sham group but was still higher than in the WS-Sham group. After surgery, FBG in the GK-RYGB group was significantly different from that in the GK-Sham and WS-Sham groups (*P* < 0.05) (Table 1).

Before surgery, fasting serum insulin (FSI) values in GK rats was significantly lower than those in Wistar rats (*P* < 0.05). At 4 wk after surgery, the FSI values in the GK-RYGB group and GK-Sham group increased compared to values before surgery (*P* > 0.05). At 4 wk after surgery, the FSI at 30 min after intragastric administration of glucose in the GK-RYGB group increased significantly compared to that before surgery and was significantly higher than in the GK-Sham group but lower than in the WS-Sham group after surgery (*P* < 0.05) (Table 2).

Before surgery, HOMA-IR in GK rats was significantly higher than that in Wistar rats (*P* < 0.05), suggesting higher insulin resistance in GK rats before surgery. At 4 wk after surgery, HOMA-IR in the GK-RYGB group was significantly lower than that before surgery and that in the GK-Sham group after surgery (*P* < 0.05), indicating that RYGB surgery can improve insulin resistance in GK rats (Table 3).

GLP-1

Before surgery, fasting GLP-1 in GK rats was significantly lower than that in Wistar rats (*P* < 0.05). At 4 wk after

Table 2 Serum insulin in different groups before and after surgery ($\bar{x} \pm s$, pmol/L)

Group	Presurgery		4 wk postsurgery	
	Fasting	30 min after intragastric glucose	Fasting	30 min after intragastric glucose
GK-RYGB	15.20 ± 0.67 ^a	27.07 ± 1.07 ^a	16.05 ± 1.41 ^a	47.57 ± 4.24 ^{a,c}
GK-Sham	15.26 ± 0.76 ^a	27.49 ± 1.29 ^a	15.43 ± 0.97 ^a	27.26 ± 1.26 ^a
WS-Sham	18.54 ± 0.99	104.00 ± 4.96	19.01 ± 0.42	103.68 ± 4.85

^a $P < 0.05$ vs WS-Sham group; ^c $P < 0.05$ vs GK-Sham group. GK: Goto-Kakizaki; RYGB: Roux-en-Y gastric bypass; WS: Wistar.

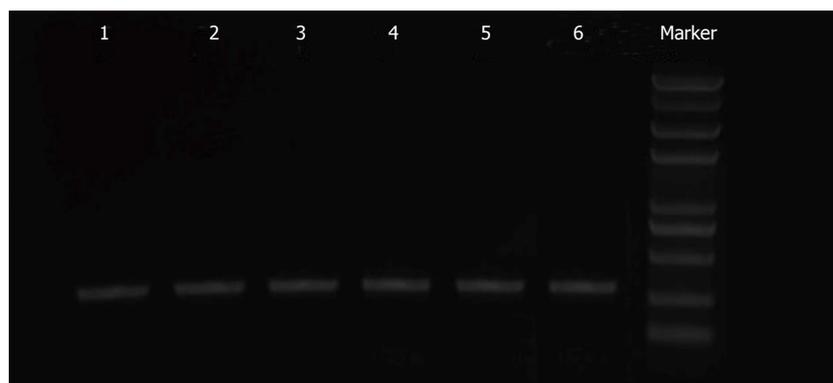


Figure 1 Electrophoresis of extracted DNA in the Goto-Kakizaki-Roux-en-Y gastric bypass surgery group.

surgery, fasting GLP-1 in the GK-RYGB surgery group was significantly higher than in the GK-Sham group ($P < 0.05$) but was comparable to that in the WS-Sham group ($P > 0.05$) (Table 4).

A. muciniphila: The extracted bacterial DNA is shown in Figure 1. The marker was a 100-bp ladder DNA marker with clear bands, suggesting that the extracted DNA was legible.

Amount of *A. muciniphila* before and after surgery in different groups

At 1 wk before surgery, the amount of *A. muciniphila* in GK rats was significantly lower than that in Wistar rats ($P < 0.05$). At 4 wk after surgery, the amount of *A. muciniphila* was 9.34 ± 0.18 copies per g stool in the GK-RYGB surgery group, which was significantly higher than that before surgery and that in the WS-Sham group and GK-Sham group ($P < 0.05$). This suggests that the amount of *A. muciniphila* in rat stool increases in GK rats after surgery (Table 5).

Correlation between intestinal *A. muciniphila* and serum GLP-1

The amount of *A. muciniphila* served as an independent variable and serum GLP-1 content as a dependent variable. A scatterplot (Figure 2) of the results showed a linear relationship between serum GLP-1 and the amount of *A. muciniphila*, and spots were found mainly within the 95%CI. Correlation analysis showed that r (the Pearson correlation coefficient) was 0.867, suggesting a significant positive correlation between serum GLP-1 and the amount of *A. muciniphila*. The amount of *A. muciniphila* was used as an independent variable and

the level of serum GLP-1 was used as a dependent variable for univariate analysis, and the results showed that $P = 0.00$.

DISCUSSION

The effectiveness of surgery in the treatment of T2DM has been widely accepted after 20 years of clinical practice, and surgery has been included in guidelines for the treatment of DM^[19,20]. Previous studies have shown that RYGB surgery can improve blood glucose with definite efficacy in obese patients with T2DM^[21-24] and that this effect is also long lasting^[14]. Moreover, this surgery may be better to mitigate T2DM-related complications compared to pharmacotherapy^[11,13,25].

Although surgery has favorable therapeutic efficacy for T2DM, the specific mechanism of action is still unclear and may be related to changes in gastrointestinal hormones^[26,27]. One of the widely studied gastrointestinal hormones is GLP-1, which, with its receptor GLP-1R, has been a focus of studies in internal medicine. To date, GLP-1 analogues (e.g., liraglutide) and GLP-1R agonists (e.g., exenatide) have been developed and used in clinical practice with favorable efficacy^[28]. Currently, published animal experiments^[26] and clinical trials^[29] have demonstrated that GLP-1 increases after RYGB surgery. In the present study, our results also showed that GLP-1 secretion increases in GK rats after RYGB surgery. GLP-1 acts mainly to increase glucose-induced insulin secretion, increase glucagon secretion, improve insulin sensitivity, promote regeneration of islet β cells, and reduce their apoptosis^[30], leading to reduction in blood glucose. In our study, the results showed that FBG remained unchanged in GK rats after RYGB surgery, but

Table 3 Homeostasis model assessment-insulin resistance in different groups before and after surgery

Group	Presurgery	4 wk postsurgery
GK-RYGB	4.72 ± 0.34 ^a	4.07 ± 0.30 ^{a,c}
GK-Sham	4.80 ± 0.51 ^a	4.83 ± 0.54
WS-Sham	3.75 ± 0.07	3.74 ± 0.20

^a*P* < 0.05 *vs* WS-Sham group; ^c*P* < 0.05 *vs* GK-Sham group; ^e*P* < 0.05 *vs* presurgery. GK: Goto-Kakizaki; RYGB: Roux-en-Y gastric bypass; WS: Wistar.

Table 4 Serum glucagon-like peptide-1 in different groups before and after surgery (x ± s, pmol/L)

Group	Presurgery	4 wk postsurgery
GK-RYGB	21.01 ± 0.90 ^a	34.36 ± 1.46 ^{c,e}
GK-Sham	21.19 ± 0.53 ^a	24.98 ± 2.63 ^a
WS-Sham	29.31 ± 1.51	32.13 ± 1.52

^a*P* < 0.05 *vs* WS-Sham group; ^c*P* < 0.05 *vs* GK-Sham group; ^e*P* < 0.05 *vs* presurgery. GK: Goto-Kakizaki; RYGB: Roux-en-Y gastric bypass; WS: Wistar.

Table 5 Amount of *Akkermansia muciniphila* in different groups before and after surgery (log10 copies/g)

Group	Presurgery	4 wk postsurgery
GK-RYGB	7.85 ± 0.09 ^a	9.34 ± 0.18 ^{a,c,e}
GK-Sham	7.79 ± 0.08 ^a	7.82 ± 0.09 ^a
WS-Sham	8.51 ± 0.08	8.82 ± 0.06

^a*P* < 0.05 *vs* WS-Sham group; ^c*P* < 0.05 *vs* GK-Sham group; ^e*P* < 0.05 *vs* presurgery. GK: Goto-Kakizaki; RYGB: Roux-en-Y gastric bypass; WS: Wistar.

serum insulin increased after intragastric administration of glucose, suggesting that RYGB surgery may elevate glucose-induced insulin secretion *via* increasing GLP-1 secretion. In addition, our results revealed that HOMA-IR in GK rats after RYGB surgery was significantly lower than that before surgery and that in the GK-Sham group, indicating that RYGB surgery can improve insulin sensitivity *via* GLP-1 induction in GK rats.

The mechanism whereby RYGB increases GLP-1 secretion is still unclear. Evidence suggests that early contact of the distal small intestine with food after food intake following RYGB surgery may induce the secretion of GLP-1^[27], but studies to date have not elucidated the mechanisms whereby food induces GLP-1 secretion. Thus, the role of food in increased GLP-1 secretion still requires clarification. Tolhurst *et al.*^[31] speculated that intestinal microorganisms were closely related to GLP-1 and their metabolites (such as short-chain fatty acids) may act on the corresponding receptors on L cells to stimulate GLP-1 secretion. However, whether intestinal microorganisms induce GLP-1 secretion after RYGB surgery and the putative mechanisms of this action are still poorly understood.

Studies^[29,32] have confirmed that intestinal microor-

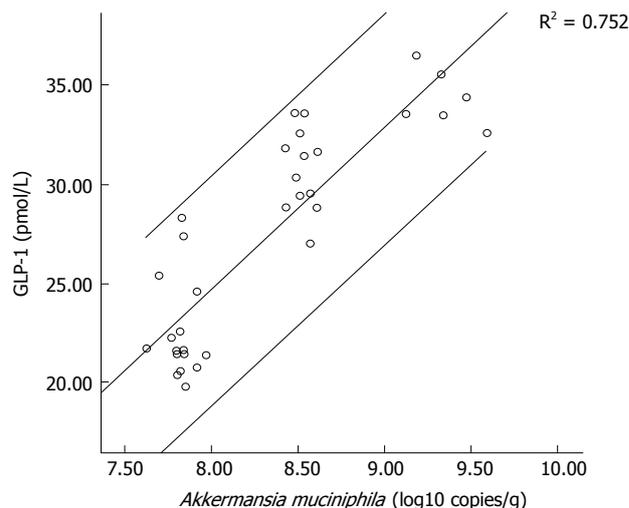


Figure 2 Scatterplot of the amount of *Akkermansia muciniphila* vs levels of glucagon-like peptide-1. GLP-1: Glucagon-like peptide-1.

ganisms may affect body weight and blood glucose. *A. muciniphila* has been a focus in current studies because apparently it can reduce body weight and improve blood glucose as well as insulin resistance^[15-18]. However, the role of *A. muciniphila* in the therapeutic effects of RYGB surgery on T2DM have never been studied. In this study, the results showed that the amount of *A. muciniphila* in the stool of GK rats was significantly lower than that in Wistar rats before surgery, suggesting that the amount of *A. muciniphila* in diabetic rats was lower than that in healthy rats. At 4 wk after RYGB surgery, the amount of *A. muciniphila* increased significantly in GK rats, suggesting that RYGB surgery can increase the intestinal amount of *A. muciniphila* in GK rats. Hansen *et al.*^[33] speculated that 2-oleoylglycerol, a metabolite produced by intestinal *A. muciniphila*, may stimulate the secretion of gastrointestinal hormones, especially GLP-1, in L cells in the distal small intestine. In the present study, correlation analysis and regression analysis confirmed that the amount of *A. muciniphila* was positively correlated with that of GLP-1. Thus, we speculate that RYGB surgery not only increases the intestinal amount of *A. muciniphila* but also elevates GLP-1.

Our findings indicate that GLP-1 increases after RYGB surgery, which then elevates serum insulin after intragastric administration of glucose and improves insulin resistance and effectively reduces blood glucose in GK rats. The increased intestinal amount of *A. muciniphila* following RYGB surgery may contribute to the elevated secretion of GLP-1 after RYGB surgery. But, the modality whereby *A. muciniphila* increases as a result of RYGB still remains undefined, nor is clear how GLP-1 increases, which needs further research in the future.

COMMENTS

Background

Type 2 diabetes mellitus (T2DM) is an endocrine and metabolic disease, which has become a significant worldwide health problem. According to the International

Diabetes Federation, T2DM has become the third most common type of non-infectious disease worldwide following cardiovascular disease and cancer. The conventional therapies include diet adjustment, exercise, self-monitoring of blood glucose and drug. But none of these therapies is adequately effective in maintaining long-term glycemic control and preventing complications. Therefore, an effective treatment for T2DM is urgently required. Of the current treatments for T2DM, Roux-en-Y gastric bypass (RYGB) surgery is considered to be an effective long-term treatment. However, the mechanisms that drive these outcomes remain incompletely understood.

Research frontiers

Recently, T2DM is characterized by altered gut microbiota, and *Akkermansia muciniphila* (*A. muciniphila*) is one of substantial gut microbiota. *A. muciniphila* which belongs to the phylum Verrucomicrobia, has been identified as a mucin-degrading bacteria that resides in the mucus layer, and it is the dominant human bacterium that abundantly colonizes this nutrient-rich environment. And its abundance inversely correlates with body weight and T2DM in mice and humans. *A. muciniphila* becomes hot gut microbiota in basic research for diabetes.

Innovations and breakthroughs

In this study, the authors used Goto-Kakizaki (GK) rats, a genetic model of T2DM, to investigate whether the RYGB surgery influenced the population of *A. muciniphila*. The authors' findings indicate that glucagon-like peptide-1 (GLP-1) increases after RYGB surgery, which then elevates serum insulin after intragastric administration of glucose and improves insulin resistance and effectively reduces blood glucose in GK rats. The increased intestinal amount of *A. muciniphila* following RYGB surgery may contribute to the elevated secretion of GLP-1 after RYGB surgery.

Applications

The authors' findings indicate that GLP-1 increases after RYGB surgery, and effectively reduces blood glucose in GK rats. The increased intestinal amount of *A. muciniphila* following RYGB surgery may contribute to the elevated secretion of GLP-1 after RYGB surgery. The authors' findings may explain the mechanism that RYGB surgery can improve blood glucose with definite efficacy in obese patients with T2DM.

Peer-review

The authors need to be congratulated for their innovative research study on relevant clinical topic. The experimental work has been scheduled and performed according to the current principles of the experimental project. The manuscript itself is concise, written in an elegant style according to all requirements of original contribution.

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Retrospective Cohort Study

Laparoscopic approach in complicated diverticular disease

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Abstract

AIM: To analyze the results of laparoscopic colectomy in complicated diverticular disease.

METHODS: This was a retrospective cohort study conducted at an academic teaching hospital. Data were collected from a database established earlier, which comprise of all patients who underwent laparoscopic colectomy for diverticular disease between 2000 and 2013. The series was divided into two groups that were compared: Patients with complicated disease (abscess, perforation, fistula, or stenosis) (G1) and patients undergoing surgery for recurrent diverticulitis (G2). Recurrent diverticulitis was defined as two or more episodes of diverticulitis regardless of patient age. Data regarding patient demographics, comorbidities, prior abdominal operations, history of acute diverticulitis, classification of acute diverticulitis at index admission and intra and postoperative variables were extracted. Univariate analysis was performed in both groups.

RESULTS: Two hundred and sixty patients were included: 28% (72 patients) belonged to G1 and 72% (188 patients) to G2. The mean age was 57 (27-89) years. The average number of episodes of diverticulitis before surgery was 2.1 (r 0-10); 43 patients had no

previous inflammatory pathology. There were significant differences between the two groups with respect to conversion rate and hospital stay (G1 18% *vs* G2 3.2%, $P = 0.001$; G1: 4.7 d *vs* G2 3.3 d, $P < 0.001$). The anastomotic dehiscence rate was 2.3%, with no statistical difference between the groups (G1 2.7% *vs* G2 2.1%, $P = 0.5$). There were no differences in demographic data (body mass index, American Society of Anesthesiology and previous abdominal surgery), operative time and intraoperative and postoperative complications between the groups. The mortality rate was 0.38% (1 patient), represented by a death secondary to septic shock in G2.

CONCLUSION: The results support that the laparoscopic approach in any kind of complicated diverticular disease can be performed with low morbidity and acceptable conversion rates when compared with patients undergoing laparoscopic surgery for recurrent diverticulitis.

Key words: Complicated diverticulitis; Laparoscopy; Recurrent diverticulitis; Sigmoid colectomy; Outcomes

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Core tip: Several studies have shown clear benefits of the use of laparoscopic colectomy in diverticular disease. However, this approach is not well defined in patients with complicated disease. In the current study, the results support that laparoscopic surgery can be performed with acceptable results for any indication of diverticular disease.

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INTRODUCTION

Traditionally, the surgical treatment of complicated diverticular disease involved the sigmoid resection and Hartmann's procedure. Over time, many authors demonstrated good results with the use of primary anastomosis with or without protective ostomy^[1-3]. Today, it is clear that the laparoscopic approach has become the gold standard for the surgical treatment of patients with recurrent diverticulitis^[4,5]. However, the application of this procedure in complicated diverticular disease remains controversial. Even more questionable is the use of the technique in patients with complicated diverticulitis on the emergency setting and the possibility of sigmoid resection in one step. The main objective of this study was to evaluate the results of the laparoscopic approach in patients with any type of complicated diverticular

disease.

MATERIALS AND METHODS

Data were collected prospectively from all patients who underwent laparoscopic sigmoid resection for diverticular disease between 2000 and 2013. Those patients with any other colorectal disease were excluded. All surgeries were performed or supervised by two surgeons with similar experience in laparoscopic surgery.

The series was divided into two groups: Patients with complicated diverticular disease (G1) and patients operated for recurrent diverticulitis without evidence of any complication (G2).

Patients with at least one of the following signs were considered to have a complicated diverticular disease: Presence of chronic abscess or severe sequelar inflammation at the time of surgery; fistula; stenosis; or free perforation with purulent or faecal peritonitis.

Demographic characteristics, previous abdominal surgeries and the number of previous episodes of diverticulitis were considered for analysis. Intraoperative variables (e.g., operative time, intraoperative complications and conversion rate) were evaluated. Finally, recovery parameters, length of hospital stay and morbidity and mortality were studied.

Conversion was considered when an unplanned incision was made or when other maneuvers beyond the extraction of the specimen were performed over the planned incision^[6].

Complications were categorized according to the classification of Dindo *et al.*^[7]. Mortality related with the procedure was considered when it occurred during hospitalization or within 30 d after surgery.

Statistical analysis

G1 to G2 were compared using univariate statistical analysis. The student's *t*-test or ANOVA were used to analyze continuous variables, whereas the χ^2 or Fisher test were used for categorical variables.

RESULTS

In a 14-year period, 260 laparoscopic sigmoid resections were performed due to diverticular disease. Seventy-two (28%) patients were included in G1 and 188 (72%) in G2.

The patients characteristics from G1 were: 31 (43%) with pericolic or pelvic abscesses; 21 (29%) with perforation; 12 (17%) with fistulae (9 colovesical and 3 colocutaneous); and 8 (11%) with stenosis.

Procedures performed in G1 were: 65 (90%) sigmoid resections with primary anastomosis; 5 (7%) sigmoid resections with primary anastomosis and protective stoma and 2 (3%) Hartmann's procedures. Fifty-two patients (72%) were operated on emergency setting without significant differences when compared with patients operated for subacute disease. In G2, sigmoid resection with primary anastomosis was performed in all cases.

Table 1 Preoperative variables *n* (%)

Examined variables	Complicated diverticular disease (G1) [<i>n</i> = 72 (28)]	Uncomplicated diverticular disease (G2) [<i>n</i> = 188 (72)]	<i>P</i> value
Sex			0.474 (N/S)
Females	24 (33)	73 (39)	χ^2
Males	48 (67)	115 (61)	
Age (yr)	58 ± 12 (29-84)	57 ± 11 (27-89)	0.178 (N/S)
			<i>t</i> -test
BMI (kg/m ²)	26 ± 4 (19-41)	26 ± 4 (17-41)	0.112 (N/S)
			<i>t</i> -test
ASA			
I	16 (22)	50 (27)	0.057 (N/S)
II	47 (65)	128 (68)	χ^2
III	9 (13)	10 (5)	
Previous abdominal surgery	37 (51)	107 (57)	0.605 (N/S)
			χ^2
Previous episodes of diverticulitis	1.36 ± 1.4 (0-5)	2.42 ± 1.3 (0-10)	< 0.05
			<i>t</i> -test

N/S: No statistical significance; BMI: Body mass index; ASA: American Society of Anesthesiology.

Table 2 Intraoperative variables *n* (%)

Examined variables	Complicated diverticular disease (G1) [<i>n</i> = 72 (28)]	Uncomplicated diverticular disease (G2) [<i>n</i> = 188 (72)]	<i>P</i> value
Operative time (min)	193 ± 66 (80-345)	156 ± 58 (65-400)	< 0.05
			<i>t</i> -test
Intra-operative complications	3 (4)	4 (2)	0.892 (N/S)
	2 iatrogenic colonic/rectal perforation 1 bladder injury	1 epigastric vessels lesion 2 spleen injuries 1 ureteric injury	χ^2
Conversion rate	13 (18)	6 (3)	< 0.05
			χ^2
Length of colon resected (cm)	23 ± 8 (11-4.5)	22 ± 8 (10-53)	0.531 (N/S)
			<i>t</i> -test

N/S: No statistical significance.

Demographic data were homogeneous between the groups but G2 patients presented more previous episodes of diverticulitis [G1: 1.36 ± 1.4 (0-5) vs G2: 2.42 ± 1.3 (0-10), *P* < 0.05] (Table 1).

G1 patients had longer operative time [G1: 193 ± 66 (80-345) min vs G2: 156 ± 58 (65-400) min, *P* < 0.05] and higher conversion rate [G1: 13/72 (18%) vs G2: 6/188 (3.2%), *P* < 0.05]. The reasons for conversion in G1 included: Presence of a bulky inflammatory tumor (5 cases); adhesions (3 cases); otherwise unclear anatomy (2 cases); hemorrhage (2 cases); and bladder injury (1 case). In G2, the causes of conversion were: Inability to identify anatomy (4 cases); spleen injury (1 case); and ureteric injury (1 case).

In patients with complicated diverticular disease, a sigmoid resection with primary anastomosis without protective stoma was performed in 65 cases (90%). In 5 cases of purulent perforation (7%), a sigmoid resection with primary anastomosis with protective stoma was necessary, whereas in 1 case of stenosis and other case of fecal peritonitis a Hartmann procedure was the surgery of choice. In 29 (40%) of these cases, a splenic flexure mobilization was performed. In patients with uncomplicated diverticular disease, a sigmoid resection

with primary anastomosis without protective stoma was performed in all cases (*P* < 0.05), with necessity of splenic flexure mobilization in 73 cases (39%, *P* = 0.887).

There were no differences in the rate of intraoperative complications (Table 2). In two cases of G1, an iatrogenic bowel perforation was found without necessity of conversion for its resolution. However, in one case of bladder injury, conversion was required. The intraoperative complications in G2 were: 1 epigastric vessels lesion; 2 spleen injuries; and 1 ureteric lesion. A conversion was necessary in one spleen injury and in the ureteric lesion.

Table 3 shows the variables of postoperative recovery. Patients in G1 had slower intestinal transit slower oral intake comparing with G2. For these reasons, among others, the hospital stay was longer in this group [G1: 4.7 ± 3.1 (2-15) vs G2: 3.3 ± 1.8 (1-17) d, *P* < 0.05]. The postoperative complication rate was also higher in G1 [G1: 16/72 (22%) vs G2: 23/188 (12%), *P* < 0.05], but there were no major complications in assessing differences (Grade III, IV and V) (Table 4). The mortality rate was 0.38% (1 patient), represented by a death secondary to septic shock in G2 without evidence of anastomotic fistula. There was no reason to believe that the death was related to the procedure.

Table 3 Gastrointestinal recovery

Examined variables	Complicated diverticular disease (G1) <i>n</i> : 72 (28%)	Uncomplicated diverticular disease (G2) <i>n</i> : 188 (72%)	<i>P</i> value
Intake > 1000 mL	Day 2.1 ± 2.1 (0-10)	Day 1 ± 0.8 (0.5)	< 0.05 <i>t</i> -test
Intake normal diet	Day 3.1 ± 2.2 (1-11)	Day 1.8 ± 1 (0-7)	< 0.05 <i>t</i> -test
Bowel sound +	Day 1 ± 0.6 (0-3)	Day 0.6 ± 0.6 (0-4)	< 0.05 <i>t</i> -test
Gases +	Day 1.9 ± 1.4 (0-7)	Day 1.4 ± 0.7 (0-5)	< 0.05 <i>t</i> -test
Length of stay (d)	4.7 ± 3.1 (2-15)	3.3 ± 1.8 (1-17)	< 0.05 <i>t</i> -test

Table 4 Postoperative complications *n* (%)

Examined variables	Complicated diverticular disease (G1) [<i>n</i> = 72 (28)]	Uncomplicated diverticular disease (G2) [<i>n</i> = 188 (72)]	<i>P</i> value
Grade I	8 (11.1) 1 urinary retention 1 vomits 1 surgical site hematoma 5 ileus > 72 h	6 (3.19) 1 urinary retention 2 vomits 2 surgical site hematoma 1 ileus	< 0.05 χ^2
Grade II	6 (8.3) 1 phlebitis 4 surgical site infection 1 fever syndrome with normal CT	9 (4.78) 4 surgical site infection 2 urinary infection 3 fever syndrome with normal CT	0.426 (N/S) χ^2
Grade IIIA	0 (0)	1 (0.53) 1 pancreatic fistula	0.610 (N/S) χ^2
Grade IIIB	2 (2.7) 2 anastomotic leak	6 (3.1) 2 hemoperitoneum 4 anastomotic leak	0.897 (N/S) χ^2
Grade IV	0 (0)	0 (0)	-
Grade V	0 (0)	1 (0.53)	0.610 (N/S) χ^2
Total	16 (22)	23 (12)	0.053 (N/S) χ^2

N/S: No statistical significance; CT: Computed tomography.

DISCUSSION

Historically, the surgical management of complicated diverticular disease has consisted of laparotomy, colonic resection and end-colostomy (Hartmann's procedure). Today, controversy exists regarding the role of primary colorectal anastomosis with or without fecal diversion^[3] and the feasibility of the use of the laparoscopic approach.

Several series have demonstrated that laparoscopic sigmoid resection can be performed with acceptable morbidity and mortality for both inflammatory and neoplastic diseases^[8-10]. The laparoscopic approach demonstrated several advantages, such as smaller wounds, shorter ileus, early resumption of dietary intake and reductions in hospital stay^[11]. Furthermore, as shown by Jensen *et al.*^[12], it results in decreased costs and equivalent quality of life, making it the preferred approach in suitable patients. Laparoscopic sigmoidectomy has been shown to be safe, feasible and equivalent to open surgery for uncomplicated diverticulitis^[4,5,13]. When expertise is available, the laparoscopic approach to elective colectomy is preferred^[14].

Since the minimally invasive approach offers important benefits, laparoscopic sigmoid resection due to recurrent diverticulitis is one of the most common procedures performed in colorectal surgery.

A prospective study published by Alves *et al.*^[5] comparing open vs laparoscopic elective sigmoidectomy for uncomplicated diverticular disease found that the minimally invasive approach has a low postoperative complications rate, with a conversion rate of 15.3%, whereas the overall morbidity rate was 16%.

A recent randomized controlled trial by Klarenbeek *et al.*^[15] comparing laparoscopic vs open sigmoidectomy for diverticular disease has shown significant advantages of laparoscopic surgery, with a 27% reduction in major morbidity for patients who underwent this approach.

The present series shows favorable results in patients who underwent laparoscopic resection for uncomplicated diverticulitis and found a 3% conversion rate to open surgery, with a 12% of morbidity rate.

Currently, the operative management of complicated diverticulitis has progressed to include laparoscopic surgical techniques. In 1978, Hinchey's classification was

described to determine which patients should undergo primary anastomosis after resections and this remains the system used in the majority of the publications^[16]. As shown in a retrospective study published by Li *et al*^[17], there has been an increase in the use of nonoperative and minimally invasive strategies in treating patients with a first episode of acute diverticulitis. However, the Hartmann procedure remains the most frequently used urgent operative approach^[17]. The laparoscopic approach has demonstrated acceptable morbidity and mortality rates, although the frequency of conversion increases with the severity of adhesions and the presence of fistulas or abscesses^[18,19]. Recently, some studies have been published that include patients with complicated diverticular disease who underwent laparoscopic sigmoid resections. These studies report a conversion rate of between 11.5% and 37% and a postoperative complication rate of between 11.5% and 28%^[20-22]. In the present series no differences in global morbidity were identified between the groups.

The safety of laparoscopic management for complicated and fistulizing diverticular disease has been previously addressed^[21,23]. Despite the fact that laparoscopic resection for complicated disease would be expected to be challenging, reports have demonstrated no differences in operative time or conversion rate^[24].

Few groups have reported their experience in laparoscopic management of colovesical or colovaginal fistula^[23,25,26]. These cited studies did not identify differences in hospital stay or postoperative complications when compared to open approach. Conversion rate ranged between 7% to 25%^[27,28]. The present series included 9 patients with colovesical and 3 patients with colocutaneous fistulas. All of these patients were successfully operated by laparoscopy.

Regarding colonic stenosis, studies have reported favorable outcomes but with an increased conversion rate^[29,30]. In this series eight patients were treated successfully due to stenosis, with a conversion rate of 12.5%.

Historically, the treatment of perforated diverticulitis was performed in stages, as in Hartmann's procedure, which remains the procedure of choice in Hinchey III-IV diverticulitis and is considered the best therapeutic option by many surgeons^[31-35]. However, this technique has a low level of recommendation based on the literature evidence. Moreover, a further disadvantage of this approach is that the majority of these patients will never have a stoma reversal^[35,36].

Recently, several studies have demonstrated the benefits of laparoscopic sigmoid resection with primary anastomosis without protective stoma^[37-40].

Richter *et al*^[2] reported that colon resections with primary anastomosis could be performed with high degree of safety in 90% of patients, although the risk increases in immunosuppressed patients or in patients with kidney or liver chronic failure.

A systematic review found no significant differences in mortality rate or other complications for patients with

Hinchey III-IV who underwent Hartmann's procedure or resection with primary anastomosis^[38].

In our series, 11 Hinchey III-IV patients were treated by laparoscopic sigmoid resection without any stoma protection and only one of them was converted to open surgery. The postoperative complication rate was 10%. Neither anastomotic leaks nor mortality rate were registered.

Recently, other groups have described the use of laparoscopic peritoneal lavage (LPL) and drainage for diverticular peritonitis, with or without posterior elective surgery^[41-44]. Karoui *et al*^[45] reported that LPL in Hinchey III complicated diverticulitis is an effective and safe alternative to colon resections with primary anastomosis or protective stoma, and demonstrate that it shortens the hospital stay, avoids a stoma in the majority of patients and decreases postoperative abdominal morbidity. Rogers *et al*^[46] reported lower mortality and morbidity than those in whom resection was considered necessary. This procedure appears promising in selected patients. However, more studies comparing LPL against laparoscopic sigmoid resection with primary anastomosis should be performed before clinical recommendations can be given.

COMMENTS

Background

Diverticular disease is among the most common diseases in developed countries. It is estimated that approximately 20% of patients with diverticulosis develop diverticulitis over their lifetime. Surgical treatment can be evaluated emergently or electively, based on the stage of the disease and clinical presentation. Laparoscopic surgery is now widely accepted for the treatment of elective diverticular disease. The benefits include reduced blood loss, pain, morbidity and length of stay. Its use for complicated diverticulitis remains controversial.

Research frontiers

In the present study, the authors reported the results of seventy-two patients with complicated diverticular disease treated by laparoscopic surgery.

Innovations and breakthroughs

In literature the laparoscopic surgery is widely recommended for diverticular disease. However, this approach is not well defined in patients with complicated disease.

Applications

The study suggests that the laparoscopic approach can be applied for the patients with any kind of complicated diverticulitis.

Terminology

A diverticulum is a saclike protrusion in the colonic wall that develops as a result of herniation of the mucosa and submucosa through points of weakness in the muscular wall of the colon. Diverticulitis describes the presence of an inflammatory process associated with diverticula. Complicated diverticular disease is defined as diverticulitis with associated abscess, phlegmon, fistula, obstruction, bleeding, or perforation.

Peer-review

This paper gives an accurate description about the role that the laparoscopy may have in the treatment of complicated acute diverticulitis, which frequency is constantly increasing in our society. This paper well structured and presented, giving to the reader, the opportunity to easily understand it.

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Retrospective Study

Over-the-scope clips in the treatment of gastrointestinal tract iatrogenic perforation: A multicenter retrospective study and a classification of gastrointestinal tract perforations

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Institutional review board statement: This is a retrospective study, a case-collection. Data of the patients treated were analyzed from the clinical data of our hospitals and OTSC clip were used not for the aim of the study. The aim of the study was only to review retrospective data from the clinical records of the patients. Then, we have no need of IRB statement.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No conflicts of interest to declare.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at b_mangiavillano@hotmail.com. Participants informed consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To determine the outcome of the management of iatrogenic gastrointestinal tract perforations treated by over-the-scope clip (OTSC) placement.

METHODS: We retrospectively enrolled 20 patients (13 female and 7 male; mean age: 70.6 ± 9.8 years) in eight high-volume tertiary referral centers with upper or lower iatrogenic gastrointestinal tract perforation treated by OTSC placement. Gastrointestinal tract perforation could be with oval-shape or with round-shape. Oval-shape perforations were closed by OTSC only by suction and the round-shape by the "twin-grasper" plus suction.

RESULTS: Main perforation diameter was 10.1 ± 4.3 mm (range 3-18 mm). The technical success rate was 100% (20/20 patients) and the clinical success rate was 90% (18/20 patients). Two patients (10%) who did not have complete sealing of the defect underwent surgery. Based upon our observations we propose two types of perforation: Round-shape "type-1 perforation" and oval-shape "type-2 perforation". Eight (40%) out of the 20 patients had a type-1 perforation and 12 patients a type-2 (60%).

CONCLUSION: OTSC placement should be attempted after perforation occurring during diagnostic or therapeutic endoscopy. A failed closure attempt does not impair subsequent surgical treatment.

Key words: Over-the-scope clip; OVESCO; Perforation; Gastrointestinal tract

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Core tip: The aim of this study was to determine the outcome of over-the-scope clip management of patients with iatrogenic gastrointestinal tract perforations in eight high-volume tertiary referral centers. Technical success was of 100% and clinical success of 90%. Moreover, after evaluating our results we did a classification of the iatrogenic perforation: We defined the perforation with round-shape "type-1 perforation" and the oval-shape one as "type-2 perforation".

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INTRODUCTION

Iatrogenic perforations that occur during endoscopic procedures are generally managed surgically^[1,2]. Some authors prefer a non-surgical approach in selected cases, despite the considerable risk of morbidity and mortality^[3,4]. Most cases of iatrogenic perforation occur during therapeutic endoscopic procedures, including bilio-pancreatic procedures, particularly in the context of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for the treatment of superficial neoplasia, but there are also descriptions of cases occurring during diagnostic upper or lower gastrointestinal (GI) endoscopy^[5-7]. The reported incidence of perforation during diagnostic endoscopy is between 0.01% and 0.6% while that during therapeutic endoscopy is between 0.6% and 5.5%. Using an over-the-scope clip (OTSC) it would be possible to close these perforations immediately during the endoscopy.

Through-the-scope (TTS) clip closure of endoscopic perforations has been described in the literature since 1997^[8,9]. However, there are limitations to closing full-thickness defects with TTS clips. The closure is confined to the mucosal and submucosal layers, with relatively low closure force, and the opening span between the jaws is restricted. A new device, the OTSC system (Ovesco Endoscopy AG, Tübingen, Germany) is designed to create full-thickness closure by using teeth arranged in the shape of a bear trap and has a simple method of application. The OTSC is made of a super-elastic, shape-memory alloy (nitinol), which takes its former, unbent shape after the clip is released, and thus exerts constant compression on the tissue between the jaws of the clip. von Renteln *et al.*^[10] showed, in a porcine model, that the OTSC clips provide a full-thickness closure of perforations.

Although the use of an OTSC has been well established during natural orifice transluminal endoscopic surgery^[11] and treatment of bleeding^[12-14] in recent years some reports have been published describing the usefulness of OTSC in closing acute iatrogenic perforations, first in animal models and then in humans^[15-17].

The aim of our study was to determine the outcome of the management of iatrogenic gastrointestinal tract perforations treated by OTSC.

MATERIALS AND METHODS

Data were retrospectively collected from eight high-volume tertiary referral endoscopy units. Data from all patients undergoing immediate or 24 h - delayed OTSC placement for acute iatrogenic perforation, during diagnostic or therapeutic endoscopy or other therapeutic maneuvers, in the period between December 2012 and January 2015 were reviewed and reported as

Table 1 Site, type of procedure being during occurred gastrointestinal perforation and type of applied over-the-scope clip

Number of patients	20 (13 F and 7 M)
Site	Esophagus (<i>n</i> = 1) Stomach (<i>n</i> = 3) Duodenum (<i>n</i> = 4) Jejunum (<i>n</i> = 2) Cecum (<i>n</i> = 1) Ascending colon (<i>n</i> = 1) Sigmoid colon (<i>n</i> = 7) Rectum (<i>n</i> = 1)
Procedure	Diagnostic colonoscopy (<i>n</i> = 7) EUS (<i>n</i> = 3) EMR (<i>n</i> = 4) ERCP (<i>n</i> = 3) ESD (<i>n</i> = 2) Tracheostomy (<i>n</i> = 1)
OTSC-type	9/t mm (<i>n</i> = 2) 10/t mm (<i>n</i> = 5) 11/a mm (<i>n</i> = 1) 11/t mm (<i>n</i> = 12)

OTSC: Over-the-scope clip; F: Female; M: Male; EUS: Endoscopic ultrasound; EMR: Endoscopic mucosal resection; ERCP: Endoscopic retrograde cholangio-pancreatography; ESD: Endoscopic submucosal dissection; a: Atraumatic teeth; t: Traumatic teeth.

mean \pm SD. All endoscopic procedures were carried out in patients who were conscious or deeply sedated with anesthesiologist support. The length of follow-up was of 3-mo.

Two different techniques were used for placing the OTSC at the site of the perforation: Only aspirating the defect inside the cap in which OTSC is mounted, or using the “twin-grasper” (Figure 1). The twin-grasper is generally used when the defect assumed a round-shape and only aspiration was used when oval-shape.

The twin-grasper, deployed through the working channel of the scope, was used to approximate the two edges of tissue, withdrawing them inside the cap, before releasing the OTSC. The twin-grasper has two independently movable lateral arms, allowing the two edges of the perforation to be grasped at two different times. The twin-grasper ensures that all layers of the gastrointestinal wall are contained in the bite, creating a full-thickness closure of the perforation. The technical success or failure of the OTSC placement was documented by contrast X-ray.

Two different OTSC clip were used in the study: With traumatic and with atraumatic teeth. Traumatic OTSC differ from the atraumatic because of the presence of a spike over the tooth, allowing a best grasping of the tissue.

RESULTS

Of the 20 patients recruited, thirteen were female and seven male. Their mean age was 70.6 ± 9.8 years. The sites of perforation were esophagus (*n* = 1), stomach (*n* = 3), duodenum (*n* = 4), jejunum (*n* = 2), cecum



Figure 1 Over-the-scope clip pre-loaded on the scope with the “twin-grasper” (from ovesco.com).

(*n* = 1), ascending colon (*n* = 1), sigmoid colon (*n* = 7) and rectum (*n* = 1). Twelve of the perforations occurred during diagnostic endoscopy [3 during endoscopic ultrasound; 7 during colonoscopy in patients with diverticular disease and 2 in a Billroth II patient with a duodenoscope during identification of the papilla of Vater during endoscopic retrograde cholangiopancreatography (ERCP)] and eight during therapeutic endoscopy (4 during endoscopic EMR, 2 during ESD, one during therapeutic ERCP and one during tracheostomy). The diameters of the OTSC used were 9 mm (*n* = 2), 10 mm (*n* = 5) and 11 mm (*n* = 13). Mean perforation diameter was 10.1 ± 4.3 mm (range 3-18 mm). Seventeen of the 20 perforations were treated by application of OTSC immediately, and 3 the day after. Most of the used OTSC clips had traumatic teeth (19 traumatic and 1 atraumatic). Results are summarized in Table 1.

In all of the 20 patients the OTSC was placed successfully (100% technical success) with the correct deployment of the OTSC clip in the site of the defect. The clinical success rate was 90% (18 of the 20 patients) (Figure 2). In two of the patients (10%) the defect was not completely sealed. The first case of unsuccessful closure was a duodenal perforation, as shown by an X-ray transit study of the upper gastrointestinal tract performed immediately after placement of the OTSC, and the patient underwent duodenocephalo-pancreatectomy on the same day because of pancreatic head neoplasia. In both failures the OTSC was applied immediately after the recognition of the perforation. The second case was a sigmoid perforation during colonoscopy; the patient underwent sigmoid laparoscopic resection the day after because developing of peritonitis and the surgical specimen showed an incompletely sealed defect. No technical difficulties were encountered by the different endoscopists in placing the clips in different sites of the gut. No adverse events or deaths were recorded after OTSC placement during 3-mo follow-up and OTSC clips were not retrieved. Eight (40%) out of the 20 patients had a round-shape perforation and 12 patients an oval-shape one (60%). In all of 8 patients with round-shape perforation the defect was closed by twin-grasper plus suction and in all of the 12 patients with oval-shape

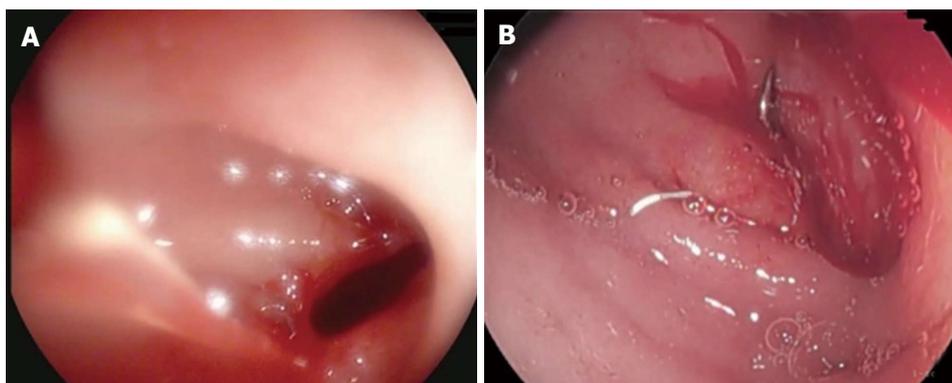


Figure 2 Duodenal type-2 perforations after endoscopic ultrasound (A) sealed by an over-the-scope clip (B).

Type-1 perforation (round-shape)	
Type-2 perforation (oval-shape)	

Figure 3 Mangiavillano's classification of gastrointestinal tract perforations.

perforation the defect was closed only by suction.

DISCUSSION

Iatrogenic perforation has always been considered a potential pitfall of diagnostic and therapeutic endoscopic maneuvers and a challenge to treat, especially before the advent of OTSC. In our series the technical success rate was 100% (20/20 patients) and the clinical success rate was 90% (18/20 patients). In two cases (10%) we did not have complete sealing of the perforation and the patients underwent surgery. Similar data were reported by Voermans *et al.*^[18] in the Clipper study, with a clinical success of 89%. Importantly, in this prospective multi-center study the mean endoscopic closure time was 5 min and 44 s ± 4 min and 15 s.

The efficacy of OTSC is based on the capacity of the clip to provide full-thickness closure of the perforation, a property well proven in some studies in animal models. At post-mortem examination executed after the OTSC placement, laparotomies revealed the full-thickness closure of the defect and peritoneum or small bowel included in the closure in some cases^[19-21].

On the analysis of our data we observed that most of the round-shape defects were closed with the aid of the "twin-grasper" and the oval-shape defect were closed by scope aspiration. On the basis of these results we can propose classification of perforations into two types: Round-shape "type-1 perforation" and oval-shape "type-2 perforation" (Figure 3). The "twin-grasper" plays an essential role in presence of large perforations for its capability to approximate the two edges of the defect

allowing a more secure grasp of the defect by the OTSC clip.

The use of suction has to be done in moderation, since excessive suction may grasp a good amount of the bowel wall and result in luminal restrictions. Excessive suction applied in the perforation area can also theoretically lead to catch of anatomical structures from outside of the bowel wall and involve them into the clipping site. The reason is the relatively low control of the tissue invagination process into the cap and the frequent limitation in visualization during suction. The suction should be used with caution in the colon, which has a relatively thin wall.

The role of OTSC in the management of endoscopic iatrogenic perforation has been discussed also in some case reports and small series. A case of spontaneous iatrogenic perforations sealed by OTSC clip have been described^[22]. Changela *et al.*^[23] recently described three cases of endoscopic perforation successfully treated by OTSC.

In 2010 Parodi *et al.*^[24] demonstrated the usefulness of the OTSC in a small series of patients with GI perforations up to 20 mm. One of the 10 treated cases was solved completely by placing two additional covered stent. More than one OTSC clip can be placed in presence of an iatrogenic perforation. A Japanese group published recently the possibility to apply as many as three OTSC clips in a series of 23 treated patients for bleeding, fistula and perforation of which 4 mucosal defect were observed during ESD^[25]. Moreover, a recent systematic review performed by Weiland *et al.*^[26] based on a small case series because of the lack of randomized and clinical trials in this field, showed OTSC clip placement to be a safe and effective method in the closure of GI tract defects, as perforations and acute anastomotic leak.

Gubler *et al.*^[27] in a series of 14 patients treated by OTSC clip placement for acute iatrogenic perforations of the GI tract demonstrated closure of the GI defects is possible in the presence of a perforation up to 30 mm diameter.

The largest study currently available in the literature about the use of OTSC in acute perforation by Haito-Chavez *et al.*^[28] including 188 patients with 48

perforations, with a median defect diameter of 7 mm. The rate of successful technical closure of the perforations was 97.5%, with an immediate clinical success of 94.9% and an overall long-term follow-up (207 d) rate of 90%; this rate was higher than that for closure of leaks (73.3%) and significantly higher than that for closure of fistulae (42.9%).

It is now established that the use of OTSC clips may reduce the rate of emergency surgery^[29] when an accidental perforation occurs and maybe considered as a mini-invasive endoscopic alternative to surgical repair. Recently, the position statement of the European Society of Gastrointestinal Endoscopy, has introduced the use of OTSC clips in GI tract acute iatrogenic perforations^[30]. However, despite the good results reported in the different published studies, OTSC clips are inappropriate in presence of delayed diagnosis by days or weeks, in individuals in whom there is significant peritoneal contamination, in long serosal tears of the colon, and perforations with endoscopic sphincterotomy where placement may result in sealing off the pancreatico-biliary orifices.

In our opinion, considering the high rates of technical and clinical success in sealing perforations of the gastrointestinal tract, OTSC placement should be performed to manage perforations occurring during diagnostic or therapeutic endoscopy or other therapeutic maneuvers, even in small endoscopic centers provided that the endoscopists' training is adequate. It allows a short stay in hospital and results in less hospital costs. Moreover, a failed attempt at OTSC deployment does not preclude subsequent surgical treatment. We suggest using the "twin-grasper" plus aspiration when a perforation type-1 occurs and only aspiration, if the endoscopist is confident with the OTSC system, in perforation type-2.

COMMENTS

Background

Gastrointestinal iatrogenic perforations are generally surgically managed. The reported incidence of perforation during diagnostic endoscopy is 0.01%-0.6%, while during therapeutic endoscopy is 0.6%-5.5%. Using an over-the-scope clip (OTSC) it is possible to close these perforations immediately.

Research frontiers

Through-the-scope (TTS) clip closure of endoscopic perforations has been described in the literature since 1997. However, there are limitations to closing full-thickness defects with TTS clips. The closure is confined to the mucosal and submucosal layers, with relatively low closure force, and the opening span between the jaws is restricted.

Innovations and breakthroughs

Iatrogenic perforation has always been considered a potential pitfall of diagnostic and therapeutic endoscopic maneuvers and a challenge to treat, especially before the advent of OTSC. In the authors' series the technical success rate was 100% (20/20 patients) and the clinical success rate was 90% (18/20 patients). Moreover, on the basis of the shape of the defect, the authors propose a classification of gastrointestinal (GI) tract perforations.

Applications

OTSC clip placement should be performed to manage perforations occurring during diagnostic or therapeutic endoscopy or other therapeutic maneuvers,

even in small endoscopic centers provided that the endoscopists' training is adequate. It allows a short stay in hospital and results in less hospital costs. Moreover, a failed attempt at OTSC deployment does not preclude subsequent surgical treatment.

Terminology

Iatrogenic perforations are defect of the entire GI wall (from mucosa to serosa) caused by diagnostic or therapeutic maneuvers.

Peer-review

The authors have performed an interesting study of 20 cases with iatrogenic gastrointestinal perforations treated by endoscopic over-the-scope-clipping with high success rate.

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Retrospective Study

Laparoscopic ventral mesh rectopexy for complete rectal prolapse: A retrospective study evaluating outcomes in North Indian population

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Abstract

AIM: To analyze the outcomes of laparoscopic ventral mesh rectopexy in the management of complete rectal prolapse (CRP) in North Indian patients with inherent bulky and redundant colon.

METHODS: The study was conducted at a tertiary health care center of North India. Between January 2010 and October 2014, 15 patients who underwent laparoscopic ventral mesh repair for CRP, were evaluated in the present study. Perioperative outcomes, improvement in bowel dysfunction or appearance of new complications were documented from the hospital records maintained prospectively.

RESULTS: Fifteen patients (9 female) with a median age of 50 years (range, 15-68) were included in the study. The median operative time was 200 min (range, 180-350 min) and the median post-operative stay was 4 d (range, 3-21 d). No operative mortality occurred. One patient with inadvertent small bowel injury required laparotomy on post-operative day 2. At a median follow-up of 22 mo (range, 4-54 mo), no prolapse recurrence was reported. No mesh-related complication was encountered. Wexner constipation score improved significantly from the preoperative value of 17 (range, 5-24) to 6 (range, 0-23) ($P < 0.001$) and the fecal incontinence severity index score from 24 (range, 0-53)

to 2 (range, 0-53) ($P = 0.007$). No *de novo* constipation or fecal incontinence was recorded during the follow-up. On personal conversation, all patients expressed satisfaction with the outcome of their treatment.

CONCLUSION: Our experience indicates that laparoscopic ventral mesh rectopexy is an effective surgical option for CRP in North Indian patients having a bulky redundant colon.

Key words: Redundant sigmoid; Constipation; Complete rectal prolapse; Ventral rectopexy; Indian population

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Core tip: Laparoscopic ventral rectopexy is a new modality for surgical correction of full thickness rectal prolapse. Avoiding a circumferential mobilization of rectum and reperitonealization of the mesh decreases the complications of rectal denervation. Authors have emphasized the results of laparoscopic ventral rectopexy on bulky and redundant sigmoid which is prevalent in Indian population. Patients were studied for a median duration of 22 mo. There were a few post-operative complications which were easily managed. Marked improvement in constipation and incontinence scores were reported. No *de novo* or worsening of existing constipation was recorded in any of the patients. In this study, no recurrence was evident during the follow-up.

Chandra A, Kumar S, Maurya AP, Gupta V, Gupta V, Rahul. Laparoscopic ventral mesh rectopexy for complete rectal prolapse: A retrospective study evaluating outcomes in North Indian population. *World J Gastrointest Surg* 2016; 8(4): 321-325 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i4/321.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i4.321>

INTRODUCTION

Complete rectal prolapse (CRP) is defined as circumferential and full-thickness protrusion of the rectum out of the anal verge. Surgical techniques described for CRP include anterior resection, rectopexy, or combined resection-rectopexy^[1]. Recently, minimally invasive technique for prolapse surgery has gained wide acceptance because of advantages like decreased operative pain, faster recovery and early discharge^[2]. Different laparoscopic techniques described are sutureless rectopexy, proctosigmoidectomy, and mesh rectopexy. In 2004, D'Hoore *et al*^[3] reported the long-term results of laparoscopic mesh ventral rectopexy (LMVR) with equivalent success rates and improved functional outcomes. Ventral rectopexy avoids the complications related to circumferential mobilization of rectum (*de novo* constipation) and colonic resection (anastomotic leak)^[4]. Data suggest LMVR without posterior rectal mobilization as the surgical procedure of choice for rectal prolapse as well as associated pelvic

organ prolapse^[5]. North Indian population being a predominantly vegetarian one is peculiar in having very bulky sigmoid colon. This also accounts for high incidence of sigmoid volvulus in this population. The aim of our study was to analyze the results of LMVR for complete prolapse in this patient group.

MATERIALS AND METHODS

Patients

Approval was obtained from the institutional ethics committee for performing the study. Informed consent was taken from all the patients before surgery, explaining them the benefits and procedure-related complications in detail. Only patients with CRP, confirmed on clinical examination and defecography were included in the study. Between January 2010 and October 2014, 25 patients with CRP were managed surgically, out of which 15 underwent LMVR. Primary objective of the study was anatomical correction of prolapse and secondary objective was evaluation of functional outcomes.

Pre-operative assessment

All patients were examined clinically, both in lying down and squatting position. If prolapse was not evident in resting position, patients were asked to "bear down" in squatting position. Barium enema examination was done in all patients to assess colon redundancy. Preoperative flexible sigmoidoscopy/colonoscopy was done to exclude organic disease. Data gathered from the prospectively maintained records included patient age, sex, duration of symptoms, associated other pelvic organ prolapse and presence of incontinence or constipation. Any previous surgical intervention for prolapse was recorded. Fecal incontinence was assessed using fecal incontinence severity index (FISI) and constipation by Wexner scoring^[6,7]. Patients with FISI score of more than 8 were considered to be incontinent whereas constipation was defined as Wexner score of more than 5. Objective assessment of patient satisfaction level following the procedure was done using a disease specific personal questionnaire (supplementary material).

Procedure

The surgery was performed under general anesthesia with patient in steep Trendelenburg position. The surgical technique was adopted from the original description by D'Hoore *et al*^[8]. Usually 4 ports were created. Supra-umbilical port was used as camera port. The retcosigmoid junction was identified and retracted to the left. A "J shaped" peritoneal incision was given extending from the sacral promontory to the anterior peritoneal reflection distally. Right hypogastric nerve and ureter were identified and safeguarded. With combined blunt and sharp dissection, a wide plane was developed in the Rectovaginal/rectovesical space. Any posterior rectal mobilization or lateral dissection was avoided at this stage. A strip of Prolene mesh (Ethicon Endosurgery, Blue Ash, Ohio, United States), trimmed to 3 cm × 17 cm,

was prepared and inserted into the pelvic cavity. One end of mesh was fixed to the anterior surface of the distal most part of the rectum using polypropylene sutures. Similarly, it was fixed to the lateral borders of the rectum. Care was taken to avoid full thickness bite into the rectal wall in order to prevent mesh contamination. Finally, the proximal end of mesh was fixed to the sacral promontory using Tackers (Covidien, Dublin, Ireland). Proximal traction on the rectum was avoided while fixing the mesh. In females, the distal part of the mesh was also fixed to the posterior vaginal fornix allowing the correction of a vaginal vault prolapse as well. The peritoneum was then re-approximated to completely cover the mesh. This also resulted in a refashioned, shallow pouch of Douglas.

Follow-up and post-operative assessment

Anorectal function was assessed 3, 6 and 12 mo postoperatively using the FISI and Wexner constipation score. Patient examined clinically at 3 and 6 mo. At 12 mo and later follow-up was done with telephonic interview using personal questionnaire.

Statistical analysis

Statistical analysis was done by a biomedical statistician. Mann-Whitney *U*-test was applied for unpaired data and Wilcoxon signed rank test was used for the analysis of paired data (two-sided *p*-test).

RESULTS

Demographics

Fifteen patients with CRP (6 men and 9 women) with a median age of 50 years (range, 15-68 years) underwent this procedure. Two patients had recurrent prolapse following failed previous surgery (one Theirsch's procedure and one mesh posterior rectopexy). Median duration of symptoms was 10 years (range, 0.5-40 years). Median duration of follow-up was 22 mo (range, 4-54 mo).

Clinicopathologic features

Five out of 15 patients had incontinence with median FISI score 24 (range, 0-53). Four patients had constipation with median Wexner score 17 (range, 5-24). Two patients had vaginal vault prolapse. Solitary rectal ulcer with anemia was present in two patients. Redundant colon was evident in 13 out of 15 patients on contrast enema examination.

Surgical result

The surgery was performed laparoscopically in all patients. Median surgical time was 200 min (range, 180-350 min). No intra-operative blood transfusion was required. Median length of hospital stay was 4 d (range, 3-21 d). Iatrogenic bowel injury requiring re-exploration resulted in prolonged hospital stay (21 d) in one case.

Morbidity and mortality

There was no perioperative mortality. One patient with

inadvertent small bowel injury required re-exploration on second postoperative day. One patient had transient urinary retention and two had surgical site infection, which was managed conservatively. No mesh-related complication was reported.

Surgical outcomes

At median follow-up of 22 mo, Wexner score declined to 6 (range, 0-23) from the preoperative value of 17 (range, 5-24) ($P < 0.001$) and the FISI score to 2 (range, 0-53) from 24 (range, 0-53) ($P = 0.007$). Recurrent prolapse was not reported in any of our patients. On personal questionnaire, patients were satisfied with the procedure. No new-onset constipation or fecal incontinence developed in any patient.

DISCUSSION

The goal of surgery in rectal prolapse is the correction of the anatomical defect, improvement of bowel function and prevention of *de novo* functional problems. Various abdominal and perineal procedures have been described for management of rectal prolapse, with later procedures now reserved only for high-risk patients who cannot withstand major abdominal surgery^[9]. However, long-term recurrences and the rate of persistent incontinence are higher than in abdominal procedures. Abdominal approach is now considered the standard of care and is used whenever feasible^[10]. Abdominal procedures imply sutured or mesh rectopexy, colonic resection or a combined resection-rectopexy technique. Conventionally these have been done through open approach and more recently by minimally invasive means. In a randomized controlled study, laparoscopic rectopexy was found to have less operative pain, rapid recovery and shorter post-operative hospital stay. Also the surgical complications were significantly lower in comparison to open procedures^[5]. Laparoscopic approach is now considered the standard approach and is routinely recommended in all cases. Abdominal procedures involving sigmoid resection with or without rectopexy have a reported recurrence rates of 2% to 5%. This technique also carries risk of anastomotic leak and chances of incontinence following bowel resection, particularly in elderly individuals^[11].

Conventionally, mesh rectopexy involved circumferential mobilization of the rectum up to pelvic floor with mesh placed ventrally or posteriorly. Complete rectal mobilization has been associated with autonomic nerve damage and disturbed rectosigmoid motility leading to *de novo* or worsening of existing constipation^[12].

D'Hoore *et al.*^[3,8] in 2004 described "nerve-sparing ventral rectopexy" as a procedure for rectal prolapse. The uniqueness of laparoscopic ventral rectopexy lies in the fact that mobilization is restricted to anterior rectum thus leaving the autonomic innervation intact^[3,8]. Currently, this technique has gained widespread acceptance and has been proposed by many the "standard of care" for management of pelvic organ prolapse^[2,13]. The combined benefits of laparoscopic approach and ventral rectopexy have made the procedure safe and effective with minimal

post-operative functional disturbance.

Several studies have reported a recurrence rate of about 5% following LMVR. Most recurrences occur within the first 2-3 years^[2,3]. The risk of recurrence is similar to that reported for other abdominal procedures (2% to 9%)^[14]. In the present study, no recurrence was found.

Ventral mesh rectopexy has been found to be associated with lower incidence of new-onset and greater improvement in pre-existing constipation as compared to the procedures that include posterior rectal dissection. Three randomized trials have shown an improvement in constipation by avoiding lateral and posterior dissection^[15-17]. Also, studies that have included the fecal incontinence data have shown improved symptoms following the LMVR. The incidence of new-onset fecal incontinence after LMVR has also been reported to be low^[3,5,18]. The results suggest that complications following LMVR are mostly minor. Our functional results are very similar to these studies. Pre-existing constipation improved in 80% of cases and no patient developed *de novo* constipation.

Previously, rectopexy surgery was thought to cause kinking of redundant sigmoid colon over the fixed rectum, resulting in worsening of preexisting or *de novo* constipation^[19]. For this reason, resection-rectopexy was advocated for patients with redundant sigmoid. However, D'Hoore *et al.*^[3] showed that the denervation of rectum resulting from its circumferential mobilization led to most of the post-rectopexy functional problems. Similarly, redundant sigmoid was present in 13 out of 15 patients in the present study, still all patients had improved constipation scores in the follow-up and none reported a new-onset constipation.

The mesh-related complications were of concern for us initially and were explained to the patients as well. However, in the present study we found the procedure to be safe. No mesh-related complication: Infections, erosions, or perforation was documented. Covering the mesh with the peritoneum prevented small bowel adhesion. The patients were not evaluated for postoperative dyspareunia/sexual dysfunction in this study.

There is a growing consensus that rectal prolapse is a component of a multi-compartment pelvic floor dysfunction^[20,21]. Thirty-five percent of prolapse cases have concomitant urinary incontinence, and another 15% complain of significant genital prolapse^[22]. During ventral mesh rectopexy, fixing the posterior vaginal fornix to the lower most part of mesh provides additional support to the pelvic floor. This suspends the middle compartment resulting in correction of the existing or impending genital prolapse^[3,4]. A posterior rectopexy, on the other hand just supports the posterior compartment. The distal fixation of the mesh on to the pelvic floor allows repair of large rectoceaes. It also results in a shallow, suspended pouch of Douglas, thus correcting associated enterocele or sigmoidocele automatically. Sparing of the rectal autonomic nerves appears to improve the outcome of surgery for constipation. Our findings indicate an

excellent improvement in fecal incontinence scores in the follow-up.

The Indian population is predominantly vegetarian having high residue fiber as a major component of their diet. The sigmoid colon is particularly bulky and often redundant in this part of the world, which makes it prone to volvulus also. There is thus a concern whether ventral rectopexy would be as effective in the treatment of CRP in this subset of patients as an alternative of resection rectopexy. Our study is the first report of ventral rectopexy, reinforcing the safety and efficacy of this procedure in the group of patients with bulky, redundant sigmoid colon.

In conclusion, laparoscopic ventral rectopexy appears to be a safe and effective surgical option for full-thickness rectal prolapse, especially in Indian patients with bulky and redundant sigmoid colon. However, in view of small sample size short follow-up, this needs to be validated in larger study with longer follow-up. Prospective randomized trials are warranted for level I evidence.

COMMENTS

Background

Laparoscopic ventral rectopexy is a new modality for the treatment of full thickness rectal prolapse. Avoiding a circumferential mobilization of rectum and reperitonealization of the mesh decreases the complications of rectal denervation.

Research frontiers

Redundant sigmoid colon has been considered an indication of resection rectopexy in the past. The authors have emphasized the results of laparoscopic ventral rectopexy on bulky and redundant sigmoid which is prevalent in Indian population.

Innovations and breakthroughs

Patients were followed-up for a median duration of 22 mo. There were a few post-operative complications which were easily managed. Marked improvement in constipation and incontinence scores were reported. No *de novo* or worsening of existing constipation was recorded in any of the patients. In this study, no recurrence was evident during the follow-up. This was similar to other researchers who have practiced laparoscopy ventral rectopexy. The fact that this procedure was equally effective in redundant sigmoid and loaded colon among Indian population has not been reported till date.

Applications

Laparoscopic ventral rectopexy appears to be a safe and effective surgical option for complete rectal prolapse. This needs validation with a larger cohort or a randomized study in Indian population.

Terminology

CRP: Complete rectal prolapse; FIS: Fecal incontinence severity index; LMVR: Laparoscopic mesh ventral rectopexy.

Peer-review

This is an interesting paper focusing the outcomes of laparoscopic ventral mesh rectopexy in the treatment of complete rectal prolapse in North Indian population with inherent bulky and redundant colon.

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Prospective Study

PERFACT procedure to treat supralelevator fistula-in-ano: A novel single stage sphincter sparing procedure

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Author contributions: Garg P conceived the idea, designed the study, did the acquisition and analysis of data, drafted, revised and submitted the manuscript.**Institutional review board statement:** The study was reviewed and approved by the Indus Hospital Ethical Committee.**Clinical trial registration statement:** Not applicable.**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.**Conflict-of-interest statement:** The author has not received any fees for serving as a speaker or in a position (such as consultant and/or an advisory board member) which could have a conflict of interest with this study. The author has not received research funding from any organization or individual. The author is not an employee of an organization and does not own stocks and/or shares in an organization which has a potential conflict of interest with the study.**Data sharing statement:** Technical appendix, statistical code and dataset are available from the corresponding author at dr gargpankaj@yahoo.com. Consent was obtained but the presented data are anonymized and the risk of identification is low.**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

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Published online: April 27, 2016**Abstract****AIM:** To prospectively perform the PERFACT procedure in supralelevator anal fistula/abscess.**METHODS:** Magnetic resonance imaging was done preoperatively in all the patients. Proximal cauterization around the internal opening, emptying regularly of fistula tracts and curettage of tracts (PERFACT) was done in all patients with supralelevator fistula or abscess. All types of anal fistula and/or abscess with supralelevator extension, whether intersphincteric or transsphincteric, were included in the study. The internal opening along with the adjacent mucosa was electrocauterized. The resulting wound was left open to heal by secondary intention so as to heal (close) the internal opening by granulation tissue. The supralelevator tract/abscess was drained and thoroughly curetted. It was regularly cleaned and kept empty in the postoperative period. The primary outcome parameter was complete fistula healing. The secondary outcome parameters were return to work and change in incontinence scores (Vaizey objective scoring system) assessed preoperatively and at 3 mo after surgery.**RESULTS:** Seventeen patients were prospectively

enrolled and followed for a median of 13 mo (range 5-21 mo). Mean age was 41.1 ± 13.4 years, M:F - 15:2. Fourteen (82.4%) had a recurrent fistula, 8 (47.1%) had an associated abscess, 14 (82.4%) had multiple tracts and 5 (29.4%) had horseshoe fistulae. Infralelevator part of fistula was intersphincteric in 4 and transsphincteric in 13 patients. Two patients were excluded. Eleven out of fifteen (73.3%) were cured and 26.7% (4/15) had a recurrence. Two patients with recurrence were reoperated on with the same procedure and one was cured. Thus, the overall healing rate was 80% (12/15). All the patients could resume normal work within 48 h of surgery. There was no deterioration in incontinence scores (Vaizey objective scoring system). This is the largest series of supralelevator fistula-in-ano (SLF) published to date.

CONCLUSION: PERFECT procedure is an effective single step sphincter saving procedure to treat SLF with minimal risk of incontinence.

Key words: Anal fistula; Complex; Simple; Horseshoe; Abscess; Supralelevator; Tracts

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Core tip: Supralelevator fistula-in-ano (SLF) and abscess are quite difficult to treat. There is no good treatment available for this dreaded disease as the risk of incontinence is quite high when operating on such fistula. PERFECT (proximal cauterization around the internal opening, emptying regularly of fistula tracts and curettage of tracts) was done in seventeen patients with SLF. The overall healing rate was 80% (12/15). All patients could resume normal work within 48 h of surgery and there was no deterioration in incontinence scores. This is the largest series of treatment of SLF published to date.

Garg P. PERFECT procedure to treat supralelevator fistula-in-ano: A novel single stage sphincter sparing procedure. *World J Gastrointest Surg* 2016; 8(4): 326-334 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i4/326.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i4.326>

INTRODUCTION

Supralelevator abscess (SLA) constitutes up to 9% of all cryptoglandular abscesses^[1-3]. These are difficult to treat as there is no satisfactory treatment procedure available which can manage these fistulas with a high success rate and minimal risk of incontinence. Conventionally adequate drainage followed by either a primary fistulotomy or a two stage fistulotomy using a seton fistula-in-ano was recommended^[3]. There had been great enthusiasm for ligation of intersphincteric tract (LIFT) and even BioLIFT procedures, but recently the results have been disappointing^[4].

Electrocauterization of the area around the internal opening can successfully close the internal opening of a fistula-in-ano^[5]. This step along with curettage of the tracts and regularly emptying fistula tracts [proximal cauterization around the internal opening, emptying regularly of fistula tracts and curettage of tracts (PERFACT) procedure] has been shown to be effective in treating complex anal fistulas^[5]. The efficacy of this procedure to manage supralelevator fistula-in-ano (SLF) was assessed in this study.

MATERIALS AND METHODS

This was a prospective analysis of all consecutive patients with cryptoglandular SLF and SLA treated from 2012 to 2014 at the referral colorectal unit of the hospital. The clearance (approval) was given by the institutional ethics committee. Informed consent was given by all the patients.

Inclusion criteria

All types of anal fistula and/or abscess with supralelevator extension, whether intersphincteric or transsphincteric, were included.

Exclusion criteria

Patients who could not follow the postoperative schedule and protocol were excluded.

The Vaizey objective incontinence scoring was done preoperatively and at 3 mo after surgery^[6]. On a scale of 0-24, a score of 0 implied perfect continence and a score of 24 meant total incontinence.

A preoperative magnetic resonance imaging (MRI) scan was done in every case to accurately map the fistula tracts. A schematic diagram of the coronal and transverse sections was made based on the MRI (Figures 1-3).

Principle/concept

Intraoperatively, the procedure had two steps: (1) Electrocauterization around the internal opening: The superficial layer (mucosa) around the internal opening was electrocauterized to create a fresh wound (Figures 2 and 4). The resulting wound was encouraged to heal by secondary intention (granulation tissue). The aim was to permanently close (heal) the internal opening. If there was an additional supralelevator opening in the rectum, the same procedure was done for that opening as well; and (2) curettage of tracts: All the tracts were thoroughly curetted and debrided of their lining with a curette. The transsphincteric supralelevator tract/abscess was drained and curetted through the ischioanal fossa through the external opening (Figure 2). The intersphincteric supralelevator tract/abscess was curetted through the external opening already present or through a small new incision in the intersphincteric groove (Figure 2). Once the intersphincteric space was opened up, a blunt curette was introduced through the incision into this space. The curette was advanced towards the supralelevator tract/

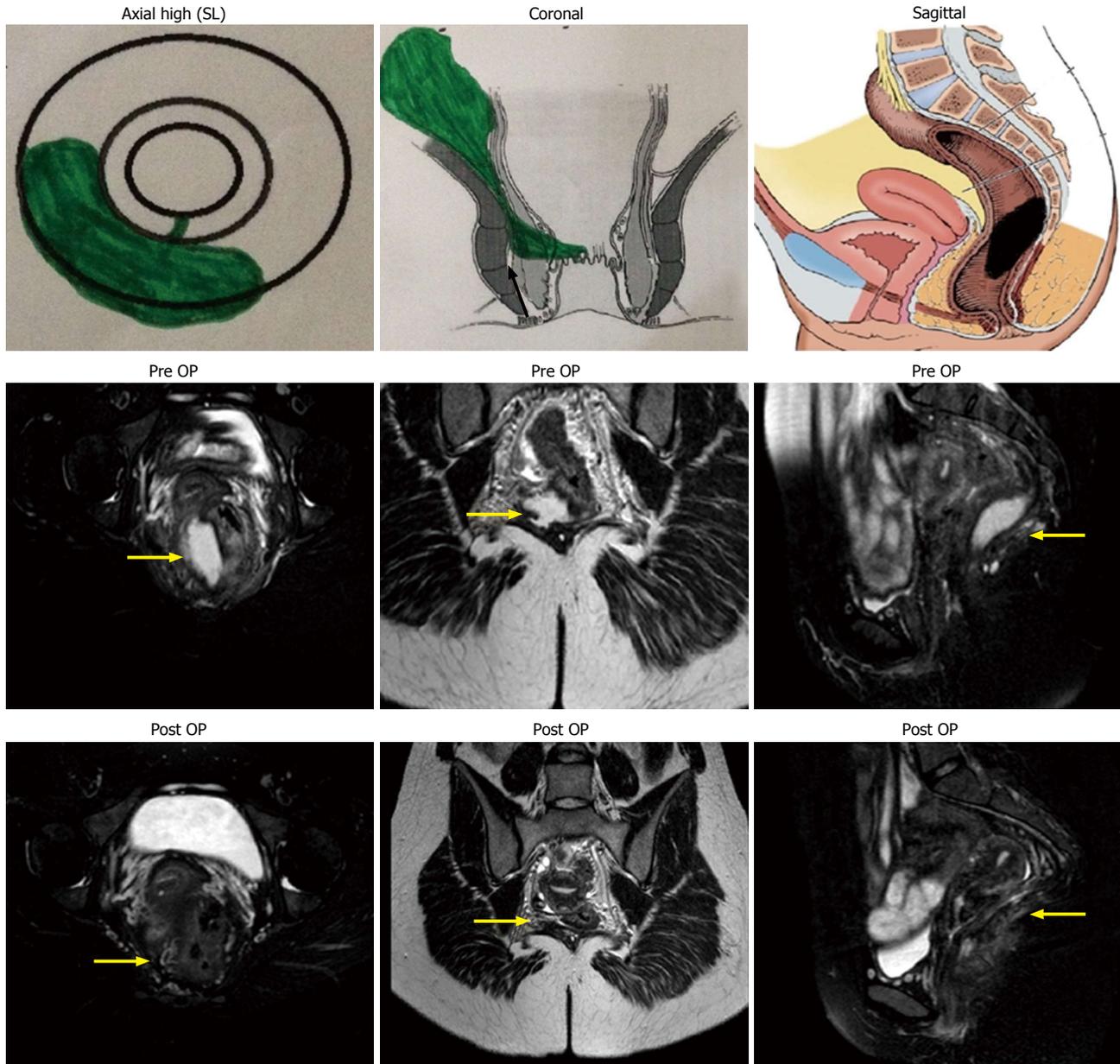


Figure 1 Intersphincteric supralelevator abscess and fistula. A 25-year-old female with supralelevator collection from 5 to 9 o'clock. Postoperative magnetic resonance images after 6 wk (bottom row) show complete disease resolution. SL: Supralelevator; OP: Operation.

collection, taking guidance from the MRI scan. A finger was kept in the rectum to prevent inadvertent injury to the rectal wall.

Postoperative management

Regularly emptying fistula tracts: The curetted tracts were kept clean and empty of any serous fluid so as to ensure that the tracts healed (closed) by granulation tissue. Keeping all the tracts clean was required for 4 to 8 wk (occasionally longer) until all the tracts healed fully. The cleaning was usually done twice a day.

To ensure proper cleaning of the tracts, the following steps (one or multiple depending upon the requirement and fistula characteristics) were done during surgery: (1) The external opening was widened and the scarred puckered skin (if present) was excised. The aim was

to make the external opening bigger than 1 cm x 1 cm (Figures 4 and 5). This facilitated cleaning of the tracts for a longer duration; (2) small tubes (red rubber, nasogastric or plastic) were put in the outer part of the tract to prevent premature closure of the outer part of the tract (Figure 5)^[7]. The tube was removed before every dressing and then reinserted after the dressing. There was no need to secure the tube with a suture as the tract held the tube in place and the tube did not usually come out while walking. The cleaning was done with a swab mounted on artery forceps^[7]. The schematic diagram (Figures 1-3) provided guidance regarding the direction and depth of the tracts. The tube size and diameter was gradually decreased as the deeper portion of the tracts healed. The insertion was stopped only after it was ensured that the deeper (including the

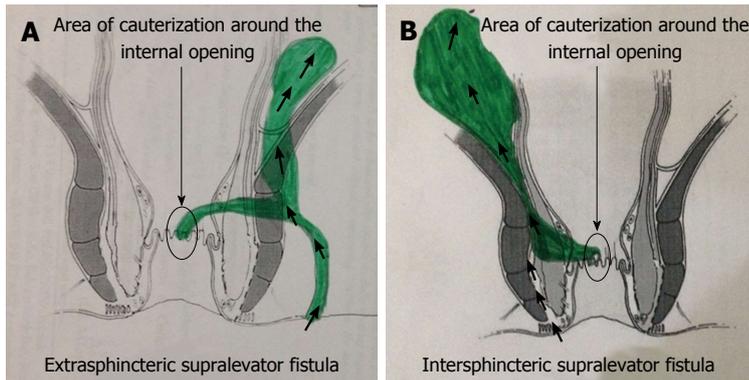


Figure 2 Approach to curette the supralelevator fistula. A: Extrasphincteric; B: Intersphincteric.

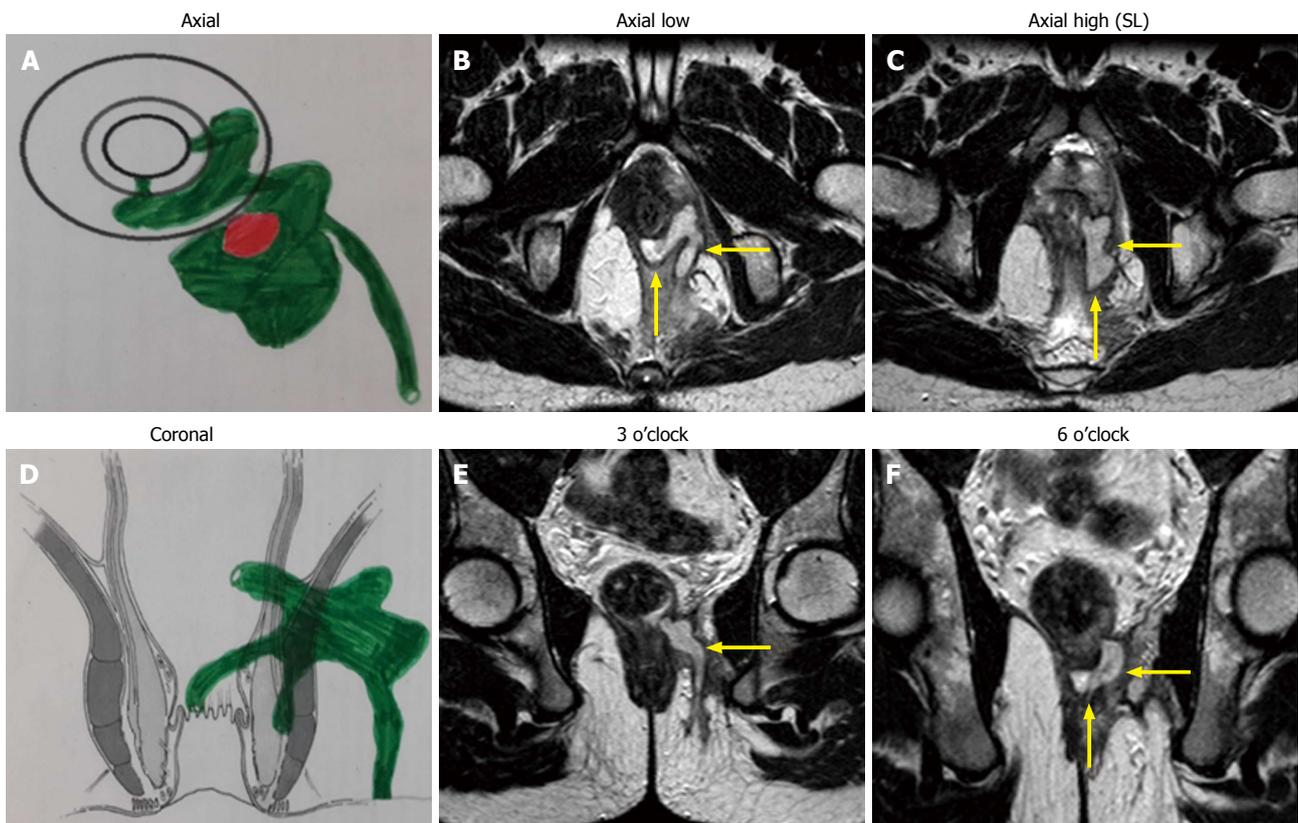


Figure 3 Transsphincteric supralelevator fistula. A 22-year-old male patient with infralevator posterior fistula opening at 6 o'clock and supralelevator opening at 3 o'clock. A-C: Axial; D-F: Coronal.

supralelevator) part of the tract had completely healed. The healing was assessed by narrowing of the tracts and non-negotiation of the swab in the upper part of the tract. Postoperative MRI was done in patients who could afford it to assess the healing (Figure 1); and (3) in cases of long multiple tracts or horseshoe tracts, multiple holes were made along the tract (Figure 5) so that all parts of the tract could be cleaned with ease.

Intraoperative procedure

A saddle block (spinal anesthesia) or general anesthesia was given. The patient was positioned in a lithotomy or prone jack-knife position. The internal opening was localized. This was facilitated by injecting saline or

povidone iodine through the external opening.

Proximal superficial cauterization (Figures 2 and 4) was carried out with electrocautery around the internal opening, cauterizing only the mucosa and superficial part of the internal sphincter. The crypt glands, the internal opening and the tissue around it were cauterized. This usually resulted in an oval cauterized area, approximately 1 cm (wide) and 2 cm (long), with an internal opening at the center of the wound (Figures 2 and 4). After cauterization, the wound was left as such and no attempt was made to close the wound or the internal opening with any suture, stapler, glue or plug.

After this, the tracts were curetted in accordance with the MRI diagram and the tract lining was scrapped out as

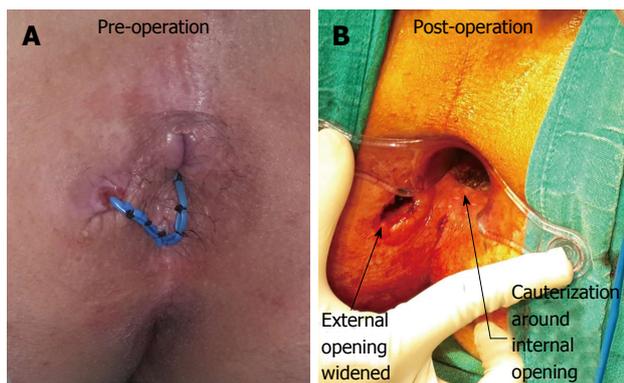


Figure 4 Cauterization around the internal opening and widening of external opening. Loose draining seton (blue color) can be seen in the preoperative (A) photograph which was inserted during the previous operation by another surgeon 3 mo before the PERFECT procedure was done. A: Preoperatively; B: Postoperatively.

much as possible with a blunt curette (Figure 2). While doing so, a finger was kept in the rectum to ensure that the curette did not accidentally perforate the rectum.

The patient was discharged on the day of operation (if done under short general anesthesia) or the first postoperative day (if done under saddle or spinal anesthesia). Antibiotics (ciprofloxacin 500 mg and ornidazole 500 mg) were prescribed twice a day for five days. The patient was instructed to resume all his/her normal activities on the same day and was encouraged to walk briskly for five kilometers every day. This helped to keep the tracts empty.

The cleaning process of the curetted tracts was done by a cotton swab mounted on artery forceps^[7]. The tube was removed before every dressing and then reinserted after the dressing (Figure 5). No povidone iodine, hydrogen peroxide or any liquid was injected in the tract during the cleaning process as this would have prevented the internal opening from closing. The cleaning was done by a trained nurse, a medical attendant or a relative. In our setting, teaching a relative was economical and easier and hence a preferred option.

The cleaning process was done two to four times a day. For the first 10 d, the patient was called to the outpatient clinic for supervised cleaning once or twice a day depending upon the complexity of the fistula. After this, the patient could do the cleaning process at home. The cleaning process was not painful, although uncomfortable at times. No sedation was required for this. The cure was defined as a complete cessation of a purulent or serous discharge and complete healing of all the tracts. Persistence of even one of the tracts was considered a failure.

The statistical methods of this study were reviewed by Pankaj Garg, MBBS, MS, Chief Colorectal Surgeon at Garg Fistula Research Institute, Panchkula, India.

RESULTS

Seventeen patients were prospectively enrolled and

followed for a median of 13 mo (3-21 mo). Mean age: 41.1 ± 13.4 years, M:F - 15:2. Fourteen (82.4%) had a recurrent fistula, 8 (47.1%) had an associated abscess, 14 (82.4%) had multiple tracts and 5 (29.4%) had horseshoe fistulae.

The infralevator part of fistula was intersphincteric in 4 (23.5%) (Figure 1) and transsphincteric in 13 (76.5%) patients (Figure 3, Table 1). All fistula were type 3 (suprasphincteric fistula) according to Park's classification^[8] and type 5 as per St James' Hospital classification^[9]. Two patients were excluded from the analysis (they could not follow the postoperative protocol). Out of 15 patients, 11 (73.3%) were cured (Figures 1 and 3) and four patients (26.7%) had a failure of treatment. All the patients with recurrence had transsphincteric supralelevator extension (Table 1). Two patients with recurrence were reoperated on with the same procedure and one was cured. Thus, the overall healing rate was 80% (12/15). The tracts, especially the supralelevator tract, did not heal in the failed treatment patients. All the patients were discharged within 24 h of the procedure and could resume normal work in 48 h. There was no deterioration in incontinence scores at 3 mo after surgery.

DISCUSSION

The study describes a novel simple method to treat supralelevator fistula with a satisfactory cure rate (80%) and minimal risk to incontinence. The morbidity was also minimal as there was no cutting of sphincter muscle and the wound was quite small. Therefore, all the patients could resume their normal work within 48 h of surgery. As per our literature search, this is the largest series of supralelevator fistula to be published.

MRI played a pivotal role in the diagnosis of supralelevator extension. Endoanal ultrasound (EUS) and MRI are recommended for recurrent or suspected supralelevator anal fistula^[10-12]. Although both these modalities are quite sensitive in detecting perianal fistulas, the specificity of MRI is better than EUS^[13]. Since ours is a referral center for anorectal fistulas, MRI is done in all our patients with perianal fistulas. The supralelevator extension was an unsuspected incidental finding in 13 (76.5%) of our patients. Twelve (92.3%) of these 13 patients had recurrent anal fistula and 11 (84.6%) had multiple tracts. These findings reaffirm the suggestion that MRI should be done in all patients with recurrent and complex anal fistula^[11-13]. MRI is perhaps the best method to assess SLA and fistula as it provides images in all three planes (axial, sagittal and coronal). The coronal view enables positioning of the abscess and the tract with respect to the levator plate and clearly shows supralelevator extension in most patients (Figures 1 and 3)^[14]. MRI is also a good modality to assess the resolution of the disease process. The photographs of preoperative and postoperative MRIs showing the resolution of the supralelevator disease process are seen in Figure 1. The postoperative MRI of all the patients could not be done due to cost constraints.

Although the route of drainage of a SLA has been

Table 1 Patient parameters, fistula characteristics and outcome

Case	Age (yr)	Sex	Previous operations	Site	Abscess	Horseshoe	Multiple tracts	Outcome
1	62	M	2	TS	N	N	N	Healed
2	45	M	1	TS	Y	Y	Y	Recurred, healed after reoperation
3	45	M	1	TS	N	N	Y	Healed
4	49	M	2	TS	N	N	Y	Not healed
5	59	M	1	TS	N	N	Y	Did not follow protocol/lost to follow-up
6	48	M	1	TS	Y	Y	Y	Healed
7	36	M	2	IS	Y	Y	Y	Healed
8	26	M	0	TS	Y	N	Y	Did not follow protocol/lost to follow-up
9	22	F	3	TS	Y	N	Y	Not healed, recurred after second operation
10	32	M	1	IS	N	Y	Y	Healed
11	55	M	5	IS	N	N	N	Healed
12	25	F	0	IS	Y	N	N	Healed
13	59	M	1	TS	N	N	Y	Healed
14	22	M	1	TS	Y	N	Y	Healed
15	34	M	2	TS	Y	N	Y	Healed
16	34	M	1	TS	N	N	Y	Not healed
17	45	M	0	TS	N	Y	Y	Healed
Total	41.1 ± 13.4	M-15/F-2	Recurrent -14	TS-13 IS-4	8	5	14	Healed-11 (73.3%) Not-4 Excluded-2

M: Male; F: Female; TS: Transsphincteric (in ischiorectal fossa); IS: Intersphincteric.

described in the past^[2,3], there is no effective method available for definitive treatment of the SLF. The standard practice is to drain a SLA abscess through the rectum when a SLA spreads upwards from an intersphincteric abscess^[15,16]. This is to avoid an iatrogenic suprasphincteric fistula if the drainage is incorrectly performed through the ischiorectal fossa. On the other hand, if a SLA is secondary to an upward extension of an ischiorectal abscess, the drainage should be performed through the ischiorectal fossa to avoid an iatrogenic extrasphincteric fistula^[2,3,8,15,17,18]. Subsequent management is opening the intersphincteric space through the rectum by dividing the internal anal sphincter (IAS) or by a staged seton procedure.

Both the internal and external anal sphincters play an important role in maintaining continence^[19-21]. Using cutting seton in high transsphincteric anal fistula can affect continence in up to 60% of patients^[19]. On the other hand, completely sparing the external anal sphincter (EAS) but dividing the IAS to open the intersphincteric space through the rectum in intersphincteric fistulas also leads to continence deficits in up to 50% of patients^[20]. Therefore, both IAS and EAS play a significant role in continence preservation^[20,21]. A recent multicenter study reported a long term incidence of major incontinence (Vaizey score > 6) in 26.8% of patients undergoing fistulotomy in low perianal fistulas^[22]. This further emphasizes the need to move towards sphincter saving procedures to treat anal fistula.

The PERFECT procedure is perhaps the first method described to treat supralevator fistula which does not involve dividing either the internal or external anal sphincter. Therefore, the continence scores did not show any deterioration in any patient postoperatively. Secondly, unlike the conventional methods^[15], this procedure aimed to cure SLA and fistula in a single step. This made it less

morbid and quite cost effective as it prevented the cost of a second admission and reoperation.

The concept behind this procedure was very simple. It aimed to close the internal opening by proximal superficial cauterization in the anal canal (Figures 2 and 4). In the postoperative period, it was ensured that the wound healed by secondary intention so that the internal opening was sealed by granulation tissue. The closure of an internal opening by natural means (granulation tissue) seems to be a good alternative to other methods of closures by primary intention, such as a plug, suture, flap, stapler or a clip^[23-25].

In the PERFECT procedure, the internal opening is not widened. If the internal opening is widened, there is a chance of stool passing through the internal opening. In this procedure, only the mucosa (superficial layer) all around the internal opening is electrocauterized so as to create a fresh raw wound which heals with granulation tissue. The internal and external sphincters are not cut. Due to this, the internal opening is not wider than it was before surgery.

The second step was curettage of the tracts. This ensured that the infected epithelium was removed and the freshened raw wound in the tracts led to the generation of the granulation tissue which facilitated the closure of the tracts. However, the serous discharge of the granulation tissue needed to be thoroughly cleaned/removed from the tracts on regular basis as otherwise the stagnant discharge would become infected, leading to a collection. The latter would not only lead to the rapid reepithelialization of the tracts, but also the collected fluid could flow into the internal opening, thereby preventing its closure.

At times, the tracts were curved and branching. Preoperative MRI, which was done in all cases, helped to accurately localize the tracts. Once this was done, it

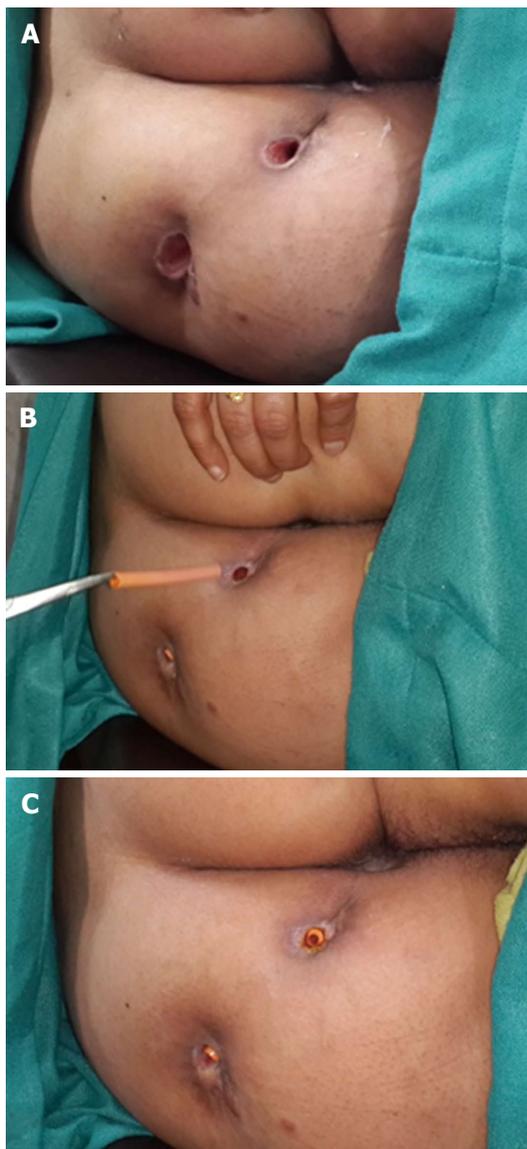


Figure 5 Widened external opening in a patient with multiple tracts (A), removal of tube to clean tracts in the office (B) and reinserted tubes in the tracts after the cleaning process (C).

helped to curette the tracts (primary tract as well as the branching secondary tracts). For this purpose, curettes of different sizes and lengths were kept handy. Cleaning the curved tracts usually did not pose much problem as the tracts were usually flexible and adapted to the shape of the curette.

The postoperative management was quite significant. It aimed to keep the tracts clean and empty and any inadequacy in this care was detrimental to the final outcome.

The cauterization of the internal opening alone was tried earlier without much success^[5]. The reason for the success of the same step in the PERFECT procedure needs explanation. Undoubtedly, the internal opening is the prime culprit in a fistula-in-ano as it allows ingress of the bacteria from the anal canal into the fistula tracts. However, once the tracts are formed and are lined by the infected epithelium, it is a mutually propagating situation.

The patent internal opening keeps the tracts infected and the infected collection in the tracts keeps the internal opening patent. Therefore, isolated attempts to close the internal opening would fail until it is accompanied by meticulous cleaning, emptying and healing of all the associated tracts. This perhaps explains the need for regular tract cleaning in the postoperative period.

The PERFECT procedure can also be done effectively in fistula cases where the internal opening cannot be localized accurately during surgery. The possible reasons of failure to identify the internal opening are twofold. Firstly, it could be due to the temporary closure of the internal opening due to debris. Secondly, it could be the closure of the collapsible fistula tract (which passes through the sphincter complex) due to the external pressure of the sphincter muscle. As per the published literature, this can happen in up to 15%-20% of cases. In the earlier published series of the PERFECT procedure, an internal opening could not be found in 15.7% (8/44) of cases^[5]. Still, this procedure was successful in 87.5% (7/8) of these patients^[5]. The MRI was done preoperatively in every case. This helped to localize the position of the tracts in the majority of cases and gave a reasonable idea where the tract is coursing towards the rectum. This information along with the examination findings during surgery (induration of the sphincter in the region of internal opening) helped to determine the most likely location of the internal opening. The superficial cauterization was done at that place. This was a safe step to do as it created only a superficial wound with no injury/damage to either of the sphincters.

The concept behind this procedure was undoubtedly simple but to achieve good results in complex anal fistulas, it required detailed analysis of the MRI scan, careful planning and mapping of the tracts (preoperatively), meticulous curettage and cleaning of all the tracts (intraoperatively) and disciplined postoperative care (postoperatively).

As discussed, the main benefit of this procedure was its ability to treat SLA/fistula in a single sitting with minimal risk to incontinence. The morbidity was also minimal as no extensive tissue cutting was done. Apart from a small superficial wound in the anal canal, the external opening was slightly widened (Figures 4 and 5). The cauterized anal wound was also small (usually about 2 cm long and 1 cm wide) (Figure 4). Due to these small wounds, the patients had little pain and were able to resume all their normal daily activities from the first postoperative day. The patients were encouraged to briskly walk 4-5 km from the first postoperative day as it facilitated keeping the tracts empty. Secondly, as both the sphincters were completely spared, the negative impact on incontinence was minimal.

The tube (mushroom catheter) has been used for drainage of perianal abscesses, both ischio-rectal abscesses^[26] and supralelevator abscesses^[15]. However, a tube has perhaps not been used in the way described in this study (to keep the outer part of the fistula tract patent). In the present procedure, a tube in the outer portion

of the fistula helped in several ways (Figure 5). First, it prevented the outer portion of the fistula tract from closing prematurely^[7]. The tube was placed until the upper inner portion of the fistula did not heal completely. Premature closure of the outer part of the tract, especially the skin, would risk accumulation of fluid which could prevent healing of the upper part^[7]. Second, unlike a loose draining seton, nothing (no seton or thread) needs to be passed through the internal opening in this technique^[7]. This helped to achieve the closure of the internal opening which would not have been possible if a draining seton had been used instead. Third, to drain supralelevator extension (with no rectal opening), a draining seton could not be used whereas a tube could be used for adequate regular drainage.

The results in fistulae with intersphincteric infralevator part (100% - 4/4) (Figure 1) were better than fistulae with transsphincteric infralevator part (72.7% - 8/11) (Figure 3). The reason for this could be that the intersphincteric space was a collapsible space. Once the abscess was adequately drained (or the fistula tract adequately curetted) and the internal opening healed by cauterization, the intersphincteric space had the tendency to collapse (close) (Figure 1).

It was observed in this series that the supralelevator component usually developed some time after the development of an infralevator anal fistula. If the infralevator anal fistula was intersphincteric, then it extended upwards in the intersphincteric plane (Figure 2). Even if the infralevator anal fistula was transsphincteric, the supralelevator extension was in the intersphincteric plane (Figure 2). Thus, the supralelevator extension was always in the intersphincteric plane. Since the supralelevator rectal opening was not present in all fistula-in-ano patients with supralelevator extension, it indicated that the supralelevator rectal opening developed later and was not as important in the pathophysiology of SLF. Mucosal papilla (granulation tissue overgrowth) was also observed at the site of the supralelevator rectal opening in four patients. Such overgrowth of granulation tissue usually occurs at the point of exudation of purulent discharge. These points indicated that the supralelevator rectal opening developed as a result of bursting the supralelevator intersphincteric abscess/collection into the rectum and this opening mainly acted as a point of drainage for the abscess/fistula. The primary source of ingress of bacteria was perhaps the opening at the dentate line. Another point in favor of this concept is that the intramural pressure during defecation in the anal canal (hence at dentate line) is quite high, whereas the intramural pressure in the rectum is comparatively low as it is a storage organ. This high pressure in the anal canal "forces" bacteria into the opening at the dentate line and this may be responsible for the persistence and propagation of the fistula and, in a few cases, development of a SLA. A small proportion of these cases then progresses to also develop a supralelevator rectal opening. Further data is needed to substantiate these observations. Unfortunately, too little

data is available on supralelevator anal fistula due to rarity of this disease and the difficulty in management it poses.

Other advantages of this procedure were the less operating time (20-30 min), the procedure was easy to perform and reproduce and no expensive gadgets were required, such as in VAAFT or an anal fistula plug^[23,25,27].

The PERFECT procedure is quite different from VAAFT. In VAAFT, the internal opening is closed by a stapler or suturing whereas in PERFECT, the mucosa (superficial layer) all around the internal opening is electrocauterized so as to create a fresh raw wound which heals with granulation tissue. The aim is to close the internal opening by secondary intention whereas in VAAFT, the aim is to close the internal opening by primary intention. Closure of tissues by primary intention put tissues under tension which increases the risk of failure. That could perhaps be the reason that the PERFECT procedure seems to be more effective than VAAFT, especially in complex and supralelevator fistulas.

This was a prospective cohort study with no control group. Undoubtedly, a control group would have added value to the study. However, a comparative study was not feasible as the prevalence of supralelevator fistula is quite low. Secondly, no other procedure in the literature has been shown to be effective in supralelevator fistula, especially in supralelevator fistula with transsphincteric component. Therefore, a comparative study could not be planned.

To conclude, the PERFECT procedure is an effective single step sphincter saving procedure to treat supralelevator anal fistula. It is associated with little morbidity and minimal risk to incontinence. Long term studies with large numbers of patients are required to substantiate the results.

COMMENTS

Background

Supralelevator fistula-in-ano (SLF) and abscess are quite difficult to treat. There is no good treatment available for this dreaded disease to date. The reason is that the risk of incontinence is quite high in operating on such fistula.

Research frontiers

SLF is extremely difficult to treat. Conventionally, drainage of the abscess is followed by either a primary fistulotomy or a two-stage fistulotomy using a seton, but these were associated with high incontinence rates. There has been great enthusiasm for ligation of intersphincteric tract and even Bio ligation of intersphincteric tract procedures, but the results have been disappointing.

Innovations and breakthroughs

This is the largest study of treatment of SLF to be published. Proximal cauterization around the internal opening, emptying regularly of fistula tracts and curettage of tracts (PERFACT) is a minimally invasive treatment in which the risk of sphincter damage is very low. This procedure was done in seventeen patients with SLF. The overall healing rate was 80% (12/15). All the patients could resume normal work within 48 h of surgery and there was no deterioration in incontinence scores.

Applications

The PERFECT procedure is a simple novel procedure with many distinct advantages. As there is no satisfactory treatment available for supralelevator fistula, this procedure provides a ray of hope to treat this dreaded disease.

Peer-review

This is a very nice study on the PERFECT procedure. The PERFECT procedure allows treating supralelevator fistula without dividing either the internal or external anal sphincter. Therefore, the continence scores showed no deterioration in any of the patients postoperatively and this procedure aimed to cure supralelevator abscess and fistula in a single step.

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Duodenal injury post laparoscopic cholecystectomy: Incidence, mechanism, management and outcome

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Abstract

AIM: To study the etiopathogenesis, management

and outcome of duodenal injury post laparoscopic cholecystectomy (LC).

METHODS: A Medline search was carried out for all articles in English, on duodenal injury post LC, using the search word duodenal injury and LC. The cross references in these articles were further searched, for potential articles on duodenal injury, which when found was studied. Inclusion criteria included, case reports, case series, and reviews. Articles even with lack of details with some of the parameters studied, were also analyzed. The study period included all the cases published till January 2015. The data extracted were demographic details, the nature and day of presentation, potential cause for duodenal injury, site of duodenal injury, investigations, management and outcome. The model (fixed or random effect) for meta analyses was selected, based on Q and I^2 statistics. STATA software was used to draw the forest plot and to compute the overall estimate and the 95%CI for the time of detection of injury and its outcome on mortality. The association between time of detection of injury and mortality was estimated using χ^2 test with Yate's correction. Based on Kaplan Meier survival curve concept, the cumulative survival probabilities at various days of injury was estimated.

RESULTS: Literature review detected 74 cases of duodenal injury, post LC. The mean age of the patients was 58 years (23-80 years) with 46% of them being males. The cause of injury was due to cautery (46%), dissection (39%) and due to retraction (14%). The injury was noted on table in 46% of the cases. The common site of injury was to the 2nd part of the duodenum with 46% above the papilla and 15% below papilla and in 31% to the 1st part of duodenum. Duodenorrhaphy (primary closure) was the predominant surgical intervention in 63% with 21% of these being carried out laparoscopically. Other procedures included, percutaneous drainage, tube duodenostomy, gastric resection, Whipple resection and pyloric exclusion. The day of detection among those who survived was a mean

of 1.6 d (including those detected on table), compared to 4.25 d in those who died. Based on the random effect model, the overall mean duration of detection of injury was 1.6 (1.0-2.2) d (95%CI). Based on the fixed effect model, the overall mortality rate from these studies was 10% (0%-25%). On application of the Kaplan Meier survival probabilities, the cumulative probability of survival was 94%, if the injury was detected on day 1 and 80% if detected on day 2. In those that were detected later, the survival probabilities dropped steeply.

CONCLUSION: Duodenal injuries are caused by thermal burns or by dissection during LC and require prompt treatment. Delay in repair could negatively influence the outcome.

Key words: Laparoscopic cholecystectomy; Duodenal injury; Duodenorrhaphy

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Core tip: Inadvertent duodenal injury is a rare potentially fatal complication of laparoscopic cholecystectomy. Such injuries often go unrecognized at the time of the procedure and manifest later with significant morbidity and mortality. Literature review revealed 74 cases of duodenal injury. The injury was caused by cautery in 46%, dissection in 39% and retraction in 14% of the cases. The predominant site of injury was to the 2nd part in 61% and in 31% to 1st part. Duodenorrhaphy was the primary treatment carried out in 63% of the cases among which 21% was laparoscopically. When detected on table, 88.9% survived in contrast to 76.5% detected later. Overall mortality was 18%. The major impact of this review in clinical practice is in emphasizing the need for prompt detection of a potential duodenal injury in every patient who has unexplained postoperative course following a difficult laparoscopic cholecystectomy due to gall bladder adhesions or dissection. The change of clinical practice it should lead to is an attempt by surgeons in early detection of potential duodenal injury in such patients, which could be achieved by estimating the amylase content in subhepatic fluid collection or by upper gastrointestinal contrast studies. It also highlights the need for immediate surgical repair as any delay beyond the first postoperative day has adverse effect on outcome.

Machado NO. Duodenal injury post laparoscopic cholecystectomy: Incidence, mechanism, management and outcome. *World J Gastrointest Surg* 2016; 8(4): 335-344 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i4/335.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i4.335>

INTRODUCTION

Laparoscopic cholecystectomy (LC) is gold standard in the management of benign gall bladder disease^[1].

Unfortunately, in a small percentage of cases, it is associated with serious complications, which could be life threatening^[2-6]. These include those patients who sustain vascular or bowel injury^[2,4,6]. Among the bowel injuries, duodenal injury is extremely rare complication of LC, with a outcome that is potentially fatal^[4-26]. It is commonly unrecognized at the time of the procedure and is unfortunately diagnosed later when sepsis, peritonitis, intraperitoneal abscess or enterocutaneous fistula sets in^[2,27]. Several factors may play a role in causing these injuries, including complexity of the case and the experience of the surgeon^[5,6,15]. The incidence, mechanism of injury, diagnosis, management and outcome is described, along with the review of literature.

MATERIALS AND METHODS

Data sources

PubMed, EBSCO were searched for articles on duodenal injury during laparoscopic cholecystectomy.

Study selection

The study included articles in English literature on duodenal injury post laparoscopic cholecystectomy. The articles included case reports and case series. The references in each of these articles were further studied for additional articles on duodenal injury, post laparoscopic cholecystectomy.

The key words used as search terms were "duodenal injury", "laparoscopic cholecystectomy", "laparoscopic complications".

Data extraction

Various details were extracted from these articles. The variables studied included demographic details, presentation of symptoms and signs, day of detection of injury, investigations used to establish the diagnosis, the site of duodenal injury, possible cause, management of complication and its outcome.

Statistical analysis

The model (fixed or random effect) for meta analyses was selected, based Q and I^2 statistics. STATA software was used to draw the forest plot and to compute the overall estimate and the 95%CI for the time of detection of injury and mortality. The association between time of detection of injury and mortality was estimated using χ^2 test with Yate's correction. Based on Kaplan Meier survival curve concept, the cumulative survival probabilities at various days of injury was derived.

The PRISMA flow chart is presented in Figure 1. There were 24 studies (case report, case series) identified from the literature. None of the study was excluded. All 24 studies have been considered for both qualitative and quantitative evaluation.

RESULTS

A total of 74 cases of duodenal injuries were identified.

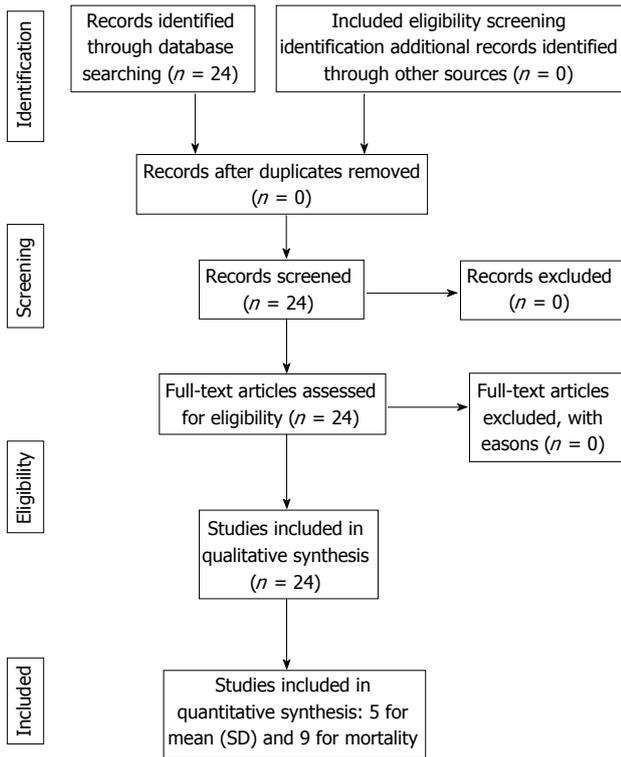


Figure 1 PRISMA flow chart.

Unfortunately details regarding the demography, presentation, investigations, management and outcome were not reported in several studies, particularly those reporting on overall complications of LC. Among the 24 cases with demography details, 11 patients (46%) were males and 13 patients (54%) were females, with a mean age of 58 years (range - 23 to 80 years) (Table 1). The mean period of detection of all the injury in the post-operative period was 1.7 d (range-immediate on table to 9th postoperative day). In 26 patients where the details of time of injury were noted, 12 (46%) of them were detected immediately on the table (day 0). Among the 28 cases where the cause of injury was reported, 13 (46%) occurred due to cautery, 11 (39%) during dissection, 4 (14%) due to retraction. There were no reported cases of injury due to veress needle or trocar insertion (Table 2). The presentation ranged from abdominal pain, nausea vomiting, abdominal tenderness, guarding, fever, peritonitis, bile drainage from the drainage tube, peritonitis, intra-abdominal abscess, sepsis and septic shock. Investigations that facilitated diagnosis included computed tomography (CT) abdomen, ultrasound with or without aspiration, estimation of amylase level in the drainage/aspirated fluid, gastrograffin study and gastroscopy and diagnostic laparoscopy (Table 1). The site of injury was reported in 13 cases of which 4 cases (31%) occurred in the 1st part, 6 cases (46%) occurred in the 2nd part above the duodenal papilla, 2 cases (15%) occurred in the 2nd part (below the papilla) and 1 case (7.6%) occurred in the 3rd part of the duodenum. Among the 30 cases where the management was reported,

19 (63%) underwent primary closure of duodenal perforation (duodenorrhaphy) among which 4 (21%) was carried out laparoscopically. The remaining procedures included percutaneous drainage in 4 cases (13.3%), tube duodenostomy (6.6%), gastric resection 2 cases (6.6%), and one each (3.3%) of Whipple resection, pyloric exclusion with gastrojejunostomy and laparoscopic endo gastrointestinal (GI) closure of perforation (Table 2). Among the 65 cases where the outcome was defined, 53 patients (82%) survived and 12 patients (18%) died (Table 2). The mean period of detection of injury in those who survived was 1.6 d (including those detected on table considered as day 0 compared to 4.25 d in those who died). However, if the ones who were detected on the table were excluded, the mean detection time for those who survived was 2.36 d compared 4.25 d for those who died.

Forest plots for duration of detection and mortality

The forest plot for time of detection of injury (in days) is presented in Figure 2. This suggests that there is no heterogeneity among studies considered in the analyses as the I^2 was about 50%. Therefore, based on the random effect model the overall mean (95%CI) duration of detection of injury is about 1.6 (1.0, 2.2) d.

The forest plot for injury related mortality is provided in Figure 3. This also suggests that there is no heterogeneity among studies, as the I^2 was about 6%. Therefore, based on the fixed effect model the overall mortality rate from these studies was 10% (0%, 25%).

Association between day of detection and mortality

Table 3 presents the mortality status according to days of detection. There were 15 patients who were detected to have injury within a day (0 or 1 d). Of them one patient died (6.7%). However, of the 13 patients who were detected to have injury after day 1, 5 of them have died (38.5%). The difference in mortality rate was significantly different suggesting that early detection was associated with lower mortality ($P < 0.05$).

Based on the Kaplan Meier survival probabilities for mortality of patients over time (days), the cumulative probability of survival was about 94%, if the injury was detected on day 1 and 80%, if the injury was detected at day 2. However, if the injuries were detected later on, then the survival probabilities dropped down steeply, especially after day 2 (Figure 4). This suggests that if the day of detection is delayed then the probability of dying is very high.

DISCUSSION

LC is the standard treatment for symptomatic cholelithiasis. Over the years, difficult LC has been conducted regularly even in patients with active inflammation, cirrhosis, adhesions and contracted fibrosed gall bladder^[1,6,28,29]. This has been possible due to the growing experience in laparoscopic surgery and advances made in

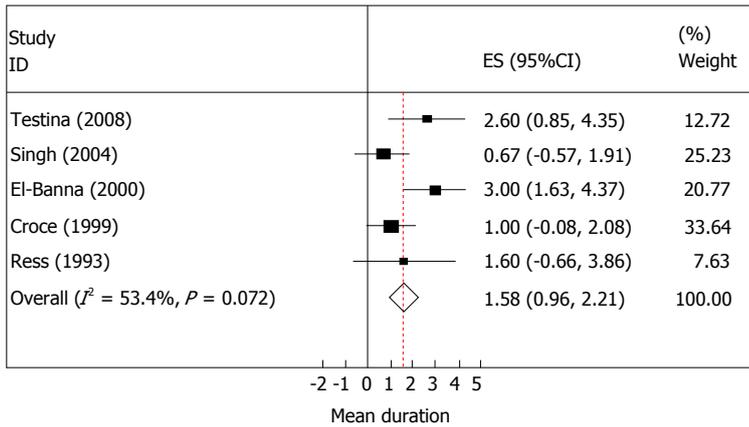


Figure 2 Forest plot of duration to detect injury (days).

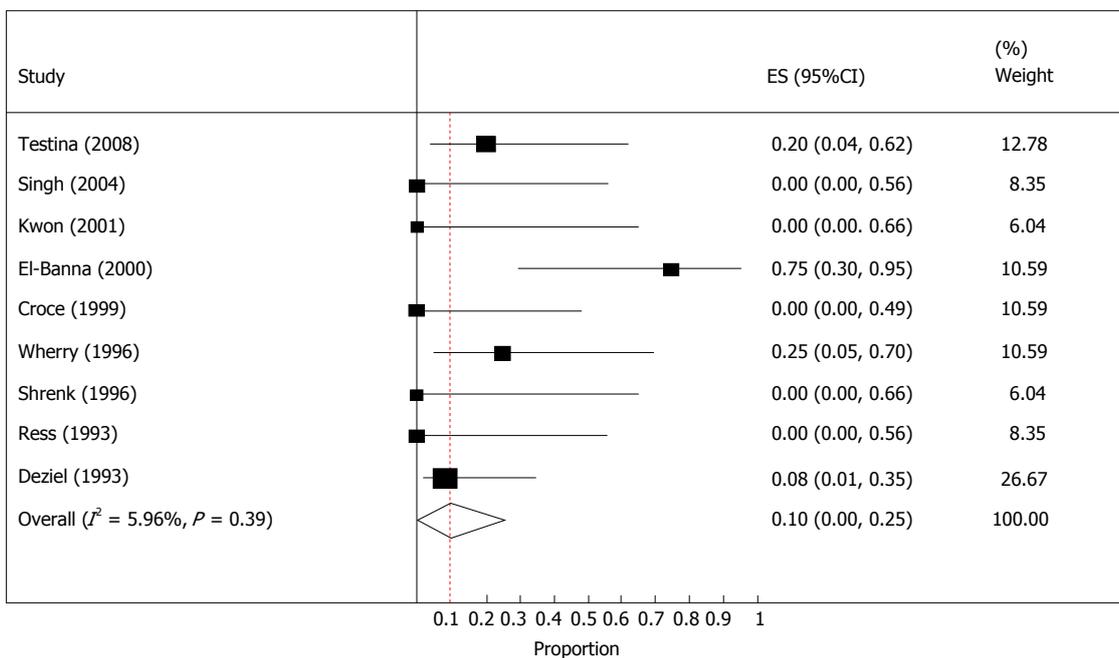


Figure 3 Forest plot of injury related mortality.

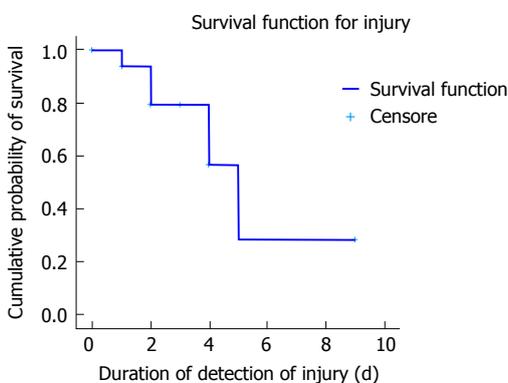


Figure 4 Survival function for injury.

instrumentation^[28,29]. Unfortunately, major complications including bowel injuries still occur, and duodenal injury among them though rare, are generally associated with significant morbidity and mortality^[4-26].

Incidence

Major complications following LC have been reported in 2% of large series among which bowel injuries occurred in 0.07%-0.9% of these cases^[15]. Among the bowel injuries, 58% occurred in small bowel, 32% in large bowel and 7% in stomach^[28]. The overall incidence of duodenal injuries is reported to be 0.04% (range 0.01%-4%)^[6]. While bile duct injury is the most common, vascular and bowel injuries are the most serious procedure related complications^[3,5,7,28-30].

Mechanism of injury

Injuries to the bowel could be related to the introduction of a Veress needle, trocar insertion, application of grasping forceps, sharp dissection with scissors and thermal contact burns or conductive burns during a laparoscopic procedure^[6,30]. In a large study of 226 bowel injuries sustained during 205969 cases of laparoscopic procedures, 50% were caused by cautery and 32% by

Table 1 Literature review-duodenal injury post laparoscopic cholecystectomy: Demographic details, presentation and investigations

Ref.	Nature of study	No. of Du/No. of LC (%)	Age (yr) mean range	Gender	Time of diagnosis From LC in days	Presentation	Investigations
Modi <i>et al</i> ^[8]	CR	1	47	M	2	BDr-1	CT-1 Fist-1 Gasc-1
Jing <i>et al</i> ^[9]	CR	1	74	M	4	Fever	CT-1 BA-St-1 US-asp-1
Yajima <i>et al</i> ^[26]	CS	1/407	NA	NA	Immed-day 0	NA	NA
Testini <i>et al</i> ^[6]	CS	5	59 (49-51)	M-4 F-1	Immed-1-day 0 1 st day-1 3 rd day-1 4 th day-1 5 th day-1	Fever-2 Tachycardia-1 Leukocytosis Rigidity/vomiting Sshock-2	Amyd-1 CT-4
Singh ^[10]	CS	3/1748 (0.17%)	33 (23-45)	F-3	Immed-2 2 nd day-1	Fever Abd. pain	CT-2
Avrutis <i>et al</i> ^[24]	CR	1	NA	NA	9 th day	Haemtemesis Intra-abd abscess	NA
Kwon <i>et al</i> ^[11]	CS	2/1190	50 68	M-2	NA	NA	NA
El-Banna <i>et al</i> ^[7]	CS	4/NA	32-73 47	M = 2 F = 2	Immed-1-day 0 3 rd day-1 4 th day-2	Sshock-2 (4 d) Local peritonitis-1 Diffuse peritonitis-1	X-ray abd CT US abd
Bishoff <i>et al</i> ^[30]	CS	1/915	NA	NA	NA	NA	NA
Croce <i>et al</i> ^[12]	CS	4/2100 (0.2%)	50 (45-56)	M = 1 F = 3	Immed = 2 -day 0 2 nd day = 2	Abd pain = 4 Tachycardia leukocytosis Rigidity = 1 vomiting	US asp-2 CT = 2 Gastrffin = 2 Amyd = 2 Relapsc = 4
Roviaro <i>et al</i> ^[13]	CS	1/1005 (0.09%)	NA	NA	NA	NA	NA
Huang ^[14]	CS	19/39238 (0.04%)	NA	NA	NA	NA	NA
Wherry <i>et al</i> ^[2]	CS	4/9130 (0.04%)	NA	NA	NA	NA	NA
Schrenk <i>et al</i> ^[15]	CS	2/1690 (0.1%)	70 80	F = 2	Immed = 2 -day 0	NA	NA
Chen <i>et al</i> ^[17]	CS	1/2428 (0.04%)	NA	NA	Immed = 1 -day 0	Immed = 1	Immed = 1
Kum <i>et al</i> ^[16]	CS	1/25 (4%)	NA	NA	Immed = 1 -day 0	Immed = 1	Immed = 1
Cala <i>et al</i> ^[19]	CS	1/1000 (0.01%)	NA	NA	NA	NA	NA
Baev <i>et al</i> ^[20]	CS	1/700 (0.14%)	NA	NA	NA	NA	NA
Yamashita <i>et al</i> ^[21]	CS	1/1054 (0.09%)	42	F	Immed = -day 0	Immed = 1	Immed = 1
Berry <i>et al</i> ^[25]	CR	1	76	F	6 th day	Tachycardia, tachypnea, nausea, vomiting, leukocytosis	CT
Ward <i>et al</i> ^[18]	CS	1/NR	NA	NA	NA	NA	NA
Ress <i>et al</i> ^[4]	CS	3/NA	NA	NA	Immed = 1 -day 0 1 st day = 1 4 th day = 1	Sshock = 1 Abd pain = 1 Immed = 1	CT US
Deziel <i>et al</i> ^[5]	CS	12/77.604 (0.01%)	NA	NA	NA	NA	NA
Peters <i>et al</i> ^[23]	CS	2/283 (0.7%)	NA	NA	NA	NA	NA

LC: Laparoscopic cholecystectomy; CR: Case report; CS: Case series; Immed: Immediate (on table); CT: Computerised tomography; US: Ultrasound abdomen; Fist: Fistulogram; BA-St: Barium study; Du: Duodenal injuries; Gasc: Gastroscopy; AmyD: Amylase level in draining fluid; US asp: Ultrasound guided aspiration; BDr: Bile drainage from drain; Abd: Abdominal; Sshock: Septic shock; Relaps: Relaparoscopy; Gastrffin: Gastrograffin study; NA: Not available; M: Male; F: Female.

Veress needle or trocar insertion^[30]. In another larger study of 430 bowel injury following 329935 cases of laparoscopic procedures, small intestine injury occurred in 55.8%, followed by large intestine (38.65%)^[31]. Importantly, 66.8% of bowel injuries were diagnosed during laparoscopy or within 24 h thereafter.

Bowel injury during access

A trocar or Veress needle insertion caused 41.8% of bowel injuries and those due to coagulator or laser were in 25.6% of the cases^[31]. Bowel injuries resulting from trocar puncture is usually readily recognized and

promptly repaired^[6]. Bowel injuries related to Veress needle or trocar insertion may have declined over the years^[11]. Duodenum being anatomically retroperitoneal and away from the umbilicus (the usual site of access for pneumoperitoneum) is unlikely to sustain injury during initial step of insufflation^[25]. This is reflected in this review, were no cases of duodenal injury have been reported due to veress needle or trocar insertion.

Bowel injury during dissection

Duodenal injury is more likely to occur due to thermal injury, sustained during the use of cautery^[6,30,32]. It was

Table 2 Literature review on duodenal injury post laparoscopic cholecystectomy: Surgery details and outcome

Series	Site of injury	Cause of injury	Nature of surgery	Day of detection and outcome
Modi <i>et al</i> ^[89]	D1/D2 junction	BlDis-1	Conservative - US guided aspiration of collection = 1	2 nd day - survived
Jing <i>et al</i> ^[91]	D1 = diverticulum	NA	Conservative - percutaneous drain = 1	4 th day - survived
Yajima <i>et al</i> ^[26]	NA	NA	NA	NA
Testini <i>et al</i> ^[6]	D2A-2	BlDis-2	Duodenoraphy + t tube = 2	Immed-day 0 - survived
	D2B-2	Caut-3	Petzer t tube = 1	1 st day = survived
	D3-1		Gastric resection = 1	3 rd day = survived
			Whipple resection = 1	4 th day = survived
				5 th day = died
Singh <i>et al</i> ^[10]	NA	Bl Dis-3	Duodenoraphy = 3	Immed-day 0 - survived
				Immed-day 0 - survived
				2 nd day = survived
Avrutis <i>et al</i> ^[24]	NA	NA	NA	NA
Kwon <i>et al</i> ^[11]	NA	Bl Dis-2	Laparoscopic Endo GI closure = 1	Day of injury = NA
			Laparoscopic intracorporeal suturing = 1	Survived
El-Banna <i>et al</i> ^[7]	NA	Caut-4	Percutaneous drain = 1	Immed-day 0 - died
			Gastrectomy + duodenostomy = 2	3 rd day = survived
			Serosal patch = 1	4 th day = died
				4 th day = died
				NA
Bishoff <i>et al</i> ^[30]	NA	Bl Dis- scissors	Laparotomy duodenoraphy = 1	NA
Croce <i>et al</i> ^[12]	D1 = 2	Retraction = 3	Laparoscopic - intracorporeal suturing = 2	Immed-day 0 = survived
	D2 = 2	Caut = 1	Laparotomy = duodenoraphy + omental patch	Immed-day 0 = survived
			Relaprosopy = missed injury, conservative (NPO/TPN/ somataostatin) = 1	2 nd day = survived
				2 nd day = survived
Roviaro <i>et al</i> ^[13]	NA	NA	NA	NA
Huang <i>et al</i> ^[14]	NA	NA	NA	NA
Wherry <i>et al</i> ^[2]	NA	NA	NA	Day of injury = NA
				Survived = 3
				Died = 1
Schrenk <i>et al</i> ^[15]	NA	Caut = 1	Duodenoraphy = 2	Immed-day 0 = survived
		Bl Dis = 1		Immed-day 0 = survived
Chen <i>et al</i> ^[17]	NA	NA	NA	NA
Kum <i>et al</i> ^[16]	NA	Caut = 1	Laparoscopy + duodenoraphy = 1	Immed-day 0 = survived
Cala <i>et al</i> ^[19]	NA	NA	NA	NA
Baev <i>et al</i> ^[20]	NA	NA	Laparotomy + duodenoraphy = 1	NA
Yamashita <i>et al</i> ^[21]	NA	Retraction	Laparotomy + duodenoraphy = 1	Immed-day 0 = survived
Berry <i>et al</i> ^[25]	D2A	Caut = 1	T tube duodenostomy + pyloric exclusion + gastrojejunostomy	6 th day = survived
Ward <i>et al</i> ^[18]	NA	NA	NA	NA
Ress <i>et al</i> ^[4]	NA	Caut = 2	Laparoscopy + serosal tear repair	Immed = day 0 = survived
		Bl dis = 1	Laparotomy + duodenoraphy = 2	1 st day = 1 = survived
				4 th day = 1 = died
Deziel <i>et al</i> ^[5]	NA	NA	Laparotomy = 12 (details NA)	Day of injury = NA
				Survived = 11
				Died = 1
Peters <i>et al</i> ^[23]	NA	NA	NA	NA

D1: Superior flexure; D2A: Above duodenal papilla; D2B: Below duodenal papilla; D3: Inferior flexure; Bl Dis: Blunt dissection; Caut: Electrocautery; NA: Not available; US: Ultrasound abdomen; GI: Gastrointestinal; Immed: Immediate (on table detection); NPO: Nil per oral; TPN: Total parenteral nutrition.

noted as a leading cause in 46% of the cases in this review. It is at risk of being overlooked in the course of surgery and may manifest itself later as a consequence of coagulation necrosis of the bowel wall^[2,5,15,31]. Bowel wall necrosis may result in delayed or walled off perforation, which may present in days or weeks^[12,15,32]. Majority of the laparoscopic duodenal injuries reported in the literature and found in our review are due to electrocautery damage, or during the dissection of difficult Calot's triangle, either due to adhesions or because of the distorted anatomy^[10,12,14,16,32]. To prevent thermal injury, the equipment should be checked regularly for defects in insulation^[4,15]. In addition, movements of

all instruments should be under direct vision by following it with camera, while the instruments are out of view^[15]. Others have suggested avoiding the use of sharp pointed suction/irrigation devices to retract the duodenum^[12]. The sharp edge of the suction device may traumatize the duodenum, when used to retract it caudally and to the left^[12]. When bowel has been grasped during manipulation, the site that is grasped is carefully inspected for any possible injury, particularly when the gut is unusually vulnerable for injury^[15]. Inadvertent bowel retraction, along with injury during the use of electrocautery is often the cause of duodenal injury^[4-6,10,14,15] (Table 2). Thermal burns can to a large

Table 3 Distribution of mortality status by days of detection of injury

Days of detection of injury	Injury detection status				Total
	Alive		Dead		
	<i>n</i>	%	<i>n</i>	%	
0	12	100	0	0.0	12
1	2	66.7	1	33.3	3
2	2	50.0	2	50.0	4
≥ 3	6	66.7	3	33.3	9
Total	22	78.6	6	21.4	28

extent be reduced by ensuring adequate insulation up to its tips, use of low power current, and nonuse of cautery in close proximity to the bowel. It should be rather used directly on tissues to be cauterized^[15]. One should also be aware of the capacitive coupling that occurs along the shaft of instruments, with relatively thin insulation coats^[33]. This stray energy may be responsible for otherwise unrecognized, unintentional injury during monopolar laparoscopic cauterization^[15,23,33].

The risk of complication during surgery is often reported to be related to surgeons experience; however, experienced surgeons often attempt to operate under less than ideal circumstances and in complex situations^[5,6,30]. In one of the reports, 60% of bowel injuries occurred with surgeons who were experienced and would have performed at least 100 LC^[6].

Diagnosis

Time at which bowel injury is recognized following the laparoscopic procedure is variable and is reported to range from 2 to 14 d (average 4.5 d) for small bowel injury and from 1 to 29 d (average 5.4 d) for large bowel injury^[30]. Duodenal injury may be detected on table or in the postoperative period [range 0 (on table) to 5 d] and is detected according to some report on an average on the 3rd postoperative day^[6]. However, this review noted the detection rate on an average at 1.7 d as in 46% of the cases it was detected on the table. Diagnosis of duodenal injury in postoperative period is often difficult and requires a high index of clinical suspicion, because of its rarity^[5,6,14,15,30]. Patients who had a difficult cholecystectomy due to adhesions of the gall bladder, particularly to the duodenum, are at a greater risk^[10,14,15]. The injury should be suspected in patients with unexplained cause of postoperative fever, nausea, vomiting, anorexia and abdominal distension^[5,6,12,14,15]. Pain, which may be undue and restricted initially to right hypochondrium, may later become generalized^[12,14,15]. Pain in the early stages is likely to be ignored as it is a relatively common finding after LC. However, it becomes significant, if it persists beyond 24 h and increases in intensity^[12]. Posterior wall duodenal perforation may not result in peritonitis, but may present with lumbar pain^[12].

Liver function tests may be normal or show mild elevation of bilirubin and serum amylase with normal alkaline phosphatase^[5,12,14,15]. The diagnosis however can be clinched, if the drain fluid shows high amylase levels,

in patients where drain was placed intraoperatively, because of difficult cholecystectomy^[12]. The amylase level could also be estimated by ultrasound guided aspiration of fluid of the duodenal leak^[12]. When carried out, contrast study with gastrograffin may confirm the leak^[12]. CT scan which is more sensitive than ultrasound abdomen, could reveal large collection of fluid around the duodenum or in the general peritoneal cavity, based on when the procedure is performed in the post operative period^[6]. The finding of significant amount of air and fluid in the abdomen, beyond what can be explained as a postoperative finding and the demonstration of contrast leak when performed with oral contrast^[9], are findings that are consistent with the diagnosis of duodenal injury^[12]. Obliteration of the right psoas muscle, evidenced by retroperitoneal gas, may indicate retroperitoneal duodenal leak. When in doubt, it is advisable to perform at least an early diagnostic laparoscopy, as time is of essence for a better outcome^[5,6,12,15]. Presence of bile on re-exploration, in the absence of leak from hepatic bed, cystic duct or common bile duct suggests the diagnosis of duodenal injury^[12]. Forward displacement of the duodenum by posterior mass, reflects the posterior location of the perforation^[23,25]. Unfortunately, laparoscopy may also fail in detecting a small perforation and this misdiagnosis may lead to intra abdominal or retroperitoneal collection in the lumbar region and sepsis leading to a protracted postoperative course^[12]. In the event the injury is not obvious during laparoscopy, then it would be worthwhile detecting the injury by upper GI endoscopy and demonstrating air leak around the duodenum by air insufflation.

Management of duodenal injury

The outcome of duodenal injury would depend to a large extent on the site and the time of diagnosis^[4-23]. The management could range from conservative in selected few^[8,9], to more complex surgeries in those with delayed intervention^[6,34,35]. While there are reports of successful conservative management^[8,9], most would agree on an immediate surgical intervention^[5,6,10,14,15,30]. Successful conservative management with drain has been reported in a patient with previous Billroth 11 gastrectomy^[9]. This patient had sustained a cautery induced perforation to a duodenal bulb diverticulum, rather than the duodenal wall. The site of perforation and diversion of gastric contents is reported to have attributed to the successful conservative management in this patient^[9]. Successful conservative management has also been reported in a patient where the drain that was inserted during the surgery, had inadvertently fistulated into the duodenal injury^[8]. The drain was used successfully to divert the duodenal content in postoperative period, allowing the patient to respond to conservative management^[8].

In those patients where surgical intervention is required, its nature would depend on the time of detection of injury and the site^[5,6,14,15,30]. Duodenal perforation may require meticulous search, by means of intraoperative upper GI endoscopy or duodenal mobilization by Kocher's

maneuver^[12]. When the injury is detected on table or following re-exploration shortly after LC, direct repair of duodenal injury with omental patch is feasible^[6]. This repair could be performed laparoscopically, when the duodenum is relatively healthy, defect is small and expertise is available^[11,12,16,22]. However, most recommend immediate laparotomy to assess the abdomen and secure a safe repair^[4,5-7,21]. However, delay in diagnosis beyond 48 h may lead to oedematous macerated duodenum, which will fail to hold sutures of repair, resulting in duodenal fistula^[5,6,10,14,15,30].

Site of duodenal injury is a critical factor, that influences both the outcome and approach to management^[5-7,10,14,15,30]. When injury occurs just above or below the duodenal ampulla of Vater, the biliary fluid and pancreatic juice leak will complicate matter^[5,6,10,14,15]. Resection of the damaged tissue and repair could be challenging in these cases, particularly in patients where there is a delay in diagnosis. Several approaches have been proposed in the literature, which include mucosal or serosal patches and a pedicle graft with a free vascular pedicle created from stomach, jejunum or ileal tissue; however their efficacy has not been proven^[36-38]. In general, the often practiced approach includes duodenal drainage with a decompression tube, temporary pyloric exclusion, gastrojejunostomy, feeding jejunostomy, gastric resection with external duodenal drainage with Foley or Petzer tubes^[6]; however, the outcome reported are conflicting^[34,39,40]. More aggressive approach may be warranted in the presence of larger defects and softer duodenal wall and may involve duodenojejunostomy or duodenopancreatectomy^[6,23,34]. The outcome depends to a large extent on the degree of peritonitis and sepsis, which in turn is related to the extent of delay in diagnosis^[5,6,10,14,15,29]. While the injury to descending duodenum is challenging to manage, those that occur at the duodenal bulb or superior flexure of duodenum, could be safely managed with gastric resection and duodenal stump closure^[5,6]. Majority of the patients in this review underwent duodenorrhaphy or duodenostomy. In exceptional case, a patient may undergo Whipple resection^[6]. In this review, in a solitary case, Whipple resection was carried out (Table 2). The injury was detected on the 4th postoperative day. While the need for pancreaticoduodenectomy is not clear, the gravity of the problem is reflected by the fact that the patient had a stormy postoperative period and was discharged two months later^[6].

The concerning aspect of duodenal injuries is the reported mortality in the range of 8.3%^[5] to 75%^[7]. Deziel *et al*^[5] reported an 8.3% mortality rate among 12 patients with duodenal injuries in their analysis of 77604 cases. El-Banna *et al*^[7] noted mortality in three of the four (75%) duodenal injuries. Huang *et al*^[14] reported that 4 out of 19 (21.05%) patients with duodenal injury died in their study of 39238 LC cases. Our review observed an overall mortality of 17%. It is most likely that the duodenal injuries are underreported^[6,41]. These patients are also at the risk of having significant morbidity, which

could lead to protracted hospital course^[6]. The morbidity includes intra-abdominal complications like abscess and peritonitis^[12], septicaemia, necrotising fasciitis^[6,31], pneumonia^[15], incisional hernia^[7] and lumbar abscess^[12] (Table 2). Posterior lumbar abscess may occur due to disruption of the posterior peritoneal membrane during cholecystectomy or during reoperation for duodenal repair^[12].

Duodenal injury is uncommon but is associated with significant morbidity and mortality. These are sustained during LC, usually due to thermal burn and blunt or sharp dissection. Unsatisfactory recovery post difficult LC, should raise the suspicion. Radiological imaging, analysis of the drain fluid for bile and or amylase levels and endoscopy, will facilitate the diagnosis. Early diagnostic laparoscopy is warranted when in doubt. Prompt surgical intervention, which may involve duodenal repair or resection may be required. Outcome would be significantly influenced by the delay in diagnosis.

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COMMENTS

Background

Inadvertent duodenal injury is a rare but potentially fatal complication of laparoscopic cholecystectomy (LC). Such injuries often go unrecognized at the time of the procedure and manifest later with significant morbidity and mortality. In this article the literature is reviewed regarding the mechanism, presentation, investigation and management of this serious, though uncommon complication. Among the 76 cases that were detected in the literature, 46% of the injury was caused by the use of cautery and in 39% during dissection. The commonest site of injury was to the 2nd part of the duodenum and in only half of these patients, the injury was detected on table. Predominant repair was duodenorrhaphy and in 21% this was carried out laparoscopically. The mean day of detection was 1.6 d among those who survived compared to 4.25 d among those who died. Mortality of 18% was noted. This article is of importance as literature lacks adequate data on the etiopathogenesis, management and outcome of this rare, yet life threatening complication. Early detection requires high index of clinical suspicion in a patient with difficult cholecystectomy who has unexpected post operative course, raised amylase levels in fluid from the drain when placed or radiological images suggestive of subhepatic fluid collection not explained otherwise.

Research frontiers

This article reviews the literature with regards to duodenal injury post LC. Review of literature indicates the commonest cause for injury is due to cautery and blunt and sharp dissection employed during cholecystectomy. The predominant finding is, that delay in diagnosis makes simple repair with duodenorrhaphy non feasible requiring more complex surgery. In addition the poor outcome is directly related to the delay in diagnosis.

Innovations and breakthroughs

This is a review article on duodenal injury post LC and aspects of innovations and breakthroughs may not be applicable to it.

Applications

This article is of importance to surgeons who perform LC. Its applicability is in warning clinicians of this potential complication when their patient develops

postoperative abdominal pain and distension unexplained by any other cause. It then guides them in investigating these patients and managing them, while reminding them of the potential mechanism for this complication.

Peer-review

This is a good review of an uncommon condition.

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Targeted therapy of gastrointestinal stromal tumours

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Abstract

Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms originating in the gastrointestinal tract, usually in the stomach or the small intestine, and rarely elsewhere in the abdomen. The malignant potential of GISTs is variable ranging from small lesions with a benign behaviour to fatal sarcomas. The majority of the tumours stain positively for the CD-117 (KIT) and discovered on GIST-1 (DOG-1 or anoctamin 1) expression, and they are characterized by the presence of a driver kinase-activating mutation in either KIT or platelet-derived growth factor receptor α . Although surgery is the primary modality of treatment, almost half of the patients have disease recurrence following surgery, which highlights the need for an effective adjuvant therapy. Traditionally, GISTs are considered chemotherapy and radiotherapy resistant. With the advent of targeted therapy (tyrosine kinase inhibitors), there has been a paradigm shift in the management of GISTs in the last decade. We present a comprehensive review of targeted therapy in the management of GISTs.

Key words: Gastrointestinal tumors; Molecular targeted therapy; Protein kinase inhibitors; Imatinib; Survival

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Core tip: Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumours of the gastrointestinal tract. They are characterized by the presence of a driver kinase-activating mutation in either CD-117 or platelet-derived growth factor receptor α . Development of tyrosine kinase inhibitors has led to a paradigm shift in the management of GISTs. Surgery is the primary

modality of treatment in localized non-metastatic GISTs. Adjuvant Imatinib for three years is a preferred option for high-risk patients to lessen disease recurrence. The role of neoadjuvant Imatinib is evolving. Imatinib, Sunitinib, and Regorafenib are recommended as first, second and third-line targeted therapies, respectively, for the management of metastatic GISTs.

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INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and hypothesised to arise from the intestinal cells of Cajal^[1]. GISTs constitute 1%-3% of all malignant gastrointestinal tumours, with an annual incidence rate of 10 to 15 cases per million^[2]. Commonly, they arise from the stomach (60%-70%) and small intestine (25%-35%); other rare intestinal sites are the colorectum, oesophagus and appendix. Rarely, they can also involve extra-intestinal sites including the omentum, retroperitoneum, and mesentery (extra-intestinal GISTs)^[3]. Histologically, GISTs can be of three types: Spindle cell type (70%), epithelioid, and mixed subtype^[3]. They are diagnosed based on clinical and morphological features which are supported by immuno-histochemistry studies. CD-117 (KIT) and discovered on GIST-1 (DOG-1 or anoctamin 1) are the most sensitive and specific markers; other diagnostic markers include CD-34 (70% positivity), smooth muscle actin (20%-30% positivity), S-100 (10% positivity), and negativity for desmin (2%-4% of GISTs may be positive for desmin). About 5% of GISTs are negative for KIT expression, however many of them express DOG-1^[3-6]. Complete resection (R0) is the primary treatment in the management of localized GISTs. Traditionally, GISTs are considered chemo-resistant and radio-resistant tumors^[7]. Half of the patients have disease relapse in the first five years of surgery, and 5-year actuarial survival rate after surgery was reported as 54%^[4]. This highlights the need for effective adjuvant therapy. Imatinib, a tyrosine-kinase inhibitor (TKI) developed in 1998 for chronic myeloid leukaemia (CML), galvanized a lot of enthusiasm in the management of GISTs due to its direct inhibition of KIT and platelet-derived growth factor receptor α (PDGFRA) mutation related tyrosine kinase activity^[7]. The last 15 years witnessed remarkable progress in the field of TKIs resulting in significant improvement in the treatment outcomes in locally advanced and metastatic GISTs. The present article reviews the current status of targeted therapy of GISTs.

RATIONALE OF TARGETED THERAPY

Around 75%-80% of GISTs have KIT mutations, mainly affecting juxta-membrane domain coded by exon 11. Deletions are the most common; however insertions, substitutions and combinations can be seen. Rarely, mutations can also affect extracellular domain (exons 8 and 9) or kinase I and II domains (exons 13 and 17)^[8-10]. Approximately 20%-25% of GISTs do not have KIT mutations; around 10% of these cases have PDGFRA mutations. The remaining (10%-15%) who do not have either KIT or PDGFRA mutations are labelled as wild-type GISTs; this group forms a heterogeneous group which have mutations acting on downstream of receptor kinases^[11-13]. Ultimately mutations of KIT and PDGFRA promote cell signalling through the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) pathways^[9,10,14]. As structural similarities were detected between BCR-ABL kinase and KIT kinase, Imatinib was used in a metastatic GIST patient and it led to a dramatic response. This success led to the beginning of multiple clinical trials to establish the role of Imatinib and other TKIs in GISTs^[7,12].

ROLE OF TARGETED THERAPY IN METASTATIC GISTS

Although there has never been a randomized controlled trial (RCT) to compare targeted therapy with chemotherapy in the management of metastatic GISTs, various studies have highlighted the potential role of targeted therapy in improving survival.

Imatinib mesylate

Imatinib, a small molecule TKI with activity against BCR-ABL, KIT and PDGFRA related kinases, was the first Food and Drug Administration approved agent in metastatic GISTs. In an open label phase II trial to assess efficacy and safety of Imatinib in 147 patients with advanced GISTs, Demetri *et al.*^[13] in 2002 reported that Imatinib resulted in partial response in 53.7% and stable disease in 27.9% of patients. Therapy was well tolerated, although mild to moderate edema, diarrhea, and fatigue were common, and gastrointestinal or intra-abdominal hemorrhage occurred in approximately 5% of patients. Long-term results of this trial, published in 2008, further confirmed that nearly 50% of patients with advanced GISTs who were treated with Imatinib survived for more than 5 years. After a follow-up of up to 71 mo, there was complete response in 1.4% and partial response in 68.1%; disease remained stable in 15.6% and progressed in 11.6%. This translated into median progression free survival (PFS) of 24 mo and median overall survival (OS) of 57 mo^[15]. These results were soon validated by two phase III multi-centric RCTs which were designed to address the optimal daily dose of Imatinib. A multi-centric RCT was conducted by

EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group to address dose dependency of response and PFS with Imatinib for metastatic GISTs^[16]. They randomized 946 patients into two groups based on daily dose of Imatinib, 400 mg either once or twice a day. At median follow-up of 760 d, higher dose Imatinib (400 mg twice a day) led to better PFS (56% vs 50%, HR = 0.82, 95%CI: 0.69-0.98, $P = 0.026$). They concluded that a dose of 400 mg twice a day leads to significantly longer PFS, as compared to once a day dosing, although both dosing achieve similar response induction. Moreover, higher dosing also resulted in a significantly higher number of treatment interruptions (64% vs 40%) or dose reductions (60% vs 16%). Relatively different results were noted by another phase III RCT, Southwest Oncology Group S0033 trial^[17]. Although the authors confirmed the effectiveness of Imatinib as a primary systemic therapy in metastatic GISTs, they concluded that higher dose (800 mg/d) does not provide any advantage over conventional dose (400 mg/d) therapy. They also reported a higher frequency of drug related toxicities among patients who received 800 mg/d Imatinib (grade 3-5 toxicities 63% vs 43%). The Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) conducted a meta-analysis exploring the data of the previously published two large, randomized, cooperative-group studies which had compared two doses of Imatinib (400 mg daily vs twice daily) in 1640 patients with advanced GISTs^[18]. They reported a small (HR = 0.89; 95%CI: 0.79-1.00) but significant ($P = 0.04$) PFS advantage for the high-dose arm; however, no significant difference was observed in OS (HR = 1.00, $P = 0.97$) between the two groups. Cox regression analysis showed that higher dose therapy would potentially delay the first occurrence of disease progression and increase objective response rate in only those patients who harbor KIT exon 9 mutations. Based on these results, 400 mg daily is established as standard first line therapy; however, due consideration for higher dose (800 mg/d) may be given in patients who have KIT exon 9 mutation or have progressed on 400 mg/d of Imatinib. The subgroup analysis of these two trials also highlighted that those patients who have exon 11 mutations would respond better to Imatinib than those who have exon 9 or wild-type allele^[16-19]. Although almost all mutant subtypes are likely to have improved PFS and OS when treated with Imatinib compared to chemotherapy (historical controls), D842V mutations in PDGFRA confer resistance to Imatinib therapy; no clinical benefit has been demonstrated with Imatinib in tumours having this mutation^[18,20,21]. How long Imatinib is to be given in metastatic GISTs is the next natural question. French Sarcoma Group designed a phase III RCT to compare continuous (CONT) compared with interrupted (INT) Imatinib beyond 1 year of treatment^[22]. They randomized 58 advanced GIST patients who had either response or stable disease after one year of Imatinib therapy into two groups - 32 patients (INT arm) stopped

while 26 patients (CONT arm) continued to receive Imatinib therapy. There was a significantly higher frequency of disease progression in INT arm - 26 of 32 (81%) patients had documented disease progression patients as compared to 8 of 26 (31%) patients in the CONT group ($P = 0.0001$). Moreover, 24 of 26 patients with documented disease progression in the INT arm responded when Imatinib was reintroduced to them. This led to the conclusion that Imatinib is to be continued in advanced GISTs till evidence of disease progression or intolerance.

Other targeted agents

Sunitinib is a TKI, which inhibits KIT, PDGFRA, vascular endothelial growth factor receptors (VEGFR) 1-3 and FLT3 receptor kinase^[23]. Apart from having an inhibitory effect on oncogenic kinases, it also has antiangiogenic properties. In an initial phase I / II study, Sunitinib has shown promising clinical activity for Imatinib resistant patients^[24]. A phase III trial randomized 312 Imatinib resistant metastatic GIST patients to receive either Sunitinib or placebo; best supportive care was given in both the arms^[25]. Time to tumour progression (TTP) was four times longer in Sunitinib arm as compared to placebo (27.3 wk vs 6.4 wk, HR = 0.33, 95%CI: 0.23-0.47, $P < 0.0001$); similarly PFS was significantly better in Sunitinib arm (24.1 wk vs 6 wk, HR = 0.33, 95%CI: 0.24-0.47; $P < 0.0001$). Although relatively low but confirmed objective response rate was better in Sunitinib arm (7% vs 0%, $P = 0.006$); 16% of patients were progression free at 6 mo in Sunitinib arm vs 1% in placebo. Despite cross-over, OS was better in Sunitinib arm than placebo (HR = 0.49, 95%CI: 0.29-0.83; $P = 0.007$). Serious treatment related adverse events were 20% in Sunitinib arm and 5% in placebo arm and only 9% discontinued treatment in Sunitinib arm due to adverse events. So, Sunitinib improved TTP, PFS and OS in patients with Imatinib resistance with acceptable toxicity profile. Presently, Sunitinib is recommended as second line therapy for patients who are intolerant or have progressive disease on Imatinib. Recommended dosing schedule is 50 mg daily orally for four weeks followed by a break for 2 wk; or a continuous regimen with daily dose of 37.5 mg can also be used^[25,26].

Regorafenib is an oral multikinase inhibitor which inhibits various protein kinases, including those involved in angiogenesis (VEGFR 1-3, PDGFRB, FGFR1) and oncogenesis (KIT, RET, BRAF)^[27]. In a multicenter phase II trial, Regorafenib at a dose of 160 mg daily for 3 wk in a 4 wk cycle showed a clinical benefit rate of 79% (95%CI: 61%-91%). Median PFS was 10.0 mo^[28]. On the basis of these results, a multicentric phase III trial, GRID, was planned to evaluate the efficacy and safety of Regorafenib in metastatic GIST patients who had progressed after initial Imatinib and Sunitinib therapy. A total of 199 patients were randomized to receive Regorafenib or placebo along with best supportive care in both the arms. Disease control rate was significantly better in Regorafenib arm than in placebo arm (52.6%

vs 9.1%, $P < 0.0001$). Median PFS was 4.8 mo (interquartile range = 1.4-9.2) in Regorafenib arm and 0.9 mo (0.9-1.8) in placebo arm (HR = 0.27, 95%CI: 0.19-0.39, $P < 0.0001$). Eighty-five percent of patients crossed over from placebo to Regorafenib group, so OS was not different (HR = 0.77). Regorafenib related grade III or more toxicity was present in 61% of patients^[29]. Thereafter, Regorafenib was approved as a third line standard of care in metastatic GIST patient who have progressed or intolerant to Imatinib and Sunitinib.

Masitinib is another highly selective TKI with significant activity against GISTs. In a recent RCT it was compared with Sunitinib in advanced GIST patients after failure of Imatinib. Trial showed encouraging results in favour of Masitinib with better safety profile^[30]. Another phase III RCT (NCT01694277) is recruiting patients to evaluate the safety and efficacy of Masitinib in comparison to Sunitinib in patients with GISTs after progression with Imatinib.

ROLE OF TARGETED THERAPY IN NON-METASTATIC GISTS

Surgery is the standard of care for localized GISTs; complete excision (R0 resection), without rupturing the pseudocapsule, is the aim of surgery. Regional lymphadenectomy is usually not a part of radical surgery as lymph node metastasis is rarely present in GISTs^[31,32]. A high frequency of post-surgery disease recurrences mandates identification of high-risk group which can be exposed to adjuvant therapy. Various risk stratification systems are available to predict post-surgery disease recurrence - National Institute of Health (NIH) consensus criteria, modified NIH criteria, Armed Forces Institute of Pathology criteria, Memorial Sloan Kettering Cancer Centre prognostication criteria and prognostic contour maps^[21]. Main factors which have been identified for predicting post-surgery recurrence are mitotic rate, tumour size, and location of the tumor^[33]. Imatinib is the only recommended adjuvant targeted therapy which has been evaluated in clinical trials.

In the ACOSOG Z9000 trial, 106 patients with a high risk of recurrence (defined as tumor size > 10 cm, intra-peritoneal tumor rupture and up to four peritoneal implants) underwent curative resection and received adjuvant Imatinib for one year. After median follow-up of 7.7 years, the 1, 3 and 5-year OS rates were 99%, 97% and 83%, respectively, which compared favourably with a historical 5-year OS rate of 35%^[4].

In ACOSOG Z9001, a phase III RCT, 713 patients were randomized to adjuvant Imatinib for one year vs placebo based on tumour size more than 3 cm. The 1-year recurrence free survival (RFS) rate was 98% in Imatinib arm in comparison to 83% in placebo arm (HR = 0.33; 95%CI: 0.20-0.53; $P < 0.0001$). Retrospective analysis of the trial suggested that adjuvant therapy was more effective in high-risk patients (tumor size > 10 cm and high mitotic rate). There was no difference

in OS (HR = 0.66, 95%CI: 0.22-2.03, $P = 0.47$) due to cross-over design of the trial. Grade 3 or 4 events occurred in 30% of patients in Imatinib arm^[34]. Recently published long term results after median follow-up of 74 mo showed no significant difference in OS. They found that high mitotic rate, large tumour size and small bowel location are associated with lower RFS irrespective of tumour genotype. Imatinib therapy improved RFS in patients with KIT exon 11 deletions but not in those with exon 11 insertions or point mutations, KIT exon 9 mutations or wild type GISTs. As 400 mg/d of Imatinib therapy was prescribed in exon-9 mutation patients, this can be argued that 800 mg/d daily dose could have improved treatment outcomes based on the experience from trials conducted in metastatic GISTs. Additional studies are needed to better define the management of wild type tumours in both adjuvant and metastatic settings^[35].

In subsequent SSG XVIII/AIO phase III RCT, 400 patients were randomized based on high risk features (at least one of the following: Tumour size > 10 cm, mitotic rate > 10/50 high power field (HPF), tumor size > 5 cm and mitotic rate > 5/50 HPF, tumour rupture before or during surgery) to either 1 or 3 years of adjuvant Imatinib^[36]. Patients in 3-year arm had longer 5-year RFS compared to 1-year arm (65.6% vs 47.9%, HR = 0.46, 95%CI: 0.32-0.65, $P < 0.001$). OS was also longer in 3-year arm compared to 1-year arm (92% vs 81.7%, HR = 0.45, 95%CI: 0.22-0.89, $P = 0.02$). However, grade 3 or 4 toxicities were also higher in 3-year arm (32.8% vs 20.1%) and more patients discontinued treatment in 3-year arm (25.8% vs 12.6%) compared to 1-year arm. Based on the results of these two trials, three-year adjuvant Imatinib therapy is presently the standard of care in high-risk patients. Recently, a clinical trial (the PERSIST-5 trial, NCT00867113; ClinicalTrials.gov, 2009) examining the role of 5 years of adjuvant Imatinib in high-risk patients completed accrual; however, final results will be available after 2018.

Neoadjuvant setting is another area of interest in the management of locally advanced GISTs which are not operable upfront. In the absence of phase III trials, role of neoadjuvant therapy remains investigational. Two phase II trials have demonstrated efficacy and safety of neoadjuvant Imatinib in locally advanced GISTs^[37,38]. The dosing and duration of targeted therapy in neoadjuvant setting are currently based on the experience gathered through trials conducted in metastatic GISTs. As phase III EORTC 62005 trial designed for metastatic GISTs showed that there was no difference in overall response rate between 400 mg vs 800 mg group, this indicates that 400 mg daily dose for neoadjuvant therapy would be appropriate to downstage the tumour. As the reported median time to best response was 4 mo, this should be taken as length of neoadjuvant treatment, and it can be extended up to 6 mo^[16]. Another study suggested that neoadjuvant TKI can be given for 9 to 12 mo; however, it should not be extended beyond 12 mo because of the risk of resistance^[39]. In a pooled database

Table 1 Published randomized controlled trials of role of targeted therapy in gastrointestinal tumours

Study	Research question	Sample size	Study arms	Response rates	PFS/RFS	OS	Toxicity (Grades 3-5)	Conclusion
SWOG S0033 ^[14]	Imatinib as first line in metastatic GISTs	746	400 mg daily vs 400 mg twice daily	ORR 45% (CR 5%, PR 40%) vs 45% (CR 3%, PR 42%)	2 yr PFS 41% vs 46% (P = 0.13)	2 yr OS 76% vs 72% (HR = 0.98)	43% vs 63%	400 mg daily is initial dose and consider dose escalation with disease progression
EORTC 62005 ^[13]	Imatinib as first line in metastatic GISTs	946	400 mg daily vs 400 mg twice daily	51% vs 54%	2 yr PFS 56% vs 50% (HR = 0.82, P = 0.026)	2 yr OS 69% vs 74%	32% vs 50%, P < 0.0001	Better PFS in 400 mg twice daily with higher toxicity
Demetri <i>et al</i> ^[25]	Sunitinib as second line in metastatic GISTs	312	Sunitinib vs placebo	7% vs 0% (SD 58% vs 48%)	Median TTP 27.3 wk vs 6.4 wk (HR = 0.33, P < 0.0001)	Better in Sunitinib arm (HR = 0.49, P = 0.007)	20% vs 5%	Sunitinib is approved as a second line therapy in metastatic GISTs
GRID ^[29]	Regorafenib as third line in metastatic GISTs	199	Regorafenib vs placebo	4.5% vs 1.5% (SD 71.4% vs 33.3%)	Median PFS 4.8 mo vs 0.9 mo (HR = 0.27, P < 0.0001)	No difference, HR = 0.77	61% vs 14%	Regorafenib is approved third line therapy in metastatic GISTs
ACOSOG Z9001 ^[35]	Imatinib as adjuvant	713	1 yr (400 mg) vs placebo	Not available	1 yr RFS 98% vs 83% (HR = 0.33, P < 0.0001)	1 yr OS 99.2% vs 99.7% (HR = 0.66, P = 0.47)	30.9% in Imatinib arm	1 yr adjuvant Imatinib is effective and safe
SSG XVIII/AIO ^[36]	Imatinib as adjuvant	400	1 yr vs 3 yr	Not available	5 yr RFS 47.9% vs 65.6% (HR = 0.46, P < 0.001)	5 yr OS 81.7% vs 92% (HR = 0.45, P = 0.02)	20.1% vs 32.8%	3 yr adjuvant Imatinib improved RFS and OS

SWOG: Southwest Oncology Group; GISTs: Gastrointestinal stromal tumours; ORR: Overall response rates; CR: Complete response; PR: Partial response; SD: Stable disease; PFS: Progression free survival; RFS: Recurrence free survival; TTP: Time to tumour progression; OS: Overall survival; HR: Hazard ratio.

Table 2 Current role of targeted therapy in gastrointestinal stromal tumours

Agent	Use	Dose	Duration
Imatinib	First line in metastatic GISTs ^[13-15]	400 mg once daily (oral)	Till progression or intolerance
	Progression on 400 mg ^[13-15]	400 mg twice daily (oral)	Till progression or intolerance
	Exon 9 mutation ^[13-15]	400 mg twice daily (oral)	Till progression or intolerance
	Adjuvant in high risk cases ^[37]	400 mg daily (oral)	3 yr
Sunitinib	Neoadjuvant setting ^[29,39,40]	400 mg daily (oral)	6-12 mo
	Second line in metastatic setting ^[21,24]	50 mg once daily for 4 wk every 6 wk (oral) or 37.5 mg once daily continuously (oral)	Till disease progression or intolerance
Regorafenib	Third line in metastatic setting ^[26]	160 mg once daily for 3 wk every 4 wk (oral)	Till disease progression or intolerance

GISTs: Gastrointestinal stromal tumours.

of ten EORTC STBSG centers, 161 patients with locally advanced, non-metastatic GISTs were identified who received neoadjuvant Imatinib. R0 resection was achieved in 83% and 5-year DFS rate was 65% with median OS of 104 mo^[40]. The National Comprehensive Cancer Network guidelines recommend neoadjuvant Imatinib therapy in locally advanced GISTs to achieve R0 resection and to minimize postoperative morbidity. Imatinib can be stopped just before surgery and again restarted as soon as patients resume oral intake^[41].

Table 1 displays the published RCTs in GISTs. Table 2 displays the current role of targeted therapy in GISTs based on available evidence.

SIDE EFFECTS OF TARGETED THERAPY

Most of the side effects of Imatinib are mild and well tolerated. Anaemia (70%-80%) and leukopenia (35%-

45%) are common haematological side effects. Non-haematological toxicities include periorbital edema (60%-75%), diarrhoea (45%-55%) and fatigue (50%). Other side effects (20%-40%) are nausea, muscle cramps, leg edema, anorexia and rashes. Most patients develop tolerance for these side effects on continuous use. Therefore, patient's education about occurrence of these common side effects and advice against interrupting treatment due to these side effects is of paramount value before starting Imatinib mesylate. Previous trials have reported a higher frequency of Grade 3 or more toxicities in high dose 800 mg/d (50%-60%) compared to conventional 400 mg/d Imatinib therapy (50%-60% vs 30%-40%)^[18-20,41]. Common side-effects seen with Sunitinib therapy include fatigue (34%), diarrhoea (29%) and skin discolouration (25%); other less-common side effects are hematological toxicity (anaemia and leukopenia), hand-foot syndrome, hypertension,

and hypothyroidism^[25]. Toxicity profile of Regorafenib includes hand-foot skin reactions (56%), hypertension (49%) and diarrhoea (40%)^[29].

DRUG RESISTANCE

In GIST patients on Imatinib, resistance can be primary or secondary. Primary (intrinsic) resistance is seen in approximately 15% patients and is due to mutations such as D842V in PDGFRA and KIT exon 9, where Imatinib is not able to bind on ATP binding site of tyrosine kinase receptor^[12,25]. Secondary (acquired) resistance usually develops after 18-24 mo of treatment. A number of mechanisms have been put forward for secondary (acquired) resistance in GISTs: Occurrence of a second mutation in KIT receptor, other gene mutations, *KIT* genomic amplification and activation of an alternative receptor tyrosine kinase protein in the absence of *KIT* expression, increased serum acid glycoprotein levels and increased multidrug resistance gene expression, lower bioavailability of Imatinib during chronic therapy possibly due to up-regulation of hepatic enzymes responsible for drug clearance, and impaired drug delivery due to formation of fibrous stroma. More than 80% of patients on treatment ultimately develop secondary resistance^[16,42]. Based on the results of previous trials, the dose of Imatinib can be increased from 400 mg to 800 mg to overcome problem of resistance; however, median time of benefit with this approach is short (11.6 wk)^[16]. Like Imatinib, Sunitinib also binds to ATP binding domain of KIT and PDGFRA, but both these agents have different binding domains. Moreover, Sunitinib also has anti-angiogenesis activities and is now approved as a second-line targeted therapy in Imatinib resistant cases^[25]. However, subsequent drug resistance to Sunitinib evolves within one year due to secondary mutations. Regorafenib is approved as a third line targeted therapy in this setting^[28].

FUTURE DIRECTIONS

Although three lines of targeted therapy are present, failure to respond to Regorafenib leaves us with no further standard options. Usual strategy in this sitting is to re-challenge with previously used therapy. Further studies are needed to address this problem of TKI resistance. Various new targeted agents are under evaluation for Imatinib resistant GISTs. Masitinib, a multi-kinase inhibitor, is under evaluation as a second-line therapy in comparison to Sunitinib. Initial results are promising and a phase III RCT is recruiting patients^[30]. Ponatinib is another multi-kinase inhibitor which was studied in CML, and now its role is being evaluated for GISTs^[43-45]. Crenolanib is an inhibitor of Imatinib resistant PDGFRA kinases including D842V in GIST patients; a phase II trial has been initiated to treat this population^[46]. Inhibitors of downstream pathway kinases (PI3K and MAPK) are under evaluation^[47,48]. Heat shock protein (HSP) protects KIT oncoproteins from degradation and agents targeting

HSP 90 are under investigation for Imatinib resistant GISTs^[49]. Many new targeted agents are under evaluation to overcome the Imatinib resistance; further research will clear the air regarding their clinical application.

CONCLUSION

Application of Imatinib revolutionized the management of GISTs, and soon after its introduction, it became the standard of care in metastatic GISTs due to its promising activity in improving PFS and OS. Use of Imatinib in adjuvant setting leads to decreased postoperative recurrences and improved survival, though presently, it is only recommended for high-risk cases. Role of Imatinib in neoadjuvant settings is increasingly being explored to escalate resection rates in locally advanced GISTs. Drug resistance is a major concern with TKIs. Intense molecular research is underway to identify other pathways of drug resistance and to develop newer targeted agents.

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Implications of preoperative hypoalbuminemia in colorectal surgery

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Abstract

Serum albumin has traditionally been used as a quantitative measure of a patient's nutritional status because of its availability and low cost. While malnutrition has a clear definition within both the American

and European Societies for Parenteral and Enteral Nutrition clinical guidelines, individual surgeons often determine nutritional status anecdotally. Preoperative albumin level has been shown to be the best predictor of mortality after colorectal cancer surgery. Specifically in colorectal surgical patients, hypoalbuminemia significantly increases the length of hospital stay, rates of surgical site infections, enterocutaneous fistula risk, and deep vein thrombosis formation. The delay of surgical procedures to allow for preoperative correction of albumin levels in hypoalbuminemic patients has been shown to improve the morbidity and mortality in patients with severe nutritional risk. The importance of preoperative albumin levels and the patient's chronic inflammatory state on the postoperative morbidity and mortality has led to the development of a variety of surgical scoring systems to predict outcomes efficiently. This review attempts to provide a systematic overview of albumin and its role and implications in colorectal surgery.

Key words: Colorectal surgery; Malnutrition; Albumin; Hypoalbuminemia; Prealbumin; Serum albumin; Nutrition

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Core tip: Although albumin remains a flawed marker of nutrition, it offers clear prognostic value in predicting patient outcomes after colorectal surgery. Hypoalbuminemia significantly influences the length of hospital stay, rates of surgical site infections, enterocutaneous fistula risk, and deep vein thrombosis formation. Despite the fact that hypoalbuminemia is classically defined < 3.0 g/dL, clinical judgment must account for albumin levels ≤ 3.4 g/dL as even modest hypoalbuminemia can affect outcomes. The subjective global assessment, modified Glasgow Prognostic Score, and Colorectal preoperative Surgical Score scoring systems provide convenient and valuable prognostic information that may help in the

counseling and risk adjustment of patients undergoing colorectal surgery.

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INTRODUCTION

Albumin is a single polypeptide responsible for five main functions: (1) maintenance of colloid osmotic pressure; (2) binding and transport of solutes; (3) free radical scavenging; (4) platelet function inhibition and antithrombotic effect; and (5) beneficial effects on vascular permeability in the setting of shock and sepsis^[1]. Albumin is a major source of sulfhydryl groups, which sequester both leukotoxin and nitric oxide, limiting vascular permeability and dilation respectively. Serum albumin has traditionally been used as a quantitative measure of a patient's nutritional status because of its ready availability and low cost. The reliability of albumin as an assessment of malnutrition is controversial because hypoalbuminemia is an acute phase reactant and is affected by systemic inflammation^[2]. The increased demand for specific amino acids for acute phase protein synthesis degrades available body protein, including albumin^[3-5]. Therefore, nutritional status is often determined anecdotally by individual care providers based on their own clinical experience and judgment in clinical practice. In this review, we cover in-depth the clinical indications and implications of serum albumin levels in the setting of colorectal surgery. We investigate the correlation between albumin and postoperative complications, inflammatory bowel disease (IBD) treatment, nutritional response, and new prognostic models.

LITERATURE RESEARCH

We performed a systematic literature review through an electronic search of MEDLINE from PubMed and the Cochrane Library until May 2015. We used the following search terms and associations: Albumin, hypoalbuminemia, serum protein, nutrition, malnutrition, colorectal surgery, gastrointestinal (GI) surgery, complications, and mortality. Articles were assessed in a tiered fashion. We first screened the titles, assessed abstracts for relevance, then analyzed the entire text of the papers. Only papers in the English language were included. After removing duplicates, 379 total records were found, 339 of which were in English. Thirty-five articles remained after screening and their full texts were analyzed. We completed our search by visiting the bibliographies of relevant articles.

HYPOALBUMINEMIA IN SURGICAL PATIENTS

In the early 1950's, hypoalbuminemia was noted to negatively influence postoperative recovery^[6,7]. This finding was followed by work from Harvey who reported that a low serum albumin was the best indicator of concurrent sepsis^[8]. A high incidence of malnutrition in the hospital setting was only first described in 1974 by Banh^[9] and Butterworth^[10]. Contemporary data currently shows that malnutrition has a prevalence of 30% to 50% in hospitalized patients, and is one of the most important patient outcome determinants, affecting length of hospitalization, cost, morbidity, and ultimately mortality^[11,12]. Most notably, hypoalbuminemia is associated with poor tissue healing, decreased collagen synthesis, and granuloma formation in surgical wounds, ultimately delaying wound healing^[13-17]. Serum albumin levels have traditionally been used as a biochemical marker of individual nutritional status prior to surgery. It is regarded as an accurate preoperative prognostic indicator in a variety of surgical procedures including cardiac^[18], trauma^[19], and general surgery^[6,20-22]. This was perhaps best illustrated in a large-scale non-randomized retrospective study using the National Veteran's Affairs Surgical Database of 54215 patients from 44 tertiary care centers by Gibbs *et al.*^[23] on major non-cardiac surgeries. Thirty-day morbidity and mortality were measured by C-index (C) where a value of 0.0-0.5 indicates any association between variables are likely due to chance, and C of 0.5-1.0 indicates a strong predictive value or correlation^[24]. Univariate analysis revealed that albumin < 3.5 g/dL was the strongest preoperative predictor of both 30-d morbidity (C = 0.68) and mortality (C = 0.78), just ahead of American Society of Anesthesiology class. Furthermore, multivariate analysis showed that albumin levels were the strongest predictor of both morbidity [odds ratio (OR) = 0.68; 95%CI: 0.56-0.60] and mortality (OR = 0.44; 95%CI: 0.41-0.48). Albumin levels also independently predicted complication rates of systemic sepsis, acute renal failure, coma, failure to wean from ventilation, and bleeding/transfusions amongst 16 other complications (C = 0.78, 0.76, 0.76, 0.75, 0.72 respectively; all *P* < 0.001). Additionally, analysis of preoperative albumin and major post operative complications in 2003 by Kudsk *et al.*^[25] identified clinical hypoalbuminemia as an independent determinant of hospital stay, serious postoperative complications (albumin < 4.25 g/dL), and mortality (albumin < 3.25 g/dL).

On the other hand, an ongoing debate continues to exist regarding the value of albumin as a clinical marker of malnutrition. There is no clear consensus amongst healthcare professionals about the definition of malnutrition. Suggested markers include albumin and prealbumin, which are widely used today, and transferrin and retinol binding protein, which are newer evolving

nutritional markers^[9]. Recent studies have attempted to dispel several myths regarding malnutrition. Albumin and prealbumin have historically been touted as indicators of nutritional risk in the hospital setting, however early literature was based off subjective data and the underlying assumption that albumin and prealbumin accurately reflected nutritional status^[26-28]. Golden previously showed that kwashiorkor was caused by lack of antioxidants, not dietary proteins^[29] and in a small study by Carlson *et al.*^[30] of 10 military burn patients, no correlation was found between nitrogen balance and albumin level, further dispelling serum protein beliefs. A retrospective study of all nutrition consults within 2 years totaling 528 patients suggested that patients' underlying acute or chronic conditions, not nourishment, was responsible for the changes in perioperative albumin^[8]. Despite this mounting evidence, consensus exists that although albumin may be a poor marker of nutrition, hypoalbuminemia offers clear prognostic value in predicting surgical outcomes^[26,31].

HYPOALBUMINEMIA AND COLORECTAL SURGERY

Despite the growing fund of research surrounding albumin status in general surgery patients, colorectal surgery maintains a unique relationship with nutritional status and albumin level. Colorectal surgery patients are often malnourished due to advanced malignancy or inflammatory bowel disease that results in poor oral intake, intestinal blockages, intestinal fistulas, poor absorptive capacity, and large volume losses from the GI tract^[32]. Kudsk *et al.*^[25] emphasized the potential for bias if the surgical site is not considered. Malnutrition is observed in up to 80% of patients with advanced colorectal cancer putting them at increased risk for postoperative complications^[33-35]. Burden *et al.*^[36] showed that 1 in 5 pre-operative colorectal cancer patients undergoing surgery were malnourished when measuring body weight (weight loss > 10%) and had a significantly lower handgrip strength ($P = 0.013$), a measure of nutritional status^[37]. Hypoalbuminemia has also been associated with delayed recovery of postoperative bowel function, further worsening postoperative nutritional recovery^[38]. Preoperative albumin levels have been shown to be the best predictor of mortality after colorectal cancer surgery^[12,39]. It is important to concede that the current research surrounding albumin levels is limited and heterogeneous; each study uses different qualifications and methods. Below is a review of the current literature surrounding hypoalbuminemia and its relationship to colorectal surgery.

COMPLICATIONS

Although the classic definition for hypoalbuminemia is < 3.0 g/dL, studies' definitions vary widely from < 2.7 in some studies to < 3.5 g/dL in others^[12,40,41]. Using

the American College of Surgeons National Quality Improvement Program (NSQIP) database to measure 30-d postoperative surgical outcomes, Moghadamyeghaneh *et al.*^[12] emphasized the effect of modest hypoalbuminemia as defined by serum albumin levels between 3.0 and 3.4 g/dL. The mortality rate in patients with modest hypoalbuminemia and without hypoalbuminemia was 6% and 1.7% respectively, and the morbidity risk was greater as well [adjusted odds ratio (AOR) = 1.876; 95%CI: 1.51-2.05; $P < 0.01$]. Not surprisingly, the highest morbidity (60.4%) and mortality (26.2%) rates occurred at serum albumin levels lower than 2 g/dL. Additionally, this study showed a linear correlation between albumin level and postoperative mortality, meaning any decrease in serum albumin level from the normal value (> 4 g/dL) had serious effects on the outcomes following colorectal resections. The rate of increase in mortality and morbidity was estimated to be approximately 49% and 24% respectively for each 1 g/dL decrease in albumin level ($P < 0.05$). Colon cancer patients had a higher rate of modest hypoalbuminemia compared to rectal cancer patients (AOR = 1.55; $P < 0.01$).

HOSPITAL STAY

Two studies published in 2010 evaluated the association between albumin level and length of hospital stay. Using a cohort of 95 patients admitted for either upper GI surgery or colorectal surgery over a 19-mo period in Australia, Garth *et al.*^[11] showed that preoperative albumin level was linear and inversely related to the length of hospital stay ($R = -0.325$; $P < 0.01$). Interestingly, grouped analysis revealed upper GI patients presented with significantly lower albumin than colorectal patients. Thirty-one percent of the upper GI group had albumin levels < 3.5 g/dL vs 14% of the colorectal group ($P < 0.05$). Hennessey *et al.*^[16] showed that an albumin level < 3.0 g/dL was associated with prolonged inpatient stay with a negative linear relationship (19.5 d vs 12 d; $P < 0.001$; $R^2 = -0.319$; $P < 0.001$). Additionally, in 2014 a compilation of 108,898 patients, the largest sample to date of hypoalbuminemic colorectal surgery patients by Moghadamyeghaneh *et al.*^[12] showed that the median length of stay after surgery was an average of 2 d longer in patients with even modest hypoalbuminemia (albumin 3.0-3.4 g/dL) compared to patients with serum albumin > 3.4 g/dL (95%CI: 1.83-2.34; $P < 0.01$). A study from Thailand showed that an albumin level < 3.5 g/dL increased the length of hospital stay from 6.8 ± 2.6 to 9.6 ± 4.7 d ($P = 0.001$)^[38].

ILEUS

Postoperative bowel function is a major determinant of the length of hospital stay and nutritional recovery of a patient. A key retrospective study of 80 patients undergoing right hemicolectomy by Lohsiriwat *et al.*^[38] showed that an albumin level < 3.5 g/dL compared to

an albumin > 3.5 g/dL was associated with increased postoperative complications (0 and 14 respectively; $P < 0.001$), time to first bowel movement (55.3 and 69.5 h respectively; $P = 0.018$), and time to resume a normal diet (4.0 to 4.9 d respectively; $P < 0.001$). In multivariate analysis, only delayed time to first bowel movement was associated with preoperative hypoalbuminemia. Similarly, Millan *et al.*^[42] showed that albumin levels < 35 mg/dL were significantly associated with postoperative ileus ($P = 0.042$) in a retrospective study of 773 patients. Kronberg *et al.*^[43] also showed in a study of 413 patients that preoperative serum albumin concentration was lower in patients who developed postoperative ileus (3.83 mg/dL vs 4.09 mg/dL; $P = 0.039$; OR = 0.90). Prolonged postoperative ileus symptoms include nausea and vomiting, inability to tolerate an oral diet, abdominal distention, and delayed passage of flatus and stool^[44,45]. Decreasing preoperative albumin was a predictor for prolonged postoperative ileus (OR = 1.11 per gram per litre unit change; 95%CI: 1.02-1.22; $P = 0.047$)^[46].

SURGICAL SITE INFECTION

A study of 524 patients undergoing GI surgery [of which 339 (64%) underwent colorectal surgery] in 4 institutions in Ireland showed that patients who developed a surgical site infection had a lower median preoperative serum albumin than those who did not develop an infection, 3.0 g/dL and 3.6 g/dL respectively ($P < 0.001$)^[16]. One hundred and thirty-eight patients (26.3%) had a low pre-operative albumin level (< 3.0 g/dL) and were found to be at increased risk for severe surgical site infections. Of the patients developing a superficial wound infection, 46.4% had a low albumin level ($P = 0.001$). In those with deep wound infections, 80% had low albumin levels ($P = 0.004$), and in those with organ space infection, 83.3% had low albumin levels ($P = 0.397$).

FISTULAS

Enteric or enterocutaneous fistulas are abnormal communications between the gastrointestinal tract to another cavity or through the skin respectively. Although uncommon, they are a significant concern within colorectal surgery due to their relatively high incidence and considerable morbidity and mortality, first described in a classic case study of 157 patients in 1960^[47-49]. An estimated 75%-85% of enterocutaneous fistulas are postoperative complications following bowel injury *via* inadvertent enterotomy and/or anastomotic leakage^[50] and 30%-80% eventually require surgical treatment despite advances in medical treatment^[51-53].

Not surprisingly, serum albumin level has been shown to be a vital prognostic factor of healing enteric fistulas^[49,54]. In a retrospective chart review of 53 GI cancer patients with postoperative enteric fistula complications, Lu *et al.*^[49] showed a significant corre-

lation between enteric fistula healing/recovery and an increased serum albumin level ($P = 0.029$) and lower fistula drainage amount (< 500 mL/d) ($P = 0.013$) after multivariate analysis. Additionally, amongst patients with both increasing albumin levels and < 500 mL/d of fistula drainage, over 90% of fistulas fully resolved with conservative therapy after total parenteral nutrition (TPN)^[49,55]. However, although TPN nutritional support has been shown to aid recovery, careful monitoring for underlying or uncontrolled sepsis is required as patients are prone to rapidly deteriorate^[52].

Once it is obvious that operative repair is unavoidable, the decision between early surgical fistula treatment vs initial nutritional support with delayed surgery is a difficult one. In a report of 135 consecutive patients with enterocutaneous fistulas by Visschers *et al.*^[53,56] hypoalbuminemic patients failed to recover well after restorative surgery. Patients with an albumin level below 2.5 g/dL continued to show signs of inflammation postoperatively despite being treated for infection, which lead to eventual deterioration and death in the majority (17/25; 68%) of patients while those who had albumin > 2.5 g/dL had lower mortality (8/25; 32%). Operative fistula repair in hypoalbuminemic patients is therefore recommended only after a nutritive recovery period of at least 6 wk.

DEEP VEIN THROMBOSIS/PULMONARY EMBOLISM

There is limited data regarding the predictive factors of postoperative venous thromboembolism in patients undergoing colorectal resection. Using data from the large national NSQIP database from 2005 to 2011, Moghadamyeghaneh *et al.*^[41] showed that a serum albumin < 3.5 mg/dL significantly increased the risk of developing a postoperative deep vein thrombosis (DVT) (AOR = 1.69; 95%CI: 1.49-1.93; $P < 0.01$). Additionally, hypoalbuminemia was also associated with an increased risk of pulmonary embolism (PE) (AOR = 1.21; 95%CI: 1.02-1.42; $P < 0.02$) although the strongest risk factor for PE was not surprisingly a DVT.

INFLAMMATORY BOWEL DISEASE AND HYPOALBUMINEMIA

Inflammatory bowel disease is broadly classified into two variants, ulcerative colitis (UC) and Crohn's disease (CD). The mainstay of UC and CD therapy is medical management, however up to 1/3 of Crohn's patients will undergo abdominal surgery within the first 5 years of diagnosis^[57]. In CD, hypoalbuminemia has been shown to be a predictor of intraabdominal septic complications after intestinal anastomosis by Yamamoto *et al.*^[58] in a retrospective chart review of 343 patients undergoing 1008 intestinal anastomoses between 1980 and 1997. In this study, albumin levels < 3.0 g/dL were considered hypoalbuminemic and significantly affected

the incidence of intra-abdominal sepsis in univariate and multivariate analysis with *P* values of 0.01 and 0.04 respectively. Intraabdominal sepsis occurred in 21% of patients with hypoalbuminemia in contrast to 12% in those without. If all significant risk factors in this study (hypoalbuminemia, steroid use at least one month immediately before surgery, and abscess or fistula at the time of laparotomy) were present, the incidence of sepsis reached 50%. Because reoperations for early postoperative complications were not included in this study, the impact of serious postoperative or refractory hypoalbuminemia could not be assessed.

Intraabdominal sepsis and delayed wound healing are significant consequences of hypoalbuminemia in IBD patients^[59]. For these reasons, ileal pouch anal anastomosis (IPAA), the treatment of choice for UC, has traditionally been avoided due to the large number of suture or staple lines and wide pelvic dissection in malnourished patients^[60,61]. An 8-year single-institution prospective study identifying 405 patients showed that an albumin level < 3.5 g/dL was significantly associated with IPAA pouch failure within 30 d to 10 years, development of anastomotic leak, postoperative transfusion, and prolonged inpatient stay using univariate analysis^[62]. Multivariate analysis revealed preoperative hypoalbuminemia as a strong predictor for anastomotic leak and prolonged median length of stay after pouch surgery, which was 60% longer than in patients with normal albumin levels.

Because of the high complication rate of pouch creation in IBD patients, a staged operation is favored. Nisar *et al*^[62] showed that hypoalbuminemic patients with IBD who underwent a single-stage total proctocolectomy (TPC) with concurrent pouch creation had a significantly longer inpatient stay and increased postoperative transfusion requirements compared to two-stage subtotal colectomy (STC) with subsequent completion proctocolectomy and IPAA. A higher risk of anastomotic leak in hypoalbuminemic patients was found in single-stage TPC and IPAA (22%) compared to initial STC with follow-up completion proctectomy and IPAA (11%). However, the sample only comprised 24 TPC patients and 10 with STC. Interestingly, this study was one of very few which analyzed serum albumin levels as a continuous variable and thus found that the improvement in albumin between the time of STC and IPAA correlated significantly with the baseline albumin ($R^2 = 0.814$), ($P < 0.0001$).

In a retrospective case series of 78 patients with CD but without hypoalbuminemia, Zerbib *et al*^[63] showed that weaning steroids and applying enteral nutrition at > 30 kcal/kg ideal body weight/day in intestinal non-occluded patients or TPN in patients with intestinal occlusion together with abscess drainage and antibiotic therapy for 2-3 wk preoperatively minimized the usage of a temporary diverting stoma [7.7% (6/78) of patients] while achieving uneventful operative outcomes in 58% of the total patients. This rate of diverting stoma utilization was significantly lower than a previously

reported series for penetrating CD by Goyer *et al*^[64] who reported a rate of 39%. This suggests a strong correlation between preoperative nutrition and Crohn's disease surgical outcomes.

PREOPERATIVE TREATMENT OF HYPOALBUMINEMIA

While the deleterious effects of hypoalbuminemia on the rate of postoperative complications have been well established, pre-surgical correction of hypoalbuminemia remains a subject of debate. While some believe a low albumin level indicates malnutrition, others postulate that the hypoalbuminemia stems from the chronic disease state and resultant inflammation and is not due to malnutrition, thus hindering any beneficial effects of nutritional therapy^[3]. Although enteral and parenteral nutrition have been shown to improve outcomes in malnourished patients undergoing major elective surgery^[65], preoperative nutrition not been well studied in populations undergoing colorectal surgery. The consensus is to stabilize baseline nutritional status and to administer enteral or parenteral nutrition to severely hypoalbuminemic patients preoperatively, even if a delay in surgery is necessary.

In 1982, a study by Rombeau *et al*^[66] of 33 consecutive IBD patients demonstrated that preoperative TPN given for at least 5 d resulted in significantly fewer postoperative complications ($P < 0.05$). All patients had an albumin < 3.5 g/dL or a transferrin level < 150 mg/dL. In a case series by Jacobson, 15 consecutive CD patients given preoperative TPN were compared to 105 control patients matched for known postoperative complication factors^[67]. TPN was given between 18 and 90 (avg = 46) d preoperatively before undergoing intestinal resection with primary hand-sewn anastomoses. In this study the average albumin level was significantly increased from 3.4 to 3.9 g/dL ($P < 0.01$) through TPN. There was a significantly higher rate of complications in the non-TPN group (29/105) compared to the TPN group (0/15) ($P < 0.05$). Although the TPN group was without postoperative complications, the risk of preoperative complications should be recognized. In the TPN group, repeated central venous catheter thromboses requiring up to 5 replacements occurred in 4 patients and a pneumothorax which resolved after 5 d of evacuation occurred in one other patient.

Lashner *et al*^[68] further quantified the significance of preoperative TPN. In a retrospective single-center/single-surgical team study of 103 CD patients, preoperative TPN was only beneficial to CD patients by reducing the length of bowel resection during small bowel resection by more than 20 cm ($P < 0.04$). There was no difference in complication rates. During ileocectomy, TPN patients had a shorter resection by approximately 11 cm when compared to non-TPN patients ($P < 0.02$). However, it appears that the cost of shorter bowel resections in TPN patients was longer hospital stays (12 d; $P < 0.001$). Although this study included patients undergoing

large bowel resection, none of them received preoperative TPN. In this study, TPN was given between 5-7 d and administration > 10 d was not recommended. In contrast, the European Society for Clinical Nutrition and Metabolism guidelines state that if a severe nutritional risk is present, preoperative nutrition therapy, if possible, by enteral route for 10-14 d before surgery is recommended even if the surgery has to be delayed^[69]. Additionally, Visschers *et al.*^[53] recommended delaying enterocutaneous fistula repair at least 6 wk to stabilize baseline nutritional status in severely malnourished patients.

NEW COLORECTAL SURGERY SCORING SYSTEMS

Broad efforts have been made to use albumin levels together with other clinical markers to create a scoring system predicting postoperative morbidity or mortality. The Subjective Global Assessment (SGA) scale combines both subjective aspects of the patient's history such as gastrointestinal symptoms and dietary change and objective aspects such as ankle edema, albumin levels, and tumor grade^[70]. The SGA stratifies patients into A, B and C categories yielding significant differences in median survival in their cohort of 235 patients (log rank 13.36; $P = 0.0013$). The SGA provides useful prognostic information in patients with advanced colorectal cancer and may identify malnourished patients quickly but suffers due to the inclusion of subjective measures exposing it to observer bias.

The modified Glasgow Prognostic Score (mGPS) ranges from 0-2 and is composed of C-reactive protein (CRP) and albumin levels. mGPS was shown by Park *et al.*^[71] in a retrospective single-center study to tightly correlate with overall survival (OS) in patients undergoing elective resection of colon cancer ($P < 0.001$). When mGPS and tumor-node-metastasis (TNM) staging were combined, they effectively stratified outcomes of patients undergoing potentially curative resection of colorectal cancer. A TNM stage I /mGPS = 0 yielded a 5-year cancer specific survival (CSS) and overall survival of 97% and 87% respectively; whereas a TNM stage III /mGPS = 2 exhibited a 5-year CSS and OS of 32% and 26% respectively ($P < 0.001$). Additionally, the mGPS stratified the survival of patients who received adjuvant chemotherapy after resection of stage III colon cancer. Patients with mGPS = 0 had a 50% relative increase in survival at 5 years with adjuvant therapy, whereas those with mGPS = 1-2 received no benefit ($P = 0.003$). The mGPS provides important prognostic information in patients undergoing colorectal resections and can help guide adjuvant therapy, especially when combined together with TNM staging.

The Colorectal preoperative Surgical Score (CrOSS) was proposed by Kong *et al.*^[39] in 2015 as a response to other scoring systems, which require postoperative variables or may be too complex or difficult to assess

at the patient's bedside. Their multivariate logistic regression analysis of 46 variables yielded 4 independent predictors for mortality following colorectal surgery: Age ≥ 70 , urgent surgery, albumin level ≤ 3.0 g/dL, and congestive heart failure, together composing the CrOSS score. CrOSS accurately predicted mortality with a receiver operating characteristic (ROC) of 0.870 and calibration P -value of 0.937. The score was internally and externally validated to the Portsmouth and Colorectal Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity and the 2012 Barwon Health model (ROC = 0.788, $P = 0.24$). CrOSS offers a simple yet robust preoperative risk stratification model, specifically tested in colorectal surgery.

NEW MARKERS FOR MALNUTRITION AND INFLAMMATION

Although albumin remains the widest studied marker for malnutrition, several other markers have been proposed to aid perioperative assessment of a colorectal surgery patient. Prealbumin, transferrin and retinol binding protein are considered traditional markers of nutrition; however, recent data demonstrates their poor relationship to nutrition status^[9]. Because the markers for a patient's nutrition status are often negative acute-phase reactants, efforts have been made to quantify a patient's inflammatory status as an indirect measure of nutrition and postoperative morbidity and mortality.

In 2012, Oberhofer *et al.*^[72] showed an increase in CRP in the early postoperative period after colorectal surgery was correlated with a significant increase in complication rates ($P < 0.001$), which agreed with Welsch *et al.*^[73] who demonstrated that CRP values greater than 140 mg/L on postoperative day 3 or 4 predicted infectious complications and anastomotic leaks after colorectal surgery. Conversely, preoperative CRP levels were not correlated with postoperative complication incidence. Oberhofer *et al.*^[72] also concluded that postoperative procalcitonin increased significantly more in patients with postoperative complications than those patients without complications, with the highest predictive value on postoperative day 5 ($P < 0.001$). Procalcitonin is also a reliable laboratory marker for early diagnosis of surgical site infection and sepsis after colorectal cancer surgery ($P < 0.001$)^[74,75].

Prealbumin (PAB), also known as transthyretin, is a visceral protein and a negative acute phase reactant similar to albumin. PAB's advantage over albumin is its shorter half-life (2-3 d), thus it may be more useful for detecting acute changes in nutritional status. However, similar to albumin, PAB has been shown to be a poor marker of nutritional status as evidenced by studies of extreme cases of starvation, which fail to show consistent or reversible decreases in PAB levels^[9,76,77]. In addition, PAB has been shown to be inferior to albumin as a predictor of colon cancer recurrence. A study of 158 patients with operable colorectal carcinoma in Japan,

56 patients (35.4%) with decreased preoperative PAB and 15 patients (9.5%) with decreased preoperative albumin levels, showed that both a low preoperative serum PAB and albumin were associated with early disease recurrence ($P = 0.0005$ and $P = 0.0002$ respectively)^[78]. However, only albumin maintained its significance in multivariate analysis ($P = 0.048$) while PAB lost significance, indicating that only albumin is an independent predictor of early colorectal carcinoma recurrence.

Additionally, interleukin-6 has recently been shown to correlate with more advanced colorectal cancer^[79] and was found to cause reactive thrombocytosis, upregulation of CRP, and downregulation of albumin production by the liver, all processes of acute inflammation^[80]. Preoperative thrombocytosis with a platelet count greater than $300 \times 10^9/L$ was related to overall survival in multivariate analysis ($P = 0.039$; OR = 1.642; 95%CI: 1.025-2.629)^[81].

Recent studies demonstrate positive survival outcomes after colorectal surgery by targeting the systemic inflammatory response with anti-inflammatory agents such as broad-spectrum nonsteroidal anti-inflammatory drugs or aspirin^[82,83]. Adequate dietary habits are also associated with both decreased colorectal cancer risk and postoperative outcomes. Increased marine n-3 polyunsaturated fatty acids consumption was protective against postoperative complications after colorectal cancer surgery^[84-86].

CONCLUSION

Although albumin remains a flawed marker of nutrition, it offers clear prognostic value in predicting patient outcomes after colorectal surgery. Hypoalbuminemia significantly influences the length of hospital stay and complication rates, specifically surgical site infection, enterocutaneous fistula, and DVT formation. However, these studies are mostly small-cohort non-randomized retrospective studies or large scale studies using national data bases and this topic would benefit from further study. Although clinical hypoalbuminemia is classically defined as serum concentrations < 3.0 g/dL, clinical judgment must account for albumin levels ≤ 3.4 g/dL as even modest hypoalbuminemia can affect outcomes. Surgical delay for preoperative nutrition has been shown to improve the morbidity and mortality in patients with severe nutritional risk. Hypoalbuminemic patients may benefit from a staged colorectal resection vs a single operation, especially in the setting of IBD. Efforts to quantify a patient's nutritional status indirectly with inflammatory markers show promise, but the data is superficial and overall inferior to albumin. However, addressing systemic inflammation with anti-inflammatory agents has demonstrated positive survival outcomes in pilot studies. How these developing new markers will be used in combination with albumin is an interesting frontier, meanwhile the SGA, mGPS, and cROSS scoring systems provide convenient and valuable

prognostic information that may help in the counseling and risk adjustment of patients undergoing colorectal surgery.

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Inflammatory bowel disease surgery in the biologic era

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Abstract

Anti-tumour necrosis factor (TNF)- α therapy has revolutionized inflammatory bowel disease (IBD) treatment. Infliximab and adalimumab either as monotherapy or in combination with an immunomodulator are able to induce clinical and biological remission in patients with moderate and severe Crohn's disease (CD) and ulcerative colitis (UC). These new therapies have led to a shift in the goals of IBD management from just

controlling clinical symptoms to preventing disease progression. However, despite these advances in medical therapy, surgery is still required in 30%-40% of patients with CD and 20%-30% of patients with UC at some point during their lifetime. While biologics certainly play a major role in the medical treatment of IBD, there is concern about the effects of these anti-TNF- α agents on postoperative complications and morbidity. The purpose of this article is to review the role of surgery in the treatment of IBD in the age of biologics and the impact of these medications on per-operative outcomes. In this manuscript we review the relationship between biologic agents and surgery in the treatment of IBD. We also discuss in detail the perioperative risks and complications.

Key words: Inflammatory bowel disease; Anti-tumour necrosis factor alpha agents; Ulcerative colitis; Crohn's disease; Infliximab

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Core tip: We review the relationship between biologic agents and surgery in the treatment of inflammatory bowel disease. We also discuss in detail perioperative risks and complications in this setting.

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INTRODUCTION

Anti-tumour necrosis factor (TNF)- α therapy has revolutionized inflammatory bowel disease (IBD) treatment. Infliximab (IFX) and adalimumab (ADA) either as monotherapy or in combination with an immuno-

modulator are able to induce clinical and biological remission in patients with moderate and severe Crohn's disease (CD)^[1-6] and ulcerative colitis (UC)^[7,8]. These new therapies have led to a shift in the goals of IBD management from just controlling clinical symptoms to preventing disease progression.

The concept of composite or deep remission based on clinical and biological remission and mucosal healing has recently emerged. The ability to achieve composite remission seems to be correlated with better long-term outcomes, improved quality of life, and fewer surgical operations^[6].

However, despite these advances in medical therapy, surgery is still required in 30%-40% of patients with CD and 20%-30% of patients with UC at some point during their lifetime^[9,10]. In CD patients, the risk for surgery seems to be related to stenosing phenotype, perianal disease, smoking, younger age at diagnosis, and delay in biologic therapy^[11]. Surgery in patients with CD is not curative but is necessary when medical therapy is unable to achieve symptomatic control. For patients with UC, surgery is curative and indicated for failure of medical management, acute complication including fulminant colitis, perforation, severe bleeding and toxic megacolon, and chronic conditions such as development of dysplasia or malignancy.

While biologics certainly play a major role in the medical treatment of IBD, there is concern about the effects of these anti-TNF- α agents on postoperative complications and morbidity. The purpose of this article is to review the role of surgery in the treatment of IBD in the age of anti-TNF- α agents and the impact of these medications on peri-operative outcomes.

CD

Luminal disease

Medical treatment for luminal CD focuses on the achievement of composite remission, which is best obtained through initiation of combination therapy with anti-TNF- α agents (IFX or ADA) and immunomodulators within 18-24 mo of diagnosis in patients with moderate to severe CD. Composite remission is correlated with fewer-hospitalization and CD-related surgeries and better quality of life. In the ACCENT I trial^[2] scheduled IFX was associated with a two-fold lower rate of surgery at 54 wk compared with on demand treatment (3% vs 7.5% respectively, $P = 0.01$). In the CHARM trial^[5] the rate of surgery at one year was 9 times lower in the group treated with ADA than in the placebo group (0.6% vs 3.8% respectively, $P = 0.001$).

However, despite improvements in medical management at least 30%-40% of patients with CD require surgery at some point during their lifetime^[9,10]. Schnitzler *et al.*^[12] found that of 614 patients treated with IFX, 24% had required major abdominal surgery at a median follow-up of 4.6 years. Peyrin-Biroulet *et al.*^[13] followed 296 patients diagnosed with CD and reported that 26% underwent at least one major abdominal surgical

procedure at a median follow-up of 57 mo. In addition, among patients treated with ADA as a second line therapy after IFX failure, the rate of surgical intervention was 18% at 130 wk^[14]. Given the continued role of surgery and the increasing use of biologic therapy in the management of CD, it is imperative to understand how these treatments influence each other.

Postoperative complications

Studies on the effect of biologic agents on postoperative complications have yielded conflicting results^[15-29]. Appau *et al.*^[15] analyzed 389 patients who underwent ileocolonic resection for CD, 60 patients had been treated with IFX within 3 mo of surgery and 329 patients had not. The IFX group appeared to have a higher rate of postoperative sepsis (20% vs 5.8%, $P = 0.021$), anastomotic leak (10% vs 1.4%, $P = 0.049$) and hospital readmission (20% vs 2.9%, $P = 0.007$).

On the contrary, a recent multicenter trial including 6 tertiary referral centers^[21] encompassing 298 patients with CD treated with IFX or ADA showed no differences in major or minor complications between patients who received biologics within 2 mo of surgery compared to patients who received biologics more than 2 mo before surgery. The rate of anastomotic leak was similar between the two groups, 7.2% in the biologic group and 8% in the non-biologic group ($P = 0.976$), and they concluded that the use of anti-TNF- α agents within 2 mo of surgery for CD with intestinal anastomosis did not increase the risk of anastomotic, infectious, or other complications. Canedo *et al.*^[17] studied 225 CD patients who underwent surgery and divided them into 3 categories based on exposure to IBD medications within 90 d of surgery: IFX, other drugs including steroids and/or immunosuppressive agents (OD), and no drugs (ND). Ileocolonic resection was the most common procedure followed by total colectomy and proctectomy. Laparoscopy was performed in 47.7%, 45.9% and 29.3% of patients in the IFX, OD and ND groups respectively ($P = 0.04$). There was no statistically significant difference in the incidence of intra-operative complications or length of hospital stay in the three groups. In addition rates of postoperative pneumonia ($P = 0.14$), wound infection ($P = 0.35$) and abscess ($P = 0.34$) were similar between the three groups. Anastomotic leak was reported in 5.7%, 6.66% and 2.43% of patients respectively for the IFX, OD and ND groups ($P = 0.39$).

Kasperek *et al.*^[22] recently analyzed their experience in 96 patients with CD of which 48 patients had received IFX within 3 mo of a Crohn's related abdominal surgery, with a median of 60 d (range 1-90 d) between the last IFX dose and surgery and compared them to a control group who had undergone abdominal surgery for CD without prior IFX treatment. They evaluated minor complications, including wound infections, urinary tract infections and paralytic ileus, and major complications such as anastomotic leak, intra-abdominal abscess, postoperative hemorrhage, small bowel enterocutaneous fistula, and death. There was a trend toward a greater

rate of anastomotic leaks and intra-abdominal abscesses in the control group (13% vs 4%, $P = 0.27$), but it did not reach statistical significance. Analysis of the interval between the last administered dose of IFX and surgery demonstrated no difference in complication rates. They recommended scheduling elective surgery halfway between infusions, 4 wk after IFX infusion assuming an 8-wk interval for maintenance therapy, and re-initiating IFX 4 wk post-operatively in the absence of complications.

We recently published our experience^[29] of 518 IBD patients, 143 treated with IFX within 12 wk of surgery (IFX group) and affected by CD (63), UC (71) and indeterminate colitis (8), and 376 not treated with biologics [non-IFX (NIFX) group]. Total abdominal colectomy followed by proctocolectomy and ileocolonic resection was the most frequent operations performed and all procedures were done laparoscopically. Operative time and blood loss were similar between the 2 groups ($P = 0.50$ and $P = 0.34$ respectively). In addition the incidence of infectious complications (12% vs 11.2%, $P = 0.92$), anastomotic leak (5.2% vs 2.9%, $P = 0.69$), and thrombotic complications (3.5% vs 5.6%, $P = 0.46$) was not statistically different between the IFX and NIFX groups. Subgroup analysis confirmed similar rates of overall, thromboembolic, anastomotic, and infections complications regardless of whether the patients had CD or UC.

With the emerging trend toward initiating biologic therapy early in the course of disease and a resultant increase in the proportion of patients on these agents pre-operatively, there has been increased debate regarding not only whether anti-TNF- α therapy needs to be discontinued prior to elective surgery but if so what the minimum interval should be between the last dose of the biologic agent and the surgery. Depending on individual metabolism, the half-life of IFX is 7-18 d^[28] and serum antibodies disappear at 3 mo.

In a series of 195 patients with IBD Waterman *et al*^[19] compared postoperative complications and infections between patients exposed to biologics (IFX or ADA) within 14 d, 15-31 d, and 31-180 d before surgery. Most of these patients receive concomitant thiopurine (double therapy) or thiopurine and corticosteroids (triple therapy). They found that biologic therapy alone was not associated with an increased rate of 30-d postoperative infectious complications, hospital stay, readmission, reoperation or anastomotic leak. However, combination therapy with thiopurine and biologics increased rates of postoperative complications including urinary tract infection, wound infection, bacteremia and the need for postoperative antibiotics. In addition, a shorter interval between the last dose of anti-TNF- α therapy and surgery did not increase postoperative complications. They concluded that it is not necessary to delay surgery until anti-TNF- α washout has been achieved. Several other recent trials have been demonstrated no correlation between overall postoperative infections or anastomotic leaks and the interval (ranging from 1-12 wk) between

last IFX administration and surgery^[17,21,22,29].

Postoperative recurrence

Several factors are related to recurrence: smoking, the *NOD2/CARD15* gene mutation, young age at diagnosis, short duration of disease prior to an operation and multiple sites of disease^[11,30-34]. Rate of recurrence may also be influenced also by surgical technique^[30,34] including the type of anastomosis, resection margin and the decision to perform a stricturoplasty vs a resection^[35]. The role of biologic therapy in reducing the incidence of surgical recurrence is yet unknown but we can infer the impact that anti-TNF- α agents may have based on mucosal healing. Early observational studies have demonstrated reduced rates in endoscopic and clinical recurrence in patients post-operatively treated with IFX^[36], Regueiro *et al*^[37] demonstrated in a placebo-controlled randomized trial that endoscopic recurrence was significantly lower in the IFX group compared to controls at 1 year (9.1% vs 84.6%, $P = 0.0006$) but the sample size was too small to detect differences in clinical recurrence. Yoshida *et al*^[38] also conducted a randomized control trial comparing IFX to placebo and found the clinical remission rate with IFX was 100% vs 68% in the placebo group ($P < 0.03$) at one year^[38].

Recently, Savarino *et al*^[39] published the results of a prospective randomized study in which 51 patients with CD who had undergone an ileocolonic resection were assigned to receive ADA at a dose of 160/80/40 mg every two weeks, azathioprine (AZA) at 2 mg/kg per day, or mesalamine at 3 g/d starting 2 wk after surgery. Patients were followed for 2 years. The rate of endoscopic recurrence was lower in the ADA group (6.3%) compared with both the AZA (64.7%; OR = 0.036; 95%CI: 0.004-0.347) and mesalamine groups (83.3%; OR = 0.013; 95%CI: 0.001-0.143). In addition patients in ADA arm had a lower rate of clinical recurrence (12.5%) compared with the AZA (64.7%; OR = 0.078; 95%CI: 0.013-0.464) and mesalamine groups (50%; OR = 0.143; 95%CI: 0.025-0.819).

The role of IFX in preventing relapse of CD after surgical resection is currently being evaluated in the multicentric randomized prevent trial^[40,41]. In this study, patients are post-operative assigned to receive either IFX or placebo. Patients in both groups are treated according to their treatment arm at week 0 and then every 8 wk through week 200. However if a patient initially randomized to the placebo group relapses, IFX therapy may be initiated. Data collection for this trial has been completed and the results are being awaited.

Perianal disease

Perianal CD (PCD) is considered an aggressive and disabling phenotype, which manifests in about 40% of patients diagnosed with CD. Quality of life is often compromised due to anal pain, discharge and fecal incontinence^[41]. Before the introduction of biologics, 40% of patients with PCD underwent proctectomy. Recently anti-TNF- α agents have been demonstrated

to induce and maintain perianal fistula closure in two randomized control trials^[42,43].

Perianal fistulas may be classified as simple if a single, low, transphincteric tract without abscess, stenosis or inflammation is present, or complex if there is more than one tract, granulomatous inflammation, presence of an abscess or it is rectovaginal^[44]. The majority of Crohn's patients experience complex fistulas during their disease course.

Treatment of perianal fistula requires a multidisciplinary approach between surgery, gastroenterology, and radiology. Initial management begins with assessment of the extent and complexity of disease^[45]. Endoscopy evaluates the presence of proctitis, which is predictive of a non-healing fistula tract. Rectal examination under anesthesia helps identify and classify fistulas and enables control of the infection through drainage of the abscess and insertion of a seton. Magnetic resonance imaging (MRI) is considered the gold standard for imaging of PCD with higher specificity compared to transrectal ultrasound. It enables evaluation of the abscess volume and maximum fistula length and can be used to restage and assess response to treatment^[46].

Once the extent and nature of the PCD is characterized combination treatment consisting of surgical and medical therapy (TNF- α with or without immunomodulator) results in improved rates of fistula healing compared with surgery or medical therapy alone^[46-50]. Depending on the study, the endpoint may be fistula healing, usually defined as absence of fistula or drainage by medical examination, or clinical improvement, defined as reduction of symptoms or drainage.

Initially, the role of surgery is to control sepsis and define the anatomy of the fistula track after which definitive treatment can be planned. Surgical options for the treatment of perirectal abscesses or fistulas in patients with CD favor conservative approaches including incision and drainage and placement of non-cutting setons. Non-cutting setons preserve the integrity of the anal sphincter, drain fistula tracts and limit abscess formation and recurrences^[45]. More aggressive procedures including fistulotomy or advancement flap may be appropriate in certain circumstances but are generally avoided because they are associated with increased morbidity and risk of fecal incontinence.

According to recent literature the most effective approach for PCD consists of seton placement prior to starting medical treatment with anti-TNF- α agents or anti-TNF- α agents plus thiopurine^[50-53]. El-Gazzaz *et al*^[50] showed complete healing in 36.6% of patients treated with biologic agents plus surgery vs 26.5% for patients treated with surgery alone with a median follow-up of over 3 years but this was not statistically significant ($P = 0.1$). Bouguen *et al*^[51] reported a study of 156 patients with PCD treated with IFX. Sixty-two percent of patients also underwent seton placement and 56% were on concomitant immunomodulators. At a median follow-up of 57 mo, 46% of total patients and 69% of patients treated with IFX and seton placement for a

median of 8 mo had sustained complete fistula closure. Haennig *et al*^[52] reported data on 81 IBD patients with perianal fistula, 62 (80.5%) underwent drainage with loose seton plus IFX therapy and 73 (90%) received treatment with immunomodulators (either Azathioprine or Methotrexate) in addition to anti-TNF- α . At a median follow-up of 64 mo fistula closure was achieved in 75% of patients.

The need and timing of seton removal and the appropriate duration of anti-TNF therapy remain debated topics^[53]. Bouguen *et al*^[51] found improved outcomes when the seton was removed within 34 wk of starting biologic therapy. Haennig *et al*^[52] hypothesize that the optimal time for seton removal should be determined by the surgeon based on clinical characteristics and recommend that it be left *in situ* between 2 and 8.5 mo. Most series evaluate the status of the fistula by clinical examination, however there is increasing data that MRI may be the more accurate instrument to guide decisions regarding timing of seton removal. MRI often shows residual inflammation and disease activity even when the external tract is closed, which is the basis for recurrence^[45,46]. In terms of how long biologic therapy should be maintained, no consensus can be found in literature but there is a suggestion that long-term anti-TNF- α therapy is associated with better long-term results.

UC

Anti-TNF- α agents are approved to treat moderate to severe UC as second line treatment in patients refractory to corticosteroids and immunomodulators^[54-56]. IFX was approved for UC refractory to standard medications in 2006^[7], adalimumab was approved in 2012^[57,58] and recently, golimumab received approval in Europe and the United States^[59,60].

A recent meta-analysis^[8] demonstrated that anti-TNF- α therapy is more effective than placebo in reducing UC-related hospitalizations. The study analyzed results of IFX^[54], ADA^[55,56] and golimumab^[7,57] trials and found that IFX and ADA achieve long-term mucosal healing at 52-54 wk in 35.6% of patients compare to 16.8% in the placebo group. In addition IFX and ADA were able to reduce UC-related hospitalizations^[61-64] and IFX alone was superior to placebo in reducing the need for colectomy.

Postoperative complications

Unlike CD, in UC a proctocolectomy is curative and removes the risk of developing colorectal cancer. In the era of conservative management, the timing of surgery vs medical therapy with biologics or other medications is challenging^[65]. A colectomy for UC may be done as an emergent/urgent or elective procedure depending on the clinical scenario. An emergent/urgent colectomy is indicated for significant hemorrhage, perforation, megacolon, and severe colitis refractory to medical management. Elective colectomies may be performed in patients with UC that experience chronic symptoms

refractory to medical therapy, those who can't tolerate the adverse effects of medication^[66] and patients with high-grade dysplasia, multifocal low-grade dysplasia or cancer^[53]. There is increasing evidence that in current practice the threshold for surgery is too high and that it is important to consider surgery an alternative therapy rather than a failure of medical therapy^[65,67,68]. Roberts *et al*^[67] compared 3 years mortality for patients who had urgent or elective surgery vs medical management in over 28000 patients hospitalized with UC. The elective colectomy group had the lowest mortality rate (3.7%), while the medical management and urgent colectomy groups had similar mortality rates (13.6% and 13.2% respectively, $P = 0.001$).

In terms of the postoperative effects of anti-TNF therapy on surgery in UC patients, studies of IFX have shown differing results^[20,29,69-76]. The Cleveland Clinic group reported that patients undergoing restorative proctocolectomy with ileoanal pouch anastomosis (IPAA) who were treated pre-operatively with IFX had a 3.54 times greater risk of developing early complications ($P = 0.004$), with the rate of sepsis increased by 13.8 fold ($P = 0.011$), even though the majority of cases were done in 3 stages^[72]. However, Gainsbury *et al*^[69] demonstrated that preoperative IFX use was not associated with an increased risk of short-term postoperative complications after IPAA performed in 2 or 3 stages. They evaluated 81 patients, 29 treated with IFX within 12 wk of surgery and 52 not exposed to IFX. Overall short-term postoperative complications were similar between the IFX and NIFX groups (44.8% vs 44.2%, $P = 0.960$). Infections complications, defined as pelvic/intra-abdominal abscess or wound infection, were similar between the IFX and NIFX groups (17.2% vs 26.9%, $P = 0.32$). In multivariate analysis the risk of wound infection while correlated with a higher body mass index (odds ratio = 0.88, 95%CI: 0.78-0.9, $P = 0.049$) was not related with biologic treatment. Similar results were found by Ferrante *et al*^[70] who analyzed 119 patients undergoing restorative proctocolectomy with IPAA in 1 or 2 stages with 22 of the patients having received IFX 12 wk before surgery. Short-term post-operative complications were not significantly different between the two groups. The two predictors of short-term postoperative complications were use of moderate to high dose corticosteroids (> 20 mg of methylprednisolone for > 2 mo) and absence of a diverting ileostomy.

A recent meta-analysis^[73] of 5 studies including 132 patients on IFX who underwent a restorative proctocolectomy with IPAA in either 2 or 3 stages demonstrated an increase in total postoperative complications (OR = 1.80, 95%CI: 1.12-2.87), but not short-term infectious complications (OR = 2.24, 95%CI: 0.63-7.95) or non-infectious complications (OR = 0.85, 95%CI: 0.50-1.45) in the IFX group.

In our experience^[29], we found no correlations between exposure to IFX within 12 wk of surgery and the rate of postoperative adverse events in 237 UC patients (71 in the IFX group and 166 in NIFX group).

The majority of patients in our study underwent a three stage restorative proctocolectomy with IPAA with only 15 (10.6%) patients in the IFX group and 37 (9.8%) patients in the NIFX group undergoing a two stage procedure ($P = 0.94$).

Higher levels of IFX are associated with increased rates of remission and improved endoscopic outcomes but there is concern that it may be correlated with postoperative complications as well. Waterman *et al*^[19] analyzed 108 IBD patients who underwent a colectomy (94/108 for UC), 51 patients had received biologics before surgery and 57 patients had not and they found that preoperative biological therapy was not associated with increased rates of infectious complications or poor wound healing. Preoperative serum levels of IFX were measured within 2 mo of surgery using a microplate Enzyme linked ImmunoSorbent Assay with a cut-off value of 1.4 mg/mL for detectable levels and the association between serum IFX levels and short-term complications was assessed in 19 patients with UC. Of those 19 patients, 10 had detectable levels of IFX and 9 were undetectable. As expected, the group with detectable levels had a shorter time interval between the last dose of IFX and surgery (median 18 d vs 34 d, $P = 0.03$) and while the rate of wound infection trended higher in the detectable group, this was not statistically significant (3/10 vs 0/9 respectively, $P = 0.21$); there was no difference in the rates of any other complications. A limitation of the study is that the sample size was quite small and data from larger populations is needed to draw more definitive conclusions.

In a recent study published by Lau *et al*^[25] anti-TNF- α levels were measured in 217 IBD patients treated with biologic therapy prior to surgery. An anti-TNF- α value of ≥ 0.98 mg/mL was considered a detectable level even though a cutoff of ≥ 3 μ g/mL is usually used for clinical efficacy. Patients were stratified into: Low (0.98-3 μ g/mL), medium (≥ 3 μ g/mL ≤ 8 μ g/mL), and high (≥ 8 μ g/mL) level groups. Ninety-four of the 217 patients were diagnosed with UC of which 42 patients had a three stage and 52 had a two stage restorative proctocolectomy with IPAA. The infectious complication rate between the undetectable and detectable serum anti-TNF- α drug level groups was not significantly different (9% vs 12%, $P = 0.78$). The rates of overall postoperative morbidity (40% vs 47%, $P = 0.59$) and hospital readmission (19% vs 24%, $P = 0.67$) also did not differ. They concluded that even detectable levels of anti-TNF- α agents were not associated with adverse outcomes postoperatively.

CONCLUSION

Anti-TNF- α therapy for the treatment of IBD has improved long-term outcomes including symptom management, mucosal healing, and endoscopic recurrence and is being used earlier in the course of the disease and with increased frequency. However, surgery continues to be an important part of the management of both UC

and CD. While the data is mixed, increasing evidence is emerging that surgery can safely be performed while patients are undergoing biologic therapy. More data is needed on the impact that anti-TNF- α agents will have on the rates of surgical recurrence in CD.

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Critical appraisal of laparoscopic lavage for Hinchey III diverticulitis

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Abstract

Laparoscopic lavage and drainage is a novel approach for managing patients with Hinchey III diverticulitis. However, this less invasive technique has important limitations, which are highlighted in this systematic review. We performed a PubMed search and identified 6 individual series reporting the results of this procedure.

An analysis was performed regarding treatment-related morbidity, success rates, and subsequent elective sigmoid resection. Data was available for 287 patients only, of which 213 (74%) were actually presenting with Hinchey III diverticulitis. Reported success rate in this group was 94%, with 3% mortality. Causes of failure were: (1) ongoing sepsis; (2) fecal fistula formation; and (3) perforated sigmoid cancer. Although few patients developed recurrent diverticulitis in follow-up, 106 patients (37%) eventually underwent elective sigmoid resection. Our data indicate that laparoscopic lavage and drainage may benefit a highly selected group of Hinchey III patients. It is unclear whether laparoscopic lavage and drainage should be considered a curative procedure or just a damage control operation. Failure to identify patients with either: (1) feculent peritonitis (Hinchey IV); (2) persistent perforation; or (3) perforated sigmoid cancer, are causes of concern, and will limit the application of this technique.

Key words: Diverticulitis; Colon; Emergency surgery; Outcome; Laparoscopy

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Core tip: Laparoscopic lavage and drainage for purulent peritonitis due to perforated diverticulitis has many limitations, which have been overlooked in the previously published case series of the literature. The available data from the unique RCT indicates that these results will not be reproduced in a trial where patients' selection is avoided. There are three main limitations to the technique: (1) the risk of missing a persistent (incompletely sealed) perforation - 30% of cases; (2) the risk of missing fecal peritonitis enclosed within the sigmoid loop - 10% of cases; and (3) the risk of missing sigmoid carcinoma - 10% of cases).

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INTRODUCTION

Severe septic complications of sigmoid diverticulitis, such as abscesses and peritonitis, are common emergencies in Western countries. While patients presenting with Hinchey stages I / II (pericolonic and extra-mesocolic abscesses) are conservatively managed, those presenting with purulent (Hinchey III) or feculent (Hinchey IV) peritonitis undergo emergency surgery^[1]. Most surgeons agree that a Hartmann procedure remains the best approach for Hinchey IV patients^[2]. This operation, however, is associated with significant morbidity and mortality, as well as the need for a second operation, 3 mo later, to restore intestinal continuity. Patients with Hinchey III diverticulitis may benefit from less invasive approaches, and since the 1990s, laparoscopic lavage and drainage (LLD) was proposed as an alternative to resection procedures (either with or without primary anastomosis) for Hinchey III patients presenting with generalized purulent peritonitis^[3] (Table 1). According to its proponents, this novel approach represents a definitive treatment for most patients presenting with diffuse purulent peritonitis of diverticular origin^[4].

Unfortunately, 20 years after its first description^[5], it appears that LLD has failed to gain popularity: There are less than 15 series published so far, and many are limited to less than 10 patients, which is surprising in the view of the large number of emergency procedures performed for complicated sigmoid diverticulitis. As an example, between 1996 and 2006, there were 500000 admissions in English NHS hospitals for a primary diagnosis of diverticular disease and 22000 patients underwent emergency surgery^[6]. The aim of this systematic review is to critically assess the existing data regarding the use of LLD for Hinchey III diverticulitis.

DEFINITIONS

Hinchey III diverticulitis

Hinchey III stage is defined by the presence of pus in the four quadrants of the abdomen. It's a generalized peritonitis of diverticular origin but there is absence of feces in the abdominal cavity. Hinchey III is a life-threatening condition with a high morbidity and mortality. Many patients present often with renal failure, dehydration, and require immediate surgical attention. Of note, the distinction between stages III and IV is not possible by clinical examination, and the definitive diagnosis is made in the operating room during surgical exploration: In some cases, computed tomography scan imaging provides useful preoperative information, and may demonstrate the presence extra-intestinal feces (Figures 1 and 2).

Either the presence of a small amount of fluid in the Douglas pouch, or the presence of free air in the

peritoneal cavity are not sufficient criteria for classifying the patient's condition as Hinchey III. Both findings are common in Hinchey I / II patients, but these latter two categories have a much better prognostic due to the absence of diffuse peritonitis.

Laparoscopic lavage-drainage

Laparoscopic lavage is a technique, which aims at treating the consequences of the perforation, and not the cause itself. Since many patients have, at the time of surgery, a perforation, which is sealed by the omentum or the small bowel, no attempt should be made to mobilize the sigmoid loop. A 4-trocars technique is recommended in order to gain access to the Douglas pouch and thoroughly wash the abdominal cavity with 5-10 L of warm saline, until the fluid in the suction catheter comes back clear. Two drains are left in the Douglas pouch and the left iliac fossa usually, and intravenous (*iv*) antibiotics prescribed for 5-10 d postoperatively^[7].

RATIONALE

Laparoscopic lavage is primarily a damage control approach, which aims at minimizing the consequences, and not treating the cause of peritonitis itself. In the case of Hinchey III diverticulitis, the assumption made by the proponents of the technique is that the sigmoid perforation is sealed at the time of the operation, so that LLD and *iv* antibiotics are sufficient to cure the patient. This may be true for some Hinchey III patients, but recent evidence suggest that 37% of patients who underwent emergency sigmoid resection showed persistent bowel perforation on review of histology^[8].

The critical point is to determine whether: (1) LLD is a definitive technique - meaning that the patients' problems of diverticulitis are for ever taken care of; or (2) LLD is merely a damage control procedure, which aims to delaying definitive treatment (elective sigmoid resection) a couple of months later^[9]? It is interesting to note that the authors of the various series do not always agree on that issue. To simplify and summarize the current debate, authors from the United Kingdom generally consider that laparoscopic lavage is a definitive treatment and that diverticulitis recurrence rarely occurs afterwards, thus precluding the need for subsequent sigmoid resection^[10]. By contrast, authors from France believe that most patients successfully managed with LLD in the emergency setting will eventually need a sigmoid resection - they consider in fact that this approach is not a definitive treatment for diverticulitis^[3]. These differences in the philosophy of this approach are important to emphasize, since its results are to be evaluated in a different manner.

DATA ANALYSIS

We performed a PubMed search with the terms "perforated diverticulitis" and "laparoscopic lavage" and



Figure 1 Computed tomography scan of Hinchey III diverticulitis.



Figure 2 Computed tomography scan of Hinchey IV diverticulitis - a contra-indication for laparoscopic lavage and drainage.

retrieved 6 series for a total of 279 patients who underwent LLD, but 200 patients only were classified as Hinchey III^[7,11-15]. No indication was given upon the selection process, therefore it is impossible to know how many patients were not considered candidates for LLD; the small number of procedures raises the question that those 200 patients were selected in some way, most probably because they presented with less severe condition. Interestingly, the literature search revealed that LLD is often performed in patients with Hinchey II diverticulitis, a condition that usually does not require operative management: Thus, 25% of patients underwent unnecessary surgery, and represent a subgroup in which a so-called “minimally invasive” approach was actually overtreatment.

Reported success rates in these 6 series were extremely good: 94% of patients were successfully managed with LLD, with minimal (2%) mortality. Causes of failure were: (1) persistent sepsis; (2) fecal fistula formation; and (3) perforated sigmoid cancer. Although few patients developed recurrent diverticulitis in follow-up, 98 (49%) eventually underwent elective sigmoid resection (Table 2). There were wide variations (2%-50%) in the rate of recurrent diverticulitis after LLD. Not surprisingly, these differences translated into wide variations in the rate of subsequent sigmoid resections (0%-100%).

Table 1 Hinchey classification and stage-adjusted outcomes and therapeutic approaches

Stage	Definition	Mortality (%)	Treatment
I	Small abscess (> 4 cm)	0	<i>iv</i> antibiotics
II	Large (> 4 cm) abscess	5	<i>iv</i> antibiotics + drainage
III	Purulent peritonitis	25	LLD, PA or Hartmann
IV	Fecal peritonitis	50	Hartmann

PA: Left colectomy with primary anastomosis; LLD: Laparoscopic lavage and drainage; *iv*: Intravenous.

Table 2 Published series of laparoscopic lavage and drainage with clinical outcomes and need for subsequent sigmoid resection

Ref.	<i>n</i>	Hinchey III (%)	Success (%)	Mortality (%)	Sigmoid resection (%)
Myers <i>et al</i> ^[7]	100	67	93	4	0
Radé <i>et al</i> ^[11]	24	75	88	0	100
Karoui <i>et al</i> ^[12]	35	100	97	0	76
White <i>et al</i> ^[13]	35	31	77	0	69
Liang <i>et al</i> ^[14]	47	76	96	0	47
Vennix <i>et al</i> ^[16]	46	100	76	9	34
Total	287	74	94	3	37

PROSPECTIVE RANDOMIZED TRIALS

So far, there is only one published RCT on this topic (LADIES^[16]), but laparoscopic lavage is currently assessed in 3 other trials, conducted in Ireland (LAPLAND) and Scandinavia (SCANDIV AND DILALA^[17,18]). The Dutch LADIEs trial, however, was prematurely interrupted because of an exceedingly high rate of complications in the LLD group. The causes of failure in the lavage group were: Death (4%); surgical re-intervention (20%); recurrent abscess (20%); even worse, 5 (11%) patients were eventually diagnosed with sigmoid carcinoma. The authors of the study reported that, since the surgeons made no attempt to free the sigmoid colon from adjacent structures, large persistent perforations were missed. In the small group (46 patients) of LLD, there were a total of 28 surgical re-interventions, and it is therefore not surprising that the Safety Monitoring Board of the study decided to interrupt patients’ inclusion in the LLD arm of the trial.

The first lesson from the RCT is therefore that LLD is definitively not indicated for Hinchey IV patients. LLD is also not a good operation for patients with a persistent perforation. These individuals present with severe comorbidities and have a high operative mortality due to sepsis. Resection surgery still remains the best option in this situation. We believe that the main problem of LLD is the absence of a surgical diagnosis: If the surgeon deliberately abandons the prospect of removing adhesions surrounding the source of infection, then he may overlook: (1) the cause of perforation (cancer vs diverticulitis); (2) the severity of perforation (sealed vs persistent); and (3) the presence of extra-digestive

feculent discharge.

DISCUSSION

LLD is not a panacea, and so far did not meet expectations, as proven by the low number of patients who benefitted from this approach in the surgical literature (less than 200, compared to the huge number of emergency laparotomies performed every year for peritonitis of diverticular origin)^[19]. LLD has no benefit in patients with Hinchey II, and no efficacy in patients with Hinchey IV diverticulitis. Thus, its indications remain strictly limited to Hinchey III, as initially proposed. A percentage of patients with perforated sigmoid carcinomas will be misdiagnosed as Hinchey III, thus these individuals also will not benefit from LLD - and this important limitation should be explained to the patient and his family before the operation. Recent evidence suggests that the rate of occult neoplasia is 10% in patients presenting with sigmoid perforation^[20,21].

Finally, a high number of patients will recur after laparoscopic lavage, and present again with similar symptoms 2-6 mo after LLD. In our experience, this approach should therefore not be considered as a definitive treatment, but preferably as an attempt to avoid sigmoidectomy in the emergency setting. In summary, this approach has important limitations: It is not needed for Hinchey I - II patients; it is not efficient for Hinchey IV patients; most patients with Hinchey III diverticulitis will not be cured, and will require a definitive resection, meaning a second operation three months later, or will be exposed to a high risk of recurrence. Finally, a small but significant percentage of patients with perforated cancers will be misdiagnosed and re-operated with a worst prognosis and probably a very difficult operation 2-4 wk later. In conclusion, this approach has important limitations, and is not a safe alternative to sigmoid resection surgery for patients with Hinchey III diverticulitis.

CONCLUSION

Laparoscopic lavage and drainage for purulent peritonitis due to perforated diverticulitis has many limitations, which have been overlooked in the previously published case series of the literature; actually, it seems likely that the excellent results of these series are a result of a strong selection bias, as well as the inclusion of many patients with Hinchey II diverticulitis. The available data from the unique RCT indicates that these results will not be reproduced in a trial where patients' selection is avoided. There are three main limitations to the technique: (1) the risk of missing a persistent (incompletely sealed) perforation - 30% of cases; (2) the risk of missing fecal peritonitis enclosed within the sigmoid loop - 10% of cases; and (3) the risk of missing sigmoid carcinoma - 10% of cases). LLD is deemed to fail in this group of patients. We conclude that LLD is not a safe approach for a majority of patients presenting

with diffuse purulent peritonitis of diverticular origin.

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Role of laparoscopic common bile duct exploration in the management of choledocholithiasis

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Abstract

Surgical fraternity has not yet arrived at any consensus for adequate treatment of choledocholithiasis. Sequential treatment in the form of pre-operative endoscopic retrograde cholangio-pancreatography followed by laparoscopic cholecystectomy (LC) is considered as

optimal treatment till date. With refinements in technique and expertise in field of minimal access surgery, many centres in the world have started offering one stage management of choledocholithiasis by LC with laparoscopic common bile duct exploration (LCBDE). Various modalities have been tried for entering into concurrent common bile duct (CBD) [transcystic (TC) vs transcholedochal (TD)], for confirming stone clearance (intraoperative cholangiogram vs choledochoscopy), and for closure of choledochotomy (T-tube vs biliary stent vs primary closure) during LCBDE. Both TC and TD approaches are safe and effective. TD stone extraction is involved with an increased risk of bile leaks and requires more expertise in intra-corporeal suturing and choledochoscopy. Choice depends on number of stones, size of stone, diameter of cystic duct and CBD. This review article was undertaken to evaluate the role of LCBDE for the management of choledocholithiasis.

Key words: Laparoscopic common bile duct exploration; Choledochoscopy; Cholangiogram; Choledocholithiasis; Primary closure

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Core tip: Various treatment modalities are available for management of choledocholithiasis. Laparoscopic common bile duct exploration offers one stage management of cholelithiasis with choledocholithiasis. This review article was undertaken to evaluate this technique and its various aspects.

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INTRODUCTION

The incidence of gallstones varies from 6%-10% in adult population^[1]. Three percent to 14.7% of patients of gallstones have concurrent common bile duct (CBD) stones as well^[2]. "Gold Standard" for management of gallstones is laparoscopic cholecystectomy (LC) but there is no consensus for treatment of CBD stones. In the era of open surgery, treatment was straight-forward; open cholecystectomy with open CBD exploration though it carried high morbidity and mortality. With the advent of non invasive and minimal invasive techniques, option of pre-operative endoscopic retrograde cholangiopancreatography (ERCP) followed by LC emerged as adequate treatment. Major disadvantages of ERCP are that it is a two stage procedure and is associated with life threatening complications like pancreatitis, bleeding and duodenal perforation. It has also been reported that sphincterotomy may cause papillary stenosis and increased risk of bile duct cancer^[2,3].

With refinements in technique and expertise in field of minimal access surgery, many centres in the world have started offering one stage management of choledocholithiasis by LC with laparoscopic CBD exploration (LCBDE). Only few randomized trials are available comparing pre-operative ERCP followed by LC with single stage LC and LCBDE^[4,5]. There is no consensus even for the technique of LCBDE. Various modalities have been tried for entering into CBD [transcystic (TC) vs transcholedochal (TD)], for confirming stone clearance [intraoperative cholangiogram (IOC) vs choledochoscopy], and for closure of choledochotomy (T-tube vs biliary stent vs primary closure).

REVIEW OF LITERATURE

Literature search was performed to answer these questions. Online search engines like PubMed, Google, springer link library and Cochrane database systematic review were utilized and review articles, prospective and retrospective studies which detailed or compared the various treatment strategies for CBD stones were selected and analyzed.

Sequential vs one stage management

Two randomized trials have compared pre-operative ERCP followed by LC with one stage LC and LCBDE^[4,5]. Results of the two modalities were comparable in terms of stone clearance and complications but duration of hospitalization was shorter with LCBDE in both studies^[4,5]. In a study done by Rogers *et al*^[5], 122 patients were randomized into either group. Hospital stay was significantly shorter for LC + LCBDE [mean (SD), 55 (45) h vs 98 (83) h; $P < 0.001$]. There was no difference in patient acceptance and quality of life scores among the two groups. A prospective analysis done ($n = 150$) by Mohamed *et al*^[6] showed that the laparoscopic management of CBD stones is as safe and effective as the sequential ERCP followed by LC with nearly the same

stone clearance rate, hospital stay, and complications.

Liu *et al*^[7] did a meta-analysis and found that there was no significant difference between laparoscopic CBD exploration group and pre-operative endoscopic sphincterotomy group in terms of complications or retained stones ($P > 0.05$). Success rate was higher in LCBDE group with reduced hospital expenses, mean operative time and duration of hospitalization ($P < 0.05$)^[7].

Another meta-analysis done by Nagaraja *et al*^[8], reported higher incidence of ERCP related complications in patients undergoing pre-operative ERCP [odds ratio (OR) = 2.40, 95%CI: 1.21-4.75].

Costi *et al*^[9] performed a case-control study comparing a single stage laparoscopic approach ($n = 22$) with sequential treatment ($n = 15$). They found two groups to be similar in terms of early and late complications. The postoperative hospitalization was significantly less in the single stage group^[9]. Bansal *et al*^[10] conducted a prospective randomized trial comparing single stage laparoscopic treatment with sequential treatment of CBD stones. Fifteen patients were randomized to each group. Stone clearance rates and complications were similar in both groups. They concluded that single stage approach seems to be better due to smaller number of procedures and hospital visits^[10].

Cochrane systematic review was done by Dasari *et al*^[11] in 2013. They included five trials ($n = 580$). Two hundred and eighty-five patients underwent LC + LCBDE and 295 patients received sequential treatment in the form of ERCP + LC. There was no significant difference among two groups in terms of mortality (0.7% vs 1%), morbidity (15% vs 13%) or incidence of retained stones (8% vs 11%).

A meta-analysis of single-stage vs sequential treatment for cholelithiasis with common bile duct stones was carried out by Zhu *et al*^[12] recently. Eight randomized controlled trials, which involved 1130 patients, were included in this study. The meta-analysis revealed that the CBD stone clearance rate in the single-stage group was higher (OR = 1.56, 95%CI: 1.05-2.33, $P = 0.03$). The lengths of hospitalization (MD = -1.02, 95%CI: -1.99 to -0.04, $P = 0.04$) and total operative times (MD = -16.78, 95%CI: -27.55 to -6.01, $P = 0.002$) were also shorter in the single-stage group. There was no statistically significant difference among the two groups regarding postoperative morbidity (OR = 1.12, 95%CI: 0.79-1.59, $P = 0.52$), mortality (OR = 0.29, 95%CI: 0.06-1.41, $P = 0.13$) and conversion to other procedures (OR = 0.82, 95%CI: 0.37-1.82, $P = 0.62$).

TC vs TD

Hongjun *et al*^[13] compared TC approach ($n = 80$) with TD approach ($n = 209$) and found that there was no significant difference between the two approaches for cystic duct diameter (0.47 ± 0.09 cm vs 0.47 ± 0.08 cm), procedure time (91.94 ± 34.21 min vs 96.13 ± 32.15 min), complications (2.5% vs 2.87%) and

duration of hospitalization (9.82 ± 3.48 d vs 10.74 ± 5.34 d) (all $P > 0.05$). A significant difference was noticed in terms of the common bile duct diameter (1.18 ± 0.29 cm vs 1.04 ± 0.24 cm, $P < 0.05$)^[13].

Wang *et al*^[14] reported that TC LCBDE is safe and effective in elderly population. TC approach was successful in 157 of 165 patients (95.15%). Five patients were converted to laparoscopic TD approach and T-tube drainage whereas three patients were managed by laparotomy and open CBD exploration. No significant complications were reported in the study. The mean blood loss was 43 ± 20 mL and mean operative time was 102 ± 35 min. The postoperative hospitalization was 3 ± 0.5 d^[14].

A systematic review done by Reinders *et al*^[15] included eight randomized trials with 965 patients. Successful bile duct clearance varied between 80.4% and 100% in the TC groups and 58.3% and 100% in the TD groups. There were more bile leaks after TD stone extraction (11%) than after TC stone extraction (1.7%). They concluded that TD stone extraction is associated with an increased risk of bile leaks and should only be done by highly experienced surgeons; TC stone extraction seems a more accessible technique with lower complication rates^[4,5,10,16-20].

Chander *et al*^[21] have concluded that TD route is better in Asian patients with multiple, large stones and dilated CBD.

IOC vs choledochoscopy

Only two studies were found comparing IOC with choledochoscopy for confirming stone clearance. Topal *et al*^[22] found similar results with both techniques, though operative time was longer in IOC group. Vindal *et al*^[23] in a prospective randomized study compared IOC ($n = 65$) with intra-operative choledochoscopy ($n = 67$). Mean operative time was 170 min in group A and 140 min in group B ($P < 0.001$). There was no significant difference in complications among the two groups^[23]. They found choledochoscopy to be better and less time consuming than IOC for determining bile duct clearance after TD LCBDE.

Primary closure vs T-tube vs biliary stent

In a retrospective study done by Yi *et al*^[24], long term results of primary closure (group P, $n = 91$) after LCBDE were compared with T-tube drainage (group T, $n = 51$). The mean operative time was significantly less in group P than group T (168.9 ± 50.1 min vs 198.0 ± 59.6 min, $P = 0.002$). The duration of hospitalization was significantly less in group P than in group T (8.59 ± 6.0 d for group P vs 14.96 ± 5.4 d for group T, $P = 0.001$). The stone recurrence rates in group P and group T were 4.4% and 5.9%, respectively ($P = 0.722$) (mean follow-up 48.8 mo). There was no sign of biliary stricture or other biliary complications in follow-up in either group. They concluded that primary closure after LCBDE with choledochoscopy is as safe and effective as T-tube drainage in terms of long-term results^[24].

Dong *et al*^[25] compared primary closure (group A, $n = 101$) with T-tube drainage (group B, $n = 93$) after LCBDE. The mean operative time was less in group A than in group B (102.6 ± 15.2 min vs 128.6 ± 20.4 min, $P < 0.05$). Postoperative hospitalization was longer in group B (4.9 ± 3.2 d) than in group A (3.2 ± 2.1 d). The hospital expenses were also significantly less in group A. Three patients experienced complications in postoperative period, which were related to T-tube usage in group B^[25].

In other study, Leida *et al*^[26] showed that patients with primary closure of the CBD returned to work faster (12.6 ± 5.1 d vs 20.4 ± 13.2 d). This group also showed advantages of significantly lower hospital expenses and less postoperative complications than T-tube drainage group (15% vs 27.5%)^[26].

Lyon *et al*^[27] compared use of biliary stent ($n = 82$) with T-tube drainage ($n = 34$) after LCBDE in a prospective non-randomized study. The duration of hospitalization for patients who underwent biliary stent or T-tube insertion after LCBDE were 1 and 3.4 d, respectively ($P < 0.001$). In the T-tube group, two patients required laparoscopic washout due to bile leaks. They concluded that ante-grade biliary stent insertion is associated with low hospital expenses and increased patient satisfaction^[27].

Dietrich *et al*^[28] compared biliary stent with T-tube drainage in a series of 48 patients who underwent LCBDE. Patients with T-tube drainage had more procedure-related complications ($P < 0.0001$) and a prolonged hospital stay ($P = 0.03$).

A retrograde study done by Abellán Morcillo *et al*^[29], compared T-tube closure ($n = 36$), biliary stent ($n = 133$) and primary closure ($n = 16$). In the stented group, they found an 11.6% incidence of pancreatitis and a 26.1% incidence of hyperamylasemia whereas in the primary closure group, a clear improvement of complications and hospital stay was observed^[29].

Chen *et al*^[30] in their study observed that primary closure is safe after LCBDE ($n = 194$).

Estellés Vidagany *et al*^[31] did primary closure after LCBDE in 160 patients. Bile leakage was reported in 11 patients (6.8%). In 7 out of 11 patients (63.6%), no further intervention was needed and the leak closed on its own. Six patients were reoperated (3.75%), two for biliary peritonitis and four for haemoperitoneum. The success rate for stone clearance was 96.2%. No mortality or CBD stricture was reported in the study. They concluded that primary closure after LCBDE is a safe technique with excellent results^[31].

Hua *et al*^[32] studied rate of bile leak following primary closure in LCBDE *via* TD approach. Of 157 LCBDE procedures, 138 (87.9%) were successfully managed with primary closure of the choledochotomy. Eight patients (5.1%) underwent closure over a T-tube after LCBDE and 11 patients (7.0%) were converted to open surgery. The success rate for CBD stone clearance was 98.1%. Postoperative bile leak was seen in 6 patients (3.8%).

Table 1 Effective and important factors in common bile duct stones approach

Factor	Trans-cystic approach	Trans-ductal approach
Single stone	Yes	Yes
Multiple stones	Yes	Yes
Stones < 6 mm diameter each	Yes	Yes
Stones > 6 mm diameter each	No	Yes
Intrahepatic stones	No	Yes
Diameter of cystic duct < 4 mm	No	Yes
Diameter of cystic duct > 4 mm	Yes	Yes
Diameter of common bile duct < 6 mm	Yes	No
Diameter of common bile duct > 6 mm	Yes	Yes
Suturing ability-poor	Yes	No

Gurusamy *et al*^[33] published a cochrane systematic review comparing T-tube with primary closure after LCBDE. They included three trials randomizing 295 participants: 147 to T-tube drainage vs 148 to primary closure. The operative time was significantly more in the T-tube drainage group compared with the primary closure group (MD 21.22 min; 95%CI: 12.44 to 30.00 min). The duration of hospitalization was significantly more in the T-tube drainage group compared with the primary closure group (MD 3.26 d; 95%CI: 2.49 to 4.04 d). According to one trial, the participants randomized to T-tube drainage took approximately eight days more to return to work than the participants randomized to the primary closure group ($P < 0.005$). They concluded that T-tube drainage is associated with significantly longer operative time and hospital stay as compared with primary closure after LCBDE. They also emphasized that currently available evidence cannot justify the routine use of T-tube drainage after LCBDE^[33].

Podda *et al*^[34] did a meta-analysis of all studies comparing primary duct closure and T-tube drainage after LCBDE (total 16 studies, 1770 patients). Primary duct closure showed a significant advantage over T-tube in terms of postoperative bile peritonitis ($P = 0.02$), operative time, duration of hospitalization, and median hospital cost (all $P < 0.00001$).

DISCUSSION

Pre-operative ERCP followed by LC is the most commonly used treatment modality for management of choledocholithiasis. ERCP carries a high rate of morbidity and mortality mostly due to post-procedure pancreatitis, duodenal perforation and bleeding. It also causes injury to sphincter of oddi which should be avoided in younger patients. LCBDE offers a one stage treatment with similar or better stone clearance rate and with a shorter hospital stay. It also preserves function of sphincter of oddi and hence prevents reflux related complications^[2,3]. LCBDE has been found to be safe even in elderly population^[14,35]. A Cochrane systematic review by Martin *et al*^[36] concluded that a single-stage treatment in the form of LCBDE *via* TC approach is the procedure of choice for intraoperatively discovered CBD calculi.

Despite the simplicity and success of LCBDE, many surgeons across the globe are still not comfortable or confident regarding the procedure. Petelin *et al*^[37] did a web based survey among United States surgeons regarding their choice for managing choledocholithiasis. For preoperatively known CBD calculi, 86% preferred preoperative ERCP. Those in metropolitan areas were more likely to choose preoperative ERCP than those in nonmetropolitan areas (88% vs 79%, $P < 0.001$). For CBD stones discovered intraoperatively, 30% chose LCBDE as their preferred method of management with no difference between metropolitan and nonmetropolitan areas ($P = 0.335$). The top reasons for not performing LCBDE were: Availability of a reliable ERCP, lack of equipment, and lack of skill performing LCBDE. They concluded that many surgeons are uncomfortable performing LCBDE, and advanced training may be needed. There is a risk of surgeons losing the art, which may still be required in cases of unavailability or failure of ERCP^[38].

Both TC and TD approaches are safe and effective. TD stone extraction is associated with a increased risk of bile leaks and requires more expertise in intracorporeal suturing and choledochoscopy^[21]. TC stone extraction seems a more accessible technique with lower complication rates. Choice depends on number of stones, size of stone, diameter of cystic duct and CBD (Table 1)^[39].

Stone clearance during LCBDE can be confirmed by IOC or choledochoscopy. Intra-operative choledochoscopy is better than IOC for determining ductal clearance after TD LCBDE and is less cumbersome and less time-consuming.

Choledochotomy after LCBDE (TD approach) is conventionally managed by T-tube closure. Primary closure of choledochotomy is a safe and effective option with less operative time and hospital stay. Biliary stent also reduces cost and hospital stay as compared to T-tube. There is lack of randomized trial comparing primary closure with biliary stent.

In patients having cholangitis, it is advisable to go for drainage of biliary obstruction by ERCP followed by LC. LCBDE can be offered to all other patients with CBD stones if expertise is available^[21]. If laparoscopic exploration fails, it is prudent to convert it to open bile duct exploration and removal of ductal stones.

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Randomized Controlled Trial

Enhanced recovery program is safe and improves postoperative insulin resistance in gastrectomy

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Abstract

AIM: To assess the safety of enhanced recovery after surgery (ERAS) program in gastrectomy and influences on nutrition state and insulin-resistance.

METHODS: Our ERAS program involved shortening the fasting periods and preoperative carbohydrate loading. Eighty gastrectomy patients were randomly assigned to either the conventional group (CG) or ERAS group (EG). We assessed the clinical characteristics and postoperative outcomes prospectively. The primary endpoint was noninferiority in timely discharge from the hospital within 12 d. Secondary endpoints were the incidence of aspiration at anesthesia induction, incidence of postoperative complications, health related quality of life (HRQOL) using the SF8 Health Survey questionnaire, nutrition state [*e.g.*, albumin, trans-thyretin (TTR), retinal-binding protein (RBP), and transferrin (Tf)], the homeostasis model assessment-insulin resistance (HOMA-R) index, postoperative urine volume,

postoperative weight change, and postoperative oral intake.

RESULTS: The ERAS program was noninferior to the conventional program in achieving discharge from the hospital within 12 d (95.0% *vs* 92.5% respectively; 95%CI: -10.0%-16.0%). There was no significant difference in postoperative morbidity between the two groups. Adverse events such as vomiting and aspiration associated with the induction of general anesthesia were not observed. There were no significant differences with respect to postoperative urine volume, weight change, and oral intake between the two groups. EG patients with preoperative HOMA-R scores above 2.5 experienced significant attenuation of their HOMA-R scores on postoperative day 1 compared to CG patients ($P = 0.014$). There were no significant differences with respect to rapid turnover proteins (TTR, RBP and Tf) or HRQOL scores using the SF8 method.

CONCLUSION: Applying the ERAS program to patients who undergo gastrectomy is safe, and improves insulin resistance with no deterioration in QOL.

Key words: Gastrectomy; Carbon hydrogen oxygen; Insulin resistance; Enhanced recovery after surgery; Randomized controlled trial

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Core tip: We conducted a prospective study in gastrectomy patients to evaluate the efficacy of enhanced recovery after surgery (ERAS) programs. ERAS was safe and improved insulin resistance in these patients.

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INTRODUCTION

Gastrectomy is a high-risk procedure owing to the stress of surgery and resulting complications. In the past few decades, oral intake was not permitted for a long period of time after surgery because of the chance that intraluminal pressure on the anastomosis would induce leakage. To that end, enhanced recovery after surgery (ERAS) programs were introduced, and found to be safe and useful for patients undergoing colectomy^[1]. Previous reports have shown the benefits of ERAS programs such as controlling preoperative carbohydrate loading to regulate blood sugar^[2,3] and early rehabilitation to prevent pneumonia, bowel obstruction, and thrombosis^[1]. Postoperative early feeding signifi-

cantly reduces hospital stay yet does not increase postoperative complications^[4,5]. Similar programs have recently been introduced for gastrectomy patients, with a number of reports having been published in the past few years^[6-10]. Moreover, postoperative oral feeding is being steadily introduced at earlier time points. In 2014, a report on the safety of commencing oral intake on postoperative day (POD) 1 after gastrectomy was published^[11]. Although this report proposed that introducing postoperative oral feeding sooner is safe, the overall consequences of early postoperative feeding are still unclear.

In April 2012, we revised our clinical pathway for gastrectomy, employing a modified ERAS protocol originally used for colorectal resection. In this study, we compared postoperative outcomes between patients who received perioperative care according to our modified ERAS protocol, which involved shorter fasting periods and increased carbohydrate loading, and those who received conventional perioperative care. We evaluated the clinical consequence of this protocol in gastric surgery, assessing safety as well as postoperative nutrition state, insulin-resistance, and quality of life (QOL).

MATERIALS AND METHODS

Patients

This study was a prospective, single center, randomized phase II clinical trial. We studied consecutive patients who underwent gastrectomy at the Department of Gastroenterological and Transplant Surgery, Hiroshima University, between September 2011 and February 2015. Eighty patients were randomly categorized into 2 groups; 40 patients were assigned to each of the conventional treatment group (CG) and the ERAS group (EG). Patients were assigned according to the stratified randomization method by age (< 70 *vs* ≥ 70) and surgical approach (abdominal *vs* laparoscopic surgery). All patients completed their treatment. This study was approved by the institutional review board of the study institution (Hiroshima University, Japan, No.Rin-269) and was conducted in accordance with the Declaration of Helsinki. The study was registered at University Hospital Medical Information Network Clinical Trial Registry (UMIN000020538). Voluntary written informed consent was obtained from all subjects enrolled in this study.

Perioperative care

Patients in both groups were managed perioperatively using equivalent standardized clinical pathway protocols except for perioperative nutrition and intravenous fluid. In the EG, intravenous fluid was restricted to a minimal daily requirement during the first 3 postoperative days. Additional intravenous fluid was administered when patient showed poor oral intake of water or food. The CG received intravenous fluid for 1 wk postoperatively.

Regarding perioperative oral nutrition, patients in the EG received 875 mL of carbohydrate-rich (157 g)

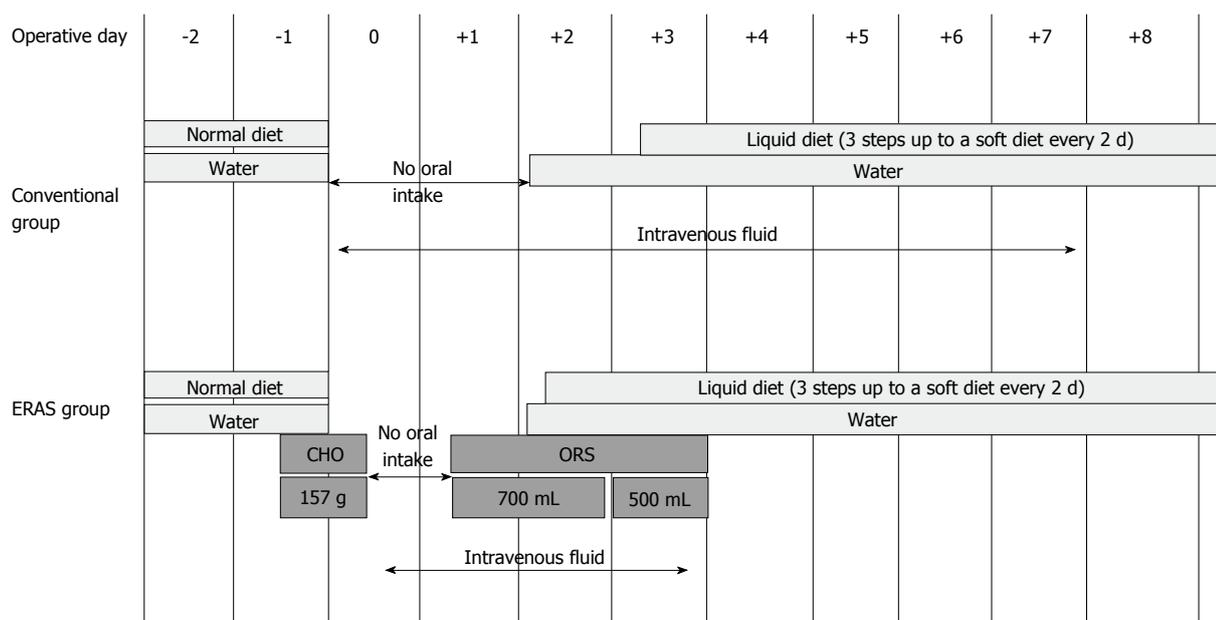


Figure 1 Schema of the study plan for patients participating in the enhanced recovery after surgery program and those subjected to conventional perioperative treatment. CHO: Carbon hydrogen oxygen; ERAS: Enhanced recovery after surgery; ORS: Oral rehydration solution.

fluid until 2 h before the surgery. On POD 1, the patients commenced oral intake with water and oral rehydration solution. On POD 2, patients began to consume a liquid diet. In the CG, patients were allowed to drink water until the day before the surgery. On POD 2, these patients commenced oral intake beginning with water; liquid diets were offered on POD 3 (Figure 1).

Hospital discharge was recommended based on the following criteria: (1) No requirement for intravenous nutrition; (2) Tolerable pain with no or oral-only analgesics; (3) The ability to fully ambulate without assistance; and (4) A willingness to go home.

Data collection

All data were retrieved from the patients' database and clinical records. The primary endpoint was noninferiority in achieving discharge from the hospital within 12 d. Secondary endpoints were the incidence of aspiration at the induction of anesthesia, incidence of postoperative complications, health related QOL (HRQOL) using the SF8 Health Survey questionnaire^[12,13], nutrition state [e.g., albumin (ALB), transthyretin (TTR), retinal-binding protein (RBP), and transferrin (Tf)], the homeostasis model assessment-insulin resistance (HOMA-R) index, postoperative urine volume, postoperative weight change, and postoperative oral intake. HRQOL comprised of 2 components: the physical component summary (PCS) and the mental component summary (MCS). Complications were defined as being of grades ≥ 2 according to the Clavien-Dindo classification within 30 d after surgery. HOMA-R was calculated as immunoreactive insulin \times fasting blood sugar/405.

Statistical analysis

All analyses were conducted according to a statistical

analysis plan. We tested the noninferiority of ERAS with respect to the rate of achievement of discharge from the hospital within 12 d; the targeted noninferiority margin was 15 percentage points.

Assuming a success rate of 85% for the achievement of hospital discharge within 12 d for EG, and a success rate of 90% achievement of the same for CG, the number of patients required to establish noninferiority with 80% power was 33 for each study group. With a presumed dropout rate of 10%, we planned to enroll 80 patients in total.

Patients' backgrounds were analyzed using the Fisher's exact test to compare categorical data (Table 1). Logistic regression analysis was used to compare outcomes between groups (Table 2). Statistical analyses were conducted using the SPSS statistical software (version 19; SPSS Inc., Chicago, IL, United States). Statistical comparisons of parameters were performed using Student's *t*-test. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

The clinical characteristics of the patients in both the CG and EG are described in Table 1. There were no significant differences with respect to gender, age, body mass index), American Society of Anesthesiologists - physical status, surgical method, surgical approach, or tumor characteristics.

Postoperative outcomes

Table 2 summarizes postoperative outcomes in both groups. For the primary endpoint (rate of achievement of discharge from the hospital within 12 d), a successful

Table 1 Comparison of characteristics between conventional group and enhanced recovery after surgery group

Characteristics	Conventional group (n = 40)	ERAS group (n = 40)	P value
Gender			1.000
Male	24	20	
Female	16	20	
Age (yr)			1.000
< 70	28	29	
≥ 70	12	11	
BMI (kg/m ²)			1.000
< 22	18	18	
≥ 22	22	22	
ASA-PS			1.000
1	10	11	
2	30	29	
Method			0.679
Partial gastrectomy	9	6	
Distal gastrectomy	27	30	
Total gastrectomy	4	4	
Approach			0.809
Abdominal surgery	12	13	
Laparoscopic surgery	28	27	
Tumor characteristics			0.568
Gastric cancer	31	34	
Submucosal tumor (GIST or schwannoma)	9	6	

BMI: Body mass index; ASA-PS: American Society of Anesthesiologists - physical status; ERAS: Enhanced recovery after surgery; GIST: Gastrointestinal mesenchymal tumor.

outcome was achieved in 38 of 40 patients (95.0%) in the EG compared to 37 of 40 (92.5%) patients in the CG (Table 2). The lower limit of the two-sided 95%CI for the difference between the study arms (10%) was within the protocol-specified noninferiority margin of 15%. Therefore, ERAS treatment met our criteria for noninferiority to conventional treatment. Mean postoperative hospital stay was also similar between the two groups, as was postoperative morbidity.

Postoperative nutrition state and insulin resistance

Figure 2A shows the results of rapid turnover proteins analysis. Mean serum ALB values on the preoperative day and PODs 1, 3 and 7 in the CG vs EG were 4.40 g/dL vs 4.41 g/dL, 3.11 g/dL vs 3.0 g/dL, 2.86 g/dL vs 2.85 g/dL, and 3.42 g/dL vs 3.44 g/dL, respectively. Mean serum TTR values on the preoperative day and PODs 1, 3 and 7 in the CG vs EG were 24.7 mg/dL vs 24.4 mg/dL, 20.4 mg/dL vs 19.0 mg/dL, 14.6 mg/dL vs 13.1 mg/dL, and 20.0 mg/dL vs 18.4 mg/dL, respectively. Mean serum RBP values on the preoperative day and PODs 1, 3 and 7 in the CG vs EG were 4.18 mg/dL vs 3.82 mg/dL, 2.46 mg/dL vs 1.87 mg/dL, 1.34 mg/dL vs 0.88 mg/dL, and 3.36 mg/dL vs 3.09 mg/dL, respectively. Mean serum Tf values on the preoperative day and POD 7 in the CG vs EG were 201.6 mg/dL vs 205.6 mg/dL and 192.7 mg/dL vs 186.4 mg/dL, respectively. There were no significant differences with respect to ALB, TTR, RBP, and Tf between the two groups. Figure 2B shows the results of HOMA-R analysis. Mean HOMA-R scores on the

preoperative day and PODs 1, 3 and 7 in the CG vs EG were 2.46 vs 3.21, 8.83 vs 6.54, 4.04 vs 2.72, and 2.23 vs 3.17, respectively. There was no significant difference between the two groups at any point. Insulin resistance is defined as the HOMA-R score being over 2.5. In a subgroup analysis of patients with insulin resistance (CG: $n = 11$, EG: $n = 20$), the mean HOMA-R scores on the preoperative day and PODs 1, 3 and 7 in the CG vs EG were 2.95 vs 2.39, 15.05 vs 6.64, 4.19 vs 3.12, and 2.23 vs 3.17, respectively. There was a significant attenuation of the HOMA-R score on POD 1 in the EG compared to the CG ($P = 0.014$).

Quality of life analyses

Figure 3 shows the HRQOL scores obtained using the SF8 Health Survey questionnaire. The mean PCS scores on the preoperative day and PODs 2 and 7 in the CG vs EG were 52.5 vs 50.8, 39.2 vs 37.7, and 44.0 vs 42.4 ($P = 0.284$), respectively. The mean MCS scores on the preoperative day and PODs 2 and 7 in the CG vs EG were 49.9 vs 48.6, 48.4 vs 47.3, and 49.7 vs 49.3, respectively. There were no significant differences with respect to PCS and MCS between the two groups.

Adverse events and other factors

Adverse events such as vomiting and aspiration associated with the induction of general anesthesia were not observed. There were no significant differences with respect to postoperative urine volume, weight change, and oral intake between the two groups (data not shown).

DISCUSSION

There are some reports on the usefulness of ERAS programs for gastrectomy^[6-11]; however, the data are not yet conclusive. Almost every report concerning gastrectomy described the safety of ERAS but not its influence on nutrition state, insulin resistance, QOL, and other such parameters. In this study, we evaluated the effect of postoperative early oral nutrition and preoperative carbohydrate loading.

Our data showed that postoperative early oral nutrition did not increase morbidity, and the rate of achieving discharge from the hospital within 12 d was not compromised. Thus, our ERAS program was deemed to be safe. In fact, the period of hospital stay tended to be shorter in the EG compared to the CG, although the difference was not significant. Most patients do not wish to be discharged until they can ingest soft foods. We surmise that hospital stay can be further shortened if we inform the patients prior to their surgeries that they can be eligible for discharge once they no longer require intravenous nutrition, in order to incentivize them.

It was reported that marked insulin resistance was present after upper abdominal surgery^[14]. Studies in diabetics undergoing surgery have shown that postoperative hyperglycemia has negative effects on wound infection^[15]. This observation is not surprising, because

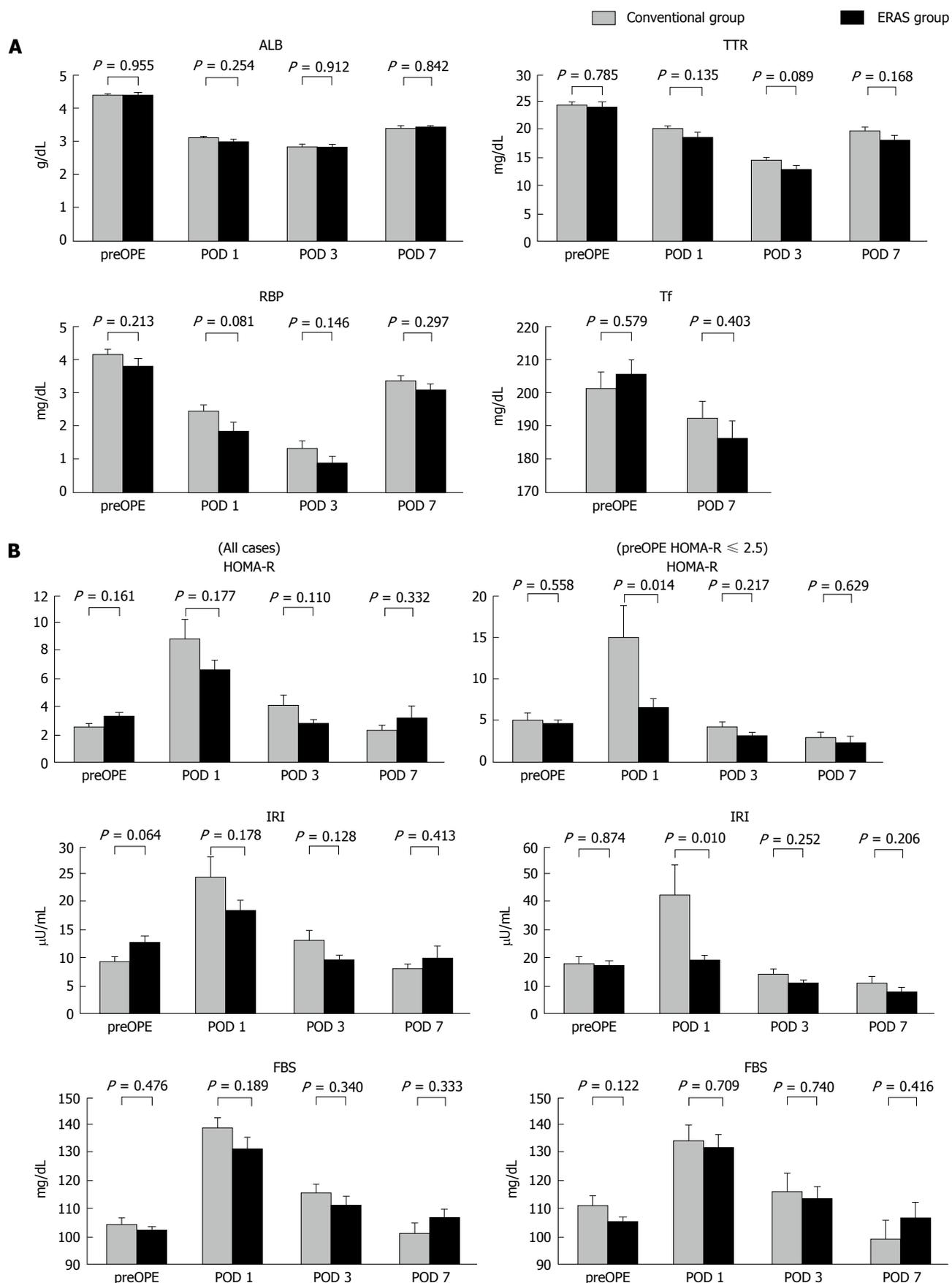


Figure 2 Changes in various serum factors during the perioperative period. A: Rapid turnover proteins; B: Insulin resistance index for all cases (left panel) and for the subgroup of patients in which the preOPE HOMA-R score was over 2.5 (right panel). ALB: Albumin; TTR: Transthyretin; RBP: Retinal-binding protein; Tf: Transferrin; HOMA-R: Homeostatic model analysis ratio-insulin resistance; IRI: Immunoreactive insulin; FBS: Fasting blood sugar; preOPE: Preoperative; POD: Postoperative day.

Table 2 Comparison of postoperative outcomes between conventional group and enhanced recovery after surgery group

	Conventional group (n = 40)	ERAS group (n = 40)	Difference (95%CI)	P value
Accomplishment of the discharge from the hospital within 12 d	92.5% (37/40)	95.0% (38/40)	2.5% (-10.0%-16.0%)	0.646
Postoperative hospital stay (d)	10.4 (7-23)	9.8 (6-20)	-0.58 (-1.63-0.48)	0.280
Postoperative morbidity (Clavien-Dindo grade \geq 2)	12.5% (5/40)	10.0% (4/40)	-2.5% (-19.0%-14.0%)	0.724

ERAS: Enhanced recovery after surgery.

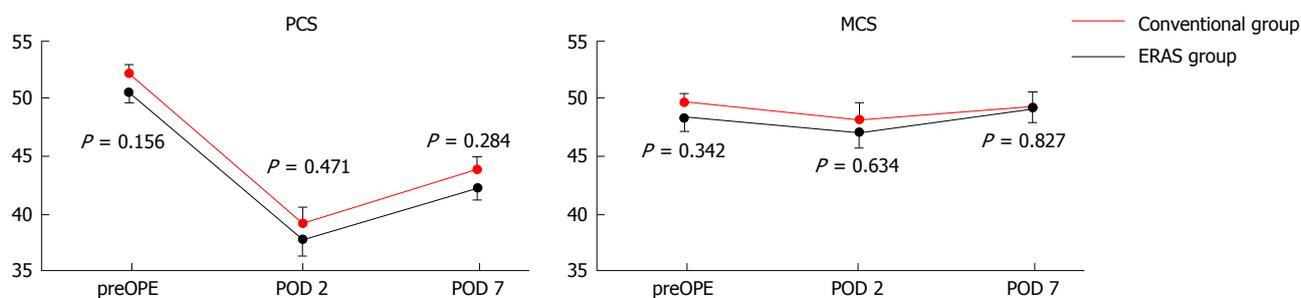


Figure 3 Scores obtained with the SF8 questionnaire during the perioperative period. PCS: Physical component summary; MCS: Mental component summary; preOPE: Preoperative; POD: Postoperative day; ERAS: Enhanced recovery after surgery.

poor glucose control in diabetes is associated with complications. There are two main reasons for experiencing postoperative insulin resistance. One is that the perioperative starvation induces the accumulation of lipid products in skeletal muscles and interferes with insulin signaling to produce insulin resistance^[16]. The other is that the reaction of a living body to the surgical stress induces stress hormones (such as catecholamines, cortisol, and glucagon) as well as the release of the inflammatory cytokine interleukin-6^[2,17,18]. To reduce postoperative insulin resistance, preoperative carbohydrate loading may be useful to counter preoperative starvation^[2,3]. In this study, therefore, patients in the EG were administered carbohydrate-rich liquids until 2 h before surgery. There were no significant differences in insulin resistance between the two groups in the overall analysis. However, in subgroup analysis of patients with high preoperative HOMA-R, there was significant improvement in postoperative insulin resistance in the EG (Figure 2), presumably due to preoperative carbohydrate loading. This study is the first to suggest that preoperative carbohydrate loading in gastrectomy patients attenuates postoperative insulin resistance and thus lowers the risk of additional complications. It is reported that preoperative carbohydrate-rich beverages also reduce preoperative thirst, hunger and anxiety^[19], and also carry postoperative benefits such as a small reduction in the length of hospital stay when compared with placebo-administered or fasting adult patients undergoing elective surgery^[20]. However, the clinical consequences of improving postoperative insulin resistance are still unclear. In our study, the morbidity rate and the length of hospital stay were similar between EG and CG; however, further investigations are required to clarify the clinical influence of improving postoperative insulin resistance.

Our study was not able to demonstrate any benefit of the ERAS program on nutritional state. In the CG, oral intake began on POD 2, whereas it commenced on POD 1 in the EG. This interval is too short to allow assessment of benefits on nutrition states. In terms of HRQOL, there was no significant difference between the two groups. We expected that a shorter period of fasting would have decreased mental stress in EG; however, data obtained through the SF8 Health Survey questionnaire did not reveal any such benefits. A more thorough questionnaire might better reflect early postoperative HRQOL status.

In conclusion, we demonstrated the non-inferiority of the ERAS program with respect to the rate of achieving discharge from the hospital within 12 d post-gastrectomy. Moreover, our results suggest that our ERAS program for gastrectomy is safe and improves postoperative insulin resistance in those patients who were originally insulin resistant. To our knowledge, this study is also the first to demonstrate that preoperative carbohydrate loading in gastrectomy patients attenuates postoperative insulin resistance. However, we did not observe any advantage in postoperative nutrition state and HRQOL due to our ERAS program. It is still uncertain whether the ERAS program is superior to conventional programs because the clinical benefits attributed to this program were not significant.

COMMENTS

Background

There are some reports on the safety of enhanced recovery after surgery (ERAS) programs for gastrectomy. In this study, the authors evaluated the effect of postoperative early oral nutrition and preoperative carbohydrate loading.

Research frontiers

Almost every report concerning gastrectomy described the safety of ERAS but

not its influence on nutrition state, insulin resistance, quality of life, and other such parameters.

Innovations and breakthroughs

The authors demonstrated that their ERAS program for gastrectomy is safe and improves postoperative insulin resistance in those patients who were originally insulin resistant.

Applications

It is still uncertain whether the ERAS program is superior to conventional programs because the clinical benefits attributed to this program were not significant.

Terminology

ERAS program consist of many elements, including preoperative education, preoperative carbohydrate loading, omission of bowel preparation, epidural analgesia without opioids, early postoperative enteral feeding, early mobilization of patients, and thromboprophylaxis.

Peer-review

The authors proposed a good trial of ERAS in patients after gastrectomy for gastric cancer. It's a promising idea to improve the recovery efficiency of patients. This manuscript was designed well, written fluently, and deduced credibly.

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Therapeutic improvement of colonic anastomotic healing under complicated conditions: A systematic review

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Abstract

AIM: To identify therapeutic agents for the prophylaxis of gastrointestinal anastomotic leakage (AL) under complicated conditions.

METHODS: The PubMed and EMBASE databases were searched for English articles published between January 1975 and September 2014. Studies with the primary purpose of improving anastomotic healing in the colon or rectum under complicated preoperative and/or intraoperative conditions were included. We excluded studies investigating the adverse effects or risk assessment of an active intervention. Furthermore, investigations of biophysical materials, sealants, electrical stimulation and nutrients were excluded. The primary study outcome was biomechanical anastomotic strength or AL. The meta-analysis focused on therapeutic agents that were investigated in one animal model using the same outcome by at least three independent research groups.

RESULTS: The 65 studies included were divided into 7 different complicated animal models: Bowel ischemia, ischemia/reperfusion, bowel obstruction, obstructive jaundice, peritonitis, chemotherapy and radiotherapy. In total, 48 different therapeutic compounds were examined. The majority of investigated agents (65%) were reported as beneficial for anastomotic healing. Twelve of the agents (25%) were tested more than once in the same model, whereas 13 (27%) of the agents were tested in two or more models of complicated healing. Two therapeutic agents met our inclusion criteria for the meta-analysis. Postoperative hyperbaric oxygen therapy significantly increased anastomotic

bursting pressure in ischemic colon anastomoses by a mean of 28 mmHg (95%CI: 17 to 39 mmHg, $P < 0.00001$). Granulocyte macrophage-colony stimulating factor failed to show a significant increase in anastomotic bursting pressure (95%CI: -20 to 21 mmHg, $P = 0.97$) vs controls in experimental chemotherapeutic models.

CONCLUSION: This systematic review identified potential therapeutic agents, but more studies are needed before concluding that any of these are useful for AL prophylaxis.

Key words: Anastomotic healing; Colorectal surgery; Breaking strength; Bursting pressure; Anastomotic leakage; Ischemia; Chemotherapy; Reperfusion; Bowel obstruction; Peritonitis; Radiotherapy

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Core tip: Anastomotic leakage is a challenging complication after colorectal surgery. Although many pharmaceutical compounds have the potential to improve anastomotic healing, none has reached the clinical setting. This study reviewed 65 experimental studies investigating 48 different therapeutic agents for the improvement of anastomotic healing under complicated conditions due to ischemia, ischemia/reperfusion, obstructive bowel, obstructive jaundice, peritonitis, chemotherapy or radiotherapy. Of the 31 agents reported to enhance anastomotic healing, one was subjected to a meta-analysis. Hyperbaric oxygen therapy significantly improved anastomotic healing in rat models complicated by bowel ischemia. Further exploration is needed to define agents that reduce AL in high-risk patients.

Nerström M, Krarup PM, Jorgensen LN, Ågren MS. Therapeutic improvement of colonic anastomotic healing under complicated conditions: A systematic review. *World J Gastrointest Surg* 2016; 8(5): 389-401 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i5/389.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i5.389>

INTRODUCTION

Colorectal surgery with construction of a primary anastomosis is performed for conditions such as cancer, diverticulitis, ulcerative colitis, ischemia or stoma reversal.

Despite improvements in preoperative management and surgical techniques, anastomotic leakage (AL) remains a major complication. The incidences of AL after colonic resection and rectal resection are 3%-7% and 10%-20%^[1-3], respectively. AL is associated with increased risk of morbidity, short-term mortality, permanent ostomy, tumor recurrence and a diminished overall long-term survival^[2,4-8].

In animal models of anastomotic healing, anastomotic bursting pressure (BPR) and anastomotic break-

ing strength (BST) are the most common surrogate outcomes of anastomotic healing. BPR reflects the resistance to increased intraluminal pressure, whereas BST reflects the increased longitudinal load. The collagen concentration is important for anastomotic integrity and declines to a minimum 3 d after the construction of colonic anastomoses under normal healing conditions^[9,10].

Previous studies have identified several local and systemic factors with deleterious effects on anastomotic wound healing, including ischemia^[11,12], reperfusion^[13-15], bowel obstruction^[16], obstructive jaundice^[17], peritonitis^[11,16,18,19], chemotherapy^[20] and radiotherapy^[3,20]. Reperfusion after intestinal ischemia provokes local and systemic inflammatory responses^[13-15], and ischemia ultimately leads to tissue necrosis and bowel perforation^[21,22]. Acute bowel obstruction is associated with ischemia, inflammation and loss of collagen in the colonic wall^[9,23,24]. Obstructive jaundice compromises systemic immune functions^[17]. Impaired collagen synthesis is observed in peritonitis^[25] and with the use of chemotherapeutic agents^[26]. Preoperative radiotherapy, which is used to downsize rectal tumors, induces inflammation^[3,27]. Despite the well-known risk of compromised anastomotic healing under these conditions, surgical resection and construction of a primary anastomosis are pivotal in the treatment algorithm.

A recent meta-analysis identified seven compounds, including iloprost, tacrolimus, erythropoietin (EPO), growth hormone (GH), insulin-like growth factor-1 (IGF-1), hyperbaric oxygen therapy (HBOT) and synthetic inhibitors of matrix metalloproteinases (MMPs), all of which have the potential to improve anastomotic healing under non-complicated conditions^[28]. Several compounds have also been tested in different experimental models of complicating conditions^[29].

The aim of the present systematic review was to identify therapeutic agents that are potentially capable of abolishing or reducing the deleterious effects on anastomotic healing caused by ischemia, ischemia/reperfusion (I/R), obstructive bowel, obstructive jaundice, peritonitis, chemotherapy or radiotherapy.

MATERIALS AND METHODS

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines^[30].

Search strategy

The PubMed and EMBASE databases were searched for articles published between January 1975 and September 2014 using the following syntax: ((Surgical anastomo*) OR (intestinal anastomo*) OR (anastomo* AND leak*) OR (anastomo* AND dehiscence) OR (surgical wound dehiscence) OR (anastomo* AND failure) OR (anastomo* AND rupture)) AND ((colorectal surgery) OR (surgical anastomo*) OR (colo* AND surgery) OR (rect* AND surgery) OR (large intestine and surgery)

OR (colorectal resection)) AND ((burst* pressure) OR (breaking strength) OR (anastomo* AND strength) OR (wound rupture) OR (biomechanical strength) OR (mechanical strength) OR (wound healing) OR (autopsy) OR (anastomo* AND leak*)) AND (((peritonitis) OR (infection) OR (sepsis)) OR ((ischemia) OR (hypoperfusion)) OR ((ileus) OR (bowel obstruction) OR (large bowel obstruction) OR (intestinal obstruction)) OR ((radiation) OR (radiotherapy) OR (radiochemotherapy) OR (chemotherapy))).

Cross-references from the included studies were manually reviewed.

Data extraction and outcomes

Titles of the articles identified in the search were reviewed, and potentially relevant abstracts or full-text articles, if necessary, were assessed for eligibility. Two or more authors decided whether a study qualified for inclusion, and disagreements were solved by discussion among the four authors.

The abstracted data included the complicated animal model used, the investigated compound, the time of administration, the species, the gender, the sample size, the dosage, the route, the day of anastomotic testing, the primary outcome and the effects on BPR, BST or AL of the compound investigated.

Missing data were gathered by contacting the authors.

Inclusion and exclusion criteria

English publications with the primary aim of investigating the potential beneficial properties of a pharmacological agent to improve anastomotic healing during complicated conditions were included. Studies on animals or humans with colo-colonic or colorectal anastomoses without a protecting ostomy reporting BPR, BST and AL relative to a proper control group were included.

Studies with the aim of clarifying adverse effects or risks of a therapeutic agent on anastomotic healing in complicated conditions were excluded. Likewise, studies on the effects of electrical stimulation, mechanical enforcement, such as biofragmentable anastomotic rings, endoluminal prosthesis/tube or amniotic membranes, together with sealants, such as fibrin glue, cyanoacrylates or collagen matrix bound coagulation factor sealants, and nutrients were also excluded.

Statistical analysis

Compounds investigated in one complicated animal model by at least three independent research groups using the same primary outcome were subjected to a meta-analysis. For these analyses, Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used. Pooled estimates were calculated using the inverse-variance weighting method with the DerSimonian-Laird random-effects model. Heterogeneity among the studies was determined using I^2 tests. The level of statistical significance was 0.05.

RESULTS

A total of 65 studies were included in the study (Figure 1). These studies were divided into 7 different animal models (Figure 2): Bowel ischemia models ($n = 21$) in rats ($n = 20$) and dogs ($n = 1$), I/R injury models ($n = 8$) in rats, models of colonic obstruction ($n = 5$) in rats ($n = 4$) and guinea pigs ($n = 1$), an obstructive jaundice model in the rat ($n = 1$), models of peritonitis ($n = 16$) in rats ($n = 15$) and mice ($n = 1$), chemotherapeutic models ($n = 8$) in rats and irradiation models ($n = 6$) in rats ($n = 5$) and pigs ($n = 1$). The reported outcomes were BPR ($n = 62$), BST ($n = 4$) and AL ($n = 5$). More than one outcome was applied in 6 studies. No human studies were retrieved by our search criteria.

Forty-eight different compounds were identified; 12 (25%) compounds were tested more than once in the same model, and 13 (27%) were tested in more than one complicated model. Enhancement of anastomotic healing was reported for 31 (65%) of the compounds; a non-significant effect was reported for 7 (15%) of the compounds, inconsistent results were reported for 9 (18%) different compounds and 1 (2%) compound was found to be detrimental to anastomotic healing.

Bowel ischemia

Twenty-two different compounds were tested in models of intestinal ischemia (Table 1). Experimentally, ischemia in the anastomotic segment was induced by ligation^[21,31-33] or coagulation^[34] of vessels in the mesocolon. The anastomosis was then constructed in the ischemic segment during the same surgical procedure.

Four studies tested the effect of postoperative HBOT in rats^[31,33,35,36]. The meta-analysis demonstrated that HBOT significantly increased anastomotic BPR by a mean 28 mmHg (95%CI: 17 to 39 mmHg, $P < 0.00001$) compared with controls (Figure 3A). The inconsistency between studies was moderately large ($I^2 = 40\%$). HBOT increases tissue oxygenation^[31,33,35,36], which may explain the elevated hydroxyproline concentration in the anastomosis^[33,35]. HBOT was ineffective when only administered preoperatively^[33]. The possible adverse effects of HBOT are oxygen toxicity, air embolization and pneumothorax^[31,33,35].

Guzel *et al.*^[35] found that rats receiving a post-operative intraperitoneal injection of β -1,3-glucan together with HBOT increased BPR by 67% compared with 50% for HBOT alone. β -1,3-glucan alone also significantly improved BPR^[35]. Supplementing post-operative HBOT with low molecular weight heparin (enoxaparin) had no further effect on BPR despite increasing neovascularization in the anastomotic area^[36]. Enoxaparin did not significantly improve BPR^[36].

Growth factors and hormones are pivotal in wound healing^[37]. Vascular endothelial growth factor (VEGF)-A and fibroblast growth factor (FGF)-2 plasmids were injected directly into the anastomotic tissue intraoperatively. The gene therapy increased VEGF and FGF-2

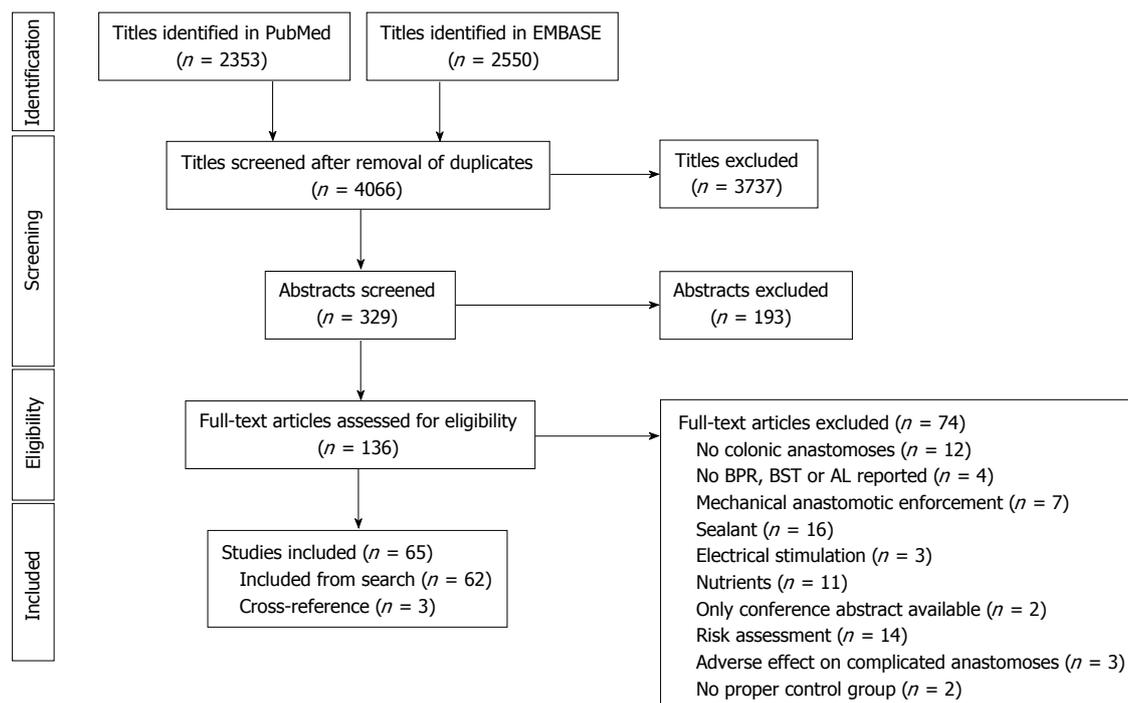


Figure 1 Flow diagram of the identified and selected studies. BPR: Bursting pressure; BST: Breaking strength; AL: Anastomotic leakage.

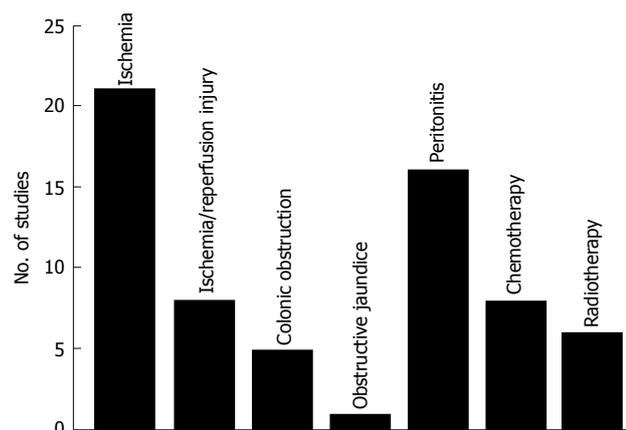


Figure 2 Number of studies included, divided into the 7 models of complicated anastomotic wound healing.

protein levels, BPR, angiogenesis, fibroblast activity and collagen deposition^[21]. VEGF-A and FGF-2 plasmids combined were more effective than the growth factor genes administered individually^[21]. The possibility of synergism between growth factors other than these two would be worthwhile to explore^[21]. Platelet-derived growth factor (PDGF)-BB in a gel applied once to the suture line immediately after construction of the anastomosis increased BPR on day 4^[38]. The mechanism remains elusive because PDGF-BB did not increase hydroxyproline as an indicator of collagen levels^[38]. The anabolic hormones, GH and nandrolone, enhanced early anastomotic healing, presumably by increasing IGF-1 and structural proteins^[32].

Although the main role of leptin is regulation of body weight and energy expenditure, *in vitro* studies have

indicated a direct mitogenic effect of leptin on colonic epithelial cells^[39]. Intraperitoneal leptin also increased the anastomotic strength of right-sided colon anastomoses in rats^[39].

Pentoxifylline enhanced anastomotic BPR on day 8^[34], but not on day 5^[40].

The vasoactive adrenomedullin increased BPR and hydroxyproline levels on postoperative days 3 and 7^[41]. Furthermore, adrenomedullin treatment decreased anastomotic tissue concentrations of tumor necrosis factor- α and interleukin-6^[41]. Increased vascularization and less oxidative damage of the anastomoses were observed with adrenomedullin^[41]. Adrenomedullin causes significant hypotension that may impair the colonic blood flow^[41]. Another caveat is that adrenomedullin may induce neoplasia^[41,42].

The beneficial effects of the endothelin receptor antagonist, bosentan, on anastomotic healing were possibly due to the increased blood flow and increased hydroxyproline level in the anastomotic area^[43]. Bosentan significantly reduced adhesion formation^[43].

Allopurinol reduced the induced superoxide anion production in ischemic anastomoses and increased the hydroxyproline levels^[22].

Allogeneic mesenchymal stem cells (MSCs) derived from bone marrow of rats were cryopreserved. The cells were thawed and injected (1×10^6 viable MSCs) into newly constructed anastomoses in ischemic rat colon. This cell therapy resulted in enhanced BPR on both day 4 and day 7^[44], whereas systemically applied MSCs resulted in a significant effect on day 4 only^[45].

Locally applied granulocyte macrophage-colony stimulating factor (GM-CSF) enhanced anastomotic BPR on days 3 and 7^[46].

Table 1 Studies on therapeutic compounds in ischemic models

Ref.	Compound	Time of administration	Species	Sex	Sample size ¹	Dosage	Route	Test	Test day	Effect ²
Yagci <i>et al</i> ^[33]	HBOT	Preoperative Postoperative Preoperative and postoperative	Rat	M	20 20 20			BPR	5	NS ↑ 23 ↑ 37
Hamzaoglu <i>et al</i> ^[31]	HBOT	Postoperative	Rat	M	16			BPR	4	↑ 32
Guzel <i>et al</i> ^[35]	HBOT	Postoperative	Rat	F	20			BPR	4	↑ 50
Kemik <i>et al</i> ^[36]	HBOT + β-1,3-glucan				20	20 ³	IP			↑ 67
	β-1,3-glucan				20	20 ³	IP			↑ 50
	HBOT	Postoperative	Rat	F	20			BPR	4	↑ 80
	HBOT + LMWH				20	1 ⁴	SC			↑ 67
Adas <i>et al</i> ^[21]	LMWH				20	1 ⁴	SC			NS
	VEGF-A plasmid	Intraoperative	Rat	M	40	0.001 ³	LO	BPR	4	↑ 16
	FGF-2 plasmid					0.001 ³				↑ 14
	VEGF-A + FGF-2 plasmids					0.001 ³ + 0.001 ³				↑ 38
Saribeyoglu <i>et al</i> ^[38]	PDGF-BB	Intraoperative	Rat	M	20	125 ³	LO	BPR	4	↑ 8
Yarimkaya <i>et al</i> ^[32]	GH	Preoperative and postoperative	Rat	M	28	1 ⁵	SC	BPR	3/7	↑ 87/↑ 32
Tasdelen <i>et al</i> ^[39]	Nandrolone	Preoperative			28	2 ⁴	IM			↑ 55/NS
	Leptin	Postoperative	Rat	N/A	20	0.001 ⁴	IP	BPR	7	↑ 27
Parra-Membrives <i>et al</i> ^[34]	Pentoxifylline	Postoperative	Rat	M, F	38	50 ⁴	IP	BPR/BST	8	↑ 74/↑ 81
Sümer <i>et al</i> ^[40]	Pentoxifylline	Postoperative	Rat	M, F	20	50 ⁴	IP	BPR	5	NS
	Vinpocetine				20	1 ⁴				NS
Karatepe <i>et al</i> ^[41]	Adrenomedullin	Postoperative	Rat	F	32	0.002 ³	SC	BPR	3/7	↑ 5/↑ 20
Cetinkaya <i>et al</i> ^[43]	Bostentan	Postoperative	Rat	F	20	3.5 ⁴	IP	BPR	6	↑ 46
Garcia <i>et al</i> ^[22]	Allopurinol	Preoperative and postoperative	Rat	M	20	50 ⁴	PO	BPR	4	↑ 74
Adas <i>et al</i> ^[44]	MSCs	Intraoperative	Rat	M	40	0.5 ⁶	LO	BPR	4/7	↑ 110/↑ 86
Adas <i>et al</i> ^[45]	MSCs	Postoperative	Rat	M	40	0.5 ⁶	<i>iv</i>	BPR	4/7	↑ 42/NS
Dinc <i>et al</i> ^[46]	GM-CSF	Intraoperative	Rat	M	72	0.050 ⁴	LO	BPR	3/7	↑ 30/↑ 26
Ikeda <i>et al</i> ^[47]	Prostacyclin analogue (OP-41483)	Intraoperative and postoperative	Dog	M, F	10 ⁷	0.00004 ⁴	<i>iv</i>	AL	3	NS
					18 ⁸					↓ 100
					12 ⁹					NS
Cohen <i>et al</i> ^[48]	Neomycin + erythromycin Clindamycin + gentamicin	Preoperative	Rat	N/A	12	20 ³	PO	AL	7	↓ 83
					12	15 ⁴ + 2 ⁴			<i>iv</i>	NS
Karataş <i>et al</i> ^[49]	Amelogenin	Intraoperative	Rat	M	16	N/A	LO	BPR	4	↑ 25
Irkocucu <i>et al</i> ^[50]	Sildenafil	Postoperative	Rat	M	27	10 ⁴ /20 ⁴	PO	BPR	4	NS/NS
Coneely <i>et al</i> ^[51]	Compound 48/80	Preoperative	Rat	M	20	1 ⁴	<i>iv</i>	BPR	4	NS

¹Total number of animals; ²↑% increase ($P < 0.05$) or ↓% decrease ($P < 0.05$) vs controls; ³mg; ⁴mg/kg; ⁵IU/kg; ⁶mL; ⁷Slight ischemia; ⁸Moderate ischemia; ⁹Severe ischemia. AL: Anastomotic leakage; BPR: Bursting pressure; BST: Breaking strength; F: Female; FGF-2: Fibroblast growth factor-2; GH: Growth hormone; GM-CSF: Granulocyte macrophage-colony stimulating factor; HBOT: Hyperbaric oxygen therapy; IP: Intraperitoneal; *iv*: Intravenous; LMWH: Low molecular weight heparin; LO: Local; M: Male; MSCs: Bone marrow derived mesenchymal stem cells; N/A: Data not available; NS: Not statistically significant; PDGF-BB: Platelet-derived growth factor-BB; PO: Per os; SC: Subcutaneous; VEGF-A: Vascular endothelial growth factor-A.

A study on the effect of a prostacyclin analogue (OP-41483) on AL was undertaken in dogs with colonic ischemia of variable severity^[47]. Colonic ischemia was induced by devascularization of marginal vessels resulting in slight (40%-60% decrease in colonic blood flow), moderate (60%-80%) or severe (80%-100%) ischemia measured by a hydrogen gas clearance method^[47]. There was no significant difference in AL in the animals with slight ischemia. In the groups with moderate ischemia, OP-41483 prevented the occurrence of AL, possibly by increasing the blood flow in the anastomotic area. All animals with severe bowel ischemia died due to major anastomotic dehiscence^[47].

The enteral combination of neomycin and erythromycin decreased AL significantly in rats, whereas a parenteral combination of clindamycin and gentamicin was ineffective^[48].

The extracellular matrix protein, amelogenin, en-

hanced anastomotic BPR. The mechanism of action remains elusive because amelogenin had no effect on hydroxyproline levels^[49].

Vinpocetine^[40], sildenafil^[50] and the mast cell degranulating agent compound 48/80^[51] had no statistically significant impact on BPR in ischemic colon.

I/R injury

All eight agents tested in rat I/R injury models were evaluated in single studies (Table 2). Before^[52] or, more commonly, after construction of an anastomosis, I/R injury is induced by occluding mesenteric vessels of a 2-3 cm segment of the left colon^[53] or by occluding the superior mesenteric artery^[54-57] with microvascular clamps for 30-60 min before reperfusion.

Notably, antithrombin III (ATIII)^[56] and ethyl pyruvate^[57] treatment increased anastomotic BPR in the I/R injured rats by more than 60%, possibly because of an

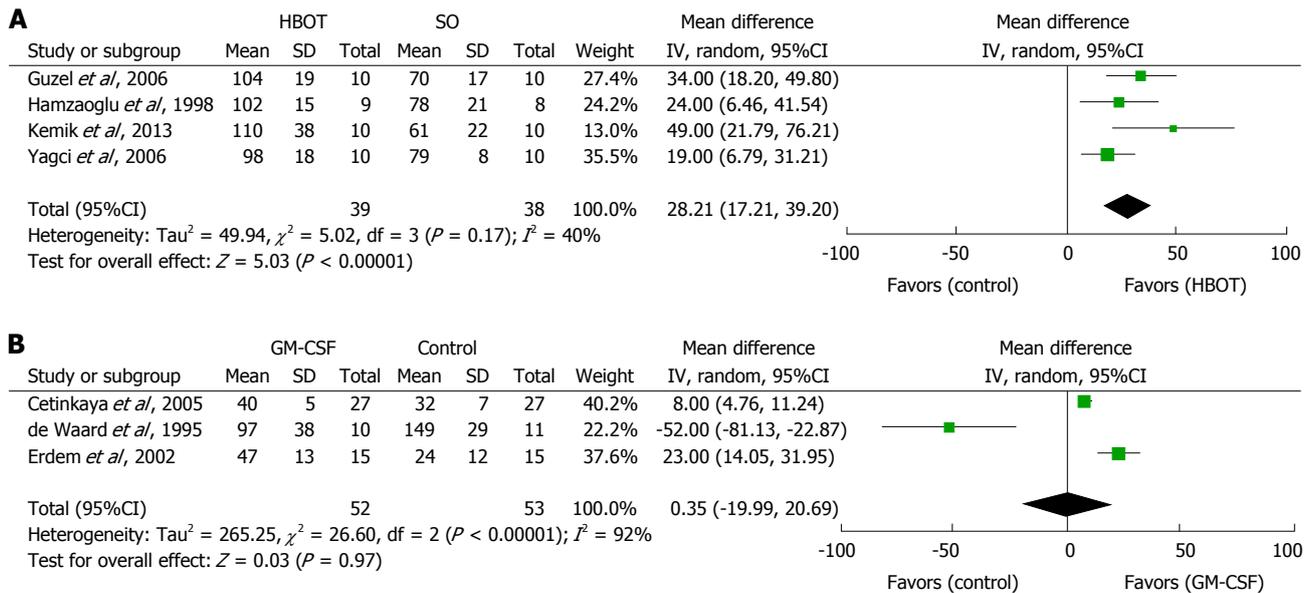


Figure 3 Forest plots of the bursting pressure in mmHg. The results of the meta-analysis for A: Hyperbaric oxygen therapy (HBOT) at days 4-5 in ischemic models (confer, Table 1); B: Granulocyte macrophage-colony stimulating factor (GM-CSF) at days 3 and 7 in chemotherapeutic models (confer, Table 5).

Table 2 Studies on therapeutic compounds in ischemia/reperfusion injury models

Ref.	Compound	Time of administration	Species	Sex	Sample size ¹	Dosage	Route	Test	Test day	Effect ²
Tekin <i>et al.</i> ^[56]	ATIII	Preoperative and postoperative	Rat	M	16	250 ³	<i>iv</i>	BPR	6	↑ 74
Unal <i>et al.</i> ^[57]	Ethyl pyruvate	Preoperative	Rat	M	24	50 ⁴	IP	BPR	5	↑ 63
		Preoperative and postoperative								↑ 69
Kabali <i>et al.</i> ^[53]	NAC	Preoperative	Rat	F	30	300 ⁴	PO/IP	BPR	7	↑ 25/↑ 37
Aydin <i>et al.</i> ^[55]	Tempol	Preoperative and postoperative	Rat	M	20	30 ⁴	<i>iv</i>	BPR	5	↑ 6
Teke <i>et al.</i> ^[58]	Activated protein C	Preoperative and postoperative	Rat	M	24	0.1 ⁴	<i>iv</i>	BPR	7	↑ 7
Teke <i>et al.</i> ^[59]	Caffeic acid phenethyl ester	Preoperative and postoperative	Rat	M	24	0.0028 ⁴	<i>iv</i> + IP	BPR	7	↑ 7
Teke <i>et al.</i> ^[54]	Pyrrolidine dithiocarbamate	Preoperative and postoperative	Rat	M	20	100 ⁴	<i>iv</i>	BPR	6	↑ 6
Celik <i>et al.</i> ^[52]	Montelukast	Preoperative and postoperative	Rat	M	24	10 ⁴	IP	BPR	5	↑ 36

¹Total number of animals; ²↑% increase ($P < 0.05$) vs controls; ³IU/kg; ⁴mg/kg; ATIII: Antithrombin III; BPR: Bursting pressure; F: Female; IP: Intraperitoneal; *iv*: Intravenous; M: Male; NAC: N-acetyl cysteine; PO: Per os.

increase in hydroxyproline concentrations.

The antioxidant N-acetyl-cysteine (NAC) significantly increased the hydroxyproline level; histological evaluation also revealed increased collagen deposition compared with the I/R injured control group, independent of the administration route^[53].

Other compounds that prevented I/R-induced reductions in anastomotic patency included tempol^[55], the immunomodulating compounds activated protein C^[58], caffeic acid phenethyl ester^[59] and pyrrolidine dithiocarbamate^[54].

One study reported significantly increased anastomotic BPR and hydroxyproline levels after treatment with montelukast administered intraperitoneally^[52].

Colonic obstruction

Four different agents were investigated in models of colonic obstruction (Table 3). In these models, typically the left-sided colon was obstructed by suture ligation for 24 h. Re-laparotomy was then performed, the obstructed segment was excised, and an end-to-end

anastomosis was constructed^[23,60-63].

In rats with an obstructed colon, intraoperative lavage with povidone iodine (PI) increased anastomotic BPR significantly on day 6 compared with untreated controls in two independent studies^[23,60]. Because the BPR was similar to lavage with saline alone, the additional value of PI remains questionable^[23,60]. NG-nitro-L-arginine methyl ester, an inhibitor of nitric oxide synthase, was found to be detrimental to anastomotic healing in rats with an obstructed colon^[23]. Intra-abdominal irrigation is time consuming, costly, cumbersome and possibly increases the risk of spillage^[64,65]. These circumstances should be taken into account when investigating new lavage agents.

EPO administered after construction of the anastomosis of the obstructed colon significantly increased BPR on day 7 in rats and guinea pigs^[61,63]. EPO possibly enhanced anastomotic healing through increased neovascularization and fibroblast proliferation leading to more collagen in the anastomotic wound^[61,63]. Therefore, further exploration of EPO to improve anastomotic

Table 3 Studies on therapeutic compounds in obstructive colon and obstructive jaundice models

Ref.	Compound	Time of administration	Species	Sex	Sample size ¹	Dosage	Route	Test	Test day	Effect ²
Erbil <i>et al</i> ^[23]	PI	Preoperative	Rat	M	144	10 ³	Lavage	BPR	3/6	↑ 44/↑ 42
Aguilar-Nascimento <i>et al</i> ^[60]	L-NAME	Preoperative	Rat	M	40	10 ³	Lavage	BPR	3/6	↓ 26/↓ 28
	PI							BST		NS/↑ 28
Faruquzzaman <i>et al</i> ^[63]	EPO	Postoperative	Guinea pig	M	20	500 ⁴	SC	BPR	7	↑ 15
Moran <i>et al</i> ^[61]	EPO	Postoperative	Rat	M	20	500 ⁴	SC	BPR	7	↑ 12
Galanopoulos <i>et al</i> ^[62]	Iloprost	Postoperative	Rat	M	40	0.002 ⁵	IP	BPR	4/8	↑ 115/↑ 74
								AL		NS/NS
⁶ Gulcelik <i>et al</i> ^[17]	GM-CSF	Intraoperative	Rat	M	44	0.050 ⁵	LO	BPR	3	↑ 24

¹Total number of animals; ²↑% increase ($P < 0.05$) or ↓% decrease ($P < 0.05$) vs controls; ³%-solution; ⁴IU/kg; ⁵mg/kg; ⁶Model of obstructive jaundice. AL: Anastomotic leakage; BPR: Bursting pressure; BST: Breaking strength; EPO: Erythropoietin; GM-CSF: Granulocyte macrophage-colony stimulating factor; IP: Intraperitoneal; L-NAME: NG-nitro-L-arginine methyl ester; LO: Local; M: Male; NS: Not statistically significant; PI: Povidone iodine; SC: Subcutaneous.

wound healing under these conditions seems justified.

Iloprost increased BPR on days 4 and 8 in rats, possibly by stimulating angiogenesis and fibroblast activity^[62]. Moreover, iloprost reduced the levels of immunodetectable MMP-13 in the anastomotic tissue, which may explain the increased collagen deposition with iloprost. Significantly more intra-abdominal adhesions formed, which were assessed according to the scale of van der Ham *et al*^[66], in the rats with obstruction compared with the animals without obstruction^[62]. The prostacycline analog iloprost did not reduce adhesion formation in the obstructed animals^[63]. Although iloprost seemed to reduce AL (10% vs 30% for saline controls), this difference did not reach statistical significance^[63].

Obstructive jaundice

Obstructive jaundice was modeled by ligation of the common bile duct. The anastomosis was constructed 7 d later^[17]. GM-CSF, the only agent investigated in this clinical condition, increased BPR and the hydroxyproline level^[17] (Table 3). Increased mononuclear infiltration of the anastomoses was suggested to be the mechanism for the improved anastomotic wound healing with GM-CSF^[17].

Peritonitis

Sixteen different compounds were identified, none of which qualified for the meta-analysis (Table 4). Experimental peritonitis is commonly established by puncture of the colon^[67], ligated cecum^[68-71], or intraperitoneal administration of fecal suspension^[72], *Escherichia coli* suspension^[73] or the Gram-negative wall component lipopolysaccharide (endotoxin)^[74]. Anastomoses were then performed 5-14 h later. In one study, the cecum was ligated and punctured after the anastomosis was performed^[75].

In one study, the vasomodulating agent sildenafil was administered intraperitoneally after the anastomoses were constructed in female rats with peritonitis. Sildenafil decreased intra-abdominal adhesions and increased BPR by 43% on day 7 compared with the controls that received saline alone^[67]. Furthermore, sildenafil stimulated new vessel formation in the anastomoses^[67].

In another rodent peritonitis model, intravenous administration of the thrombin inhibitor ATIII increased anastomotic BPR by 34% on day 2 and by 38% on day 7 compared with the peritonitis control^[74]. Diller *et al*^[74] attributed the improved anastomotic healing with ATIII to increased numbers of perfused capillaries and reduced clot formation, although these improvements failed to reach the levels of the non-infected controls.

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) prevented the reduction in BPR in animals with peritonitis^[72]. Histopathological examinations revealed increased vascularization and collagen formation of the anastomotic wounds treated with UFH and LMWH^[72]. Notably, UFH and LMWH facilitate intraperitoneal bacterial clearance by preventing formation of fibrin that may act as a reservoir for bacteria^[72].

Ethyl pyruvate increased BPR by 51%, possibly due to its anti-inflammatory effects^[76].

Reactive oxygen species (ROS) are thought to delay wound healing under septic conditions. Tempol is a stable piperidine nitroxide that may dampen the negative impact of ROS through its intracellular scavenging capacity. Tempol also restored glutathione levels and decreased the polymorphonuclear neutrophil counts in the anastomoses^[68]. These effects contributed to the elevated hydroxyproline and BPR levels with tempol^[68].

The anti-inflammatory immunomodulating granulocyte-CSF (G-CSF)^[75], activated protein C^[69], caffeic acid phenethyl ester^[70] and pyrrolidine dithiocarbamate^[71] are attractive for prevention of the deleterious effects of peritonitis and also increase anastomotic BPR. Although G-CSF increased hydroxyproline levels, they were still lower than in the normal control group without peritonitis^[75]. Activated protein C has been shown to reduce 28-d all-cause mortality in sepsis patients and is now approved for the treatment of patients with severe sepsis^[69,77]. The usefulness of activated protein C in colonic anastomotic wound healing in the presence of peritonitis will require more study because of the increased risk of bleeding^[77].

Abdominal lavage with the taurine derivative tauro-

Table 4 Studies on therapeutic compounds in models of peritonitis

Ref.	Compound	Time of administration	Species	Sex	Sample size ¹	Dosage	Route	Test	Test day	Effect ²
Ayten <i>et al</i> ^[67]	Sildenafil	Postoperative	Rat	F	14	8 ³	IP	BPR	7	↑ 43
Diller <i>et al</i> ^[74]	ATIII	Intraoperative	Mouse	M	60	250 ⁴	<i>iv</i>	BPR	2	↑ 34
									4	NS
									7	↑ 38
Gunerhan <i>et al</i> ^[72]	UFH	Postoperative	Rat	M	45	50 ³	SC	BPR	7	↑ 12
	LMWH					1.5 ³				↑ 19
Onur <i>et al</i> ^[76]	Ethyl pyruvate	Postoperative	Rat	N/A	20	50 ³	IP	BPR	7	↑ 51
Aytekin <i>et al</i> ^[68]	Tempol	Preoperative and postoperative	Rat	M	20	30 ³	<i>iv</i>	BPR	6	↑ 10
Ergin <i>et al</i> ^[75]	G-CSF	Preoperative and postoperative	Rat	M	20	0.050 ³	SC	BPR	4	↑ 26
	Levamisole				20	5 ³	PO			NS
Teke <i>et al</i> ^[69]	Activated protein C	Preoperative and postoperative	Rat	M	24	0.1 ³	<i>iv</i>	BPR	7	↑ 9
Teke <i>et al</i> ^[70]	Caffeic acid phenethyl ester	Preoperative and postoperative	Rat	M	24	0.0028 ³	IP	BPR	7	↑ 9
Teke <i>et al</i> ^[71]	Pyrrolidine dithiocarbamate	Preoperative and postoperative	Rat	M	20	100 ³	<i>iv</i>	BPR	6	↑ 7
Akkuş <i>et al</i> ^[73]	Taurolidine	Intraoperative	Rat	F	40	0.5 ⁵	Lavage	BPR	3/7	↑ 26/↑ 12
Bicalho <i>et al</i> ^[78]	Chlorhexidine	Intraoperative	Rat	M	16	0.05 ⁵	Lavage	BPR	7	NS
Wang <i>et al</i> ^[79]	Hydroxyethyl starch	Preoperative and postoperative	Rat	M	32	7.5 ⁶	<i>iv</i>	BPR	5	NS
						15 ⁶				↑ 9
						30 ⁶				↓ 5
Wang <i>et al</i> ^[80]	Hydroxyethyl starch	Preoperative and postoperative	Rat	M	20	15 ⁶	<i>iv</i>	BPR	5	↑ 9
Sucullu <i>et al</i> ^[81]	HBOT	Postoperative	Rat	M,F	32			BPR	3/7	↑ 186/↑ 74
Rocha <i>et al</i> ^[82]	HBOT	Postoperative	Rat	M	30			BST	5	NS
Vaneerdeweg <i>et al</i> ^[83]	Gentamicin	Intraoperative	Rat	M	30	2.6 ⁷ /12 ³	LO/IM	BPR	4	NS/NS

¹Total number of animals; ²↑% increase ($P < 0.05$) or ↓% decrease ($P < 0.05$) *vs* controls; ³mg/kg; ⁴IU/kg; ⁵%-solution; ⁶mL/kg; ⁷mg. ATIII: Antithrombin III; BPR: Bursting pressure; BST: Breaking strength; F: Female; G-CSF: Granulocyte-colony stimulating factor; HBOT: Hyperbaric oxygen therapy; IM: Intramuscular; IP: Intraperitoneal; *iv*: Intravenous; LMWH: Low molecular weight heparin; LO: Local; M: Male; N/A: Data not available; NS: Not statistically significant; PO: Per os; SC: Subcutaneous; UFH: Unfractionated heparin.

lidine increased BPR on days 3 and 7^[73]. Chlorhexidine lavage had no significant effect on BPR compared with 4-time lavage with 5 mL of sterile saline prior to construction of the anastomosis^[78].

Intravenous administration of hydroxyethyl starch (HES) at 15 mL/kg increased BPR on postoperative day 5 in two studies carried out by the same research group^[79,80], whereas 30 mL/kg was detrimental to anastomotic healing^[80]. These findings may be explained by the anti-inflammatory effects of HES at 15 mL/kg^[79,80], whereas at higher doses, HES reduces platelet aggregation to the injured endothelium^[80]. These facts make HES less practical for use in a clinical setting.

Postoperative HBOT in rats increased BPR by 186% on day 3 and by 74% on day 7^[81]. In another study, HBOT had no effect on BST on day 5^[82].

Local or systemic application of gentamicin^[83], as well as levamisole^[75], had no effect on BPR in male rats with peritonitis.

Chemotherapy

Five different compounds were tested in rats treated with different chemotherapeutic agents (Table 5). In these studies, 5-fluorouracil was given preoperatively^[84,85] or on postoperative days 3-8^[86-90]. Mitomycin-C was given as a single intraoperative dose^[91].

Three studies investigated the effect of GM-CSF^[86,87,91] and were subjected to meta-analysis. The combined estimate demonstrated that GM-CSF failed to increase anastomotic BPR (95%CI: -20 to 21 mmHg, $P = 0.97$) compared with controls (Figure 3B). The inconsistency between studies was large ($I^2 = 92\%$). The two studies demonstrating improved anastomotic healing also reported a significantly increased hydroxyproline concentration in the anastomoses, as well as distinct histological changes, including increased mononuclear infiltration compared with chemotherapy alone (fluorouracil or mitomycin-C)^[86,91]. de Waard *et al*^[87] found that GM-CSF increased BPR, but not BST, in fluorouracil-treated rats. They also applied a considerably lower dose of GM-CSF (5 µg)^[87] than the other two research groups (50 µg)^[86,91]. In addition, GM-CSF was administered intraperitoneally and not locally. Taken together, these data indicate that the GM-CSF dose used by de Waard *et al*^[87] was too low. In contrast, a single local application of GM-CSF in expanded polytetrafluoroethylene tubes implanted subcutaneously in humans inhibited collagen deposition dose-dependently and resulted in systemic effects on wound healing at doses of 4 µg or more^[92].

Iloprost enhanced BPR anastomotic healing on postoperative day 3^[88] and day 5^[89] compared with both the chemotherapeutic group and the non-chemotherapeutic

Table 5 Studies on therapeutic compounds in chemotherapeutic model

Ref.	Compound	Time of administration	Species	Sex	Sample size ¹	Dosage	Route	Test	Test day	Effect ²
Cetinkaya <i>et al</i> ^[91]	GM-CSF	Postoperative	Rat	N/A	54	0.050 ³	LO	BPR	3	↑ 26
Erdem <i>et al</i> ^[86]	GM-CSF	Postoperative	Rat	N/A	30	0.050 ³	LO	BPR	3	↑ 98
de Waard <i>et al</i> ^[87]	GM-CSF	Postoperative	Rat	M	31	0.005 ³	IP	BPR/BST	7	↓ 35/NS
	Interleukin-2					⁴ 2 × 10 ⁶	SC			NS/NS
Bostanoğlu <i>et al</i> ^[88]	Iloprost	Postoperative	Rat	M	38	0.002 ³	N/A	BPR	3/7	↑ 63/NS
Vasiliadis <i>et al</i> ^[90]	Iloprost	Postoperative	Rat	F	34	0.002 ³	IP	BPR	5/8	↑ 44/NS
								AL		↓ 30/↓ 30
Zacharakis <i>et al</i> ^[89]	IGF-1	Postoperative	Rat	M	32	2 ³	IP	BPR/AL	7	↑ 53/NS
Erenoglu <i>et al</i> ^[84]	HBOT	Postoperative	Rat	M	20			BPR	7	↑ 26
⁵ Yildiz <i>et al</i> ^[85]	HBOT	Postoperative	Rat	F	24			BPR	5	NS

¹Total number of animals; ²↑% increase ($P < 0.05$) or ↓% decrease ($P < 0.05$) vs controls; ³mg/kg; ⁴IU/kg; ⁵Chemoradiotherapy model. AL: Anastomotic leakage; BPR: Bursting pressure; BST: Breaking strength; F: Female; GM-CSF: Granulocyte macrophage-colony stimulating factor; HBOT: Hyperbaric oxygen therapy; IGF-1: Insulin-like growth factor-1; IP: Intraperitoneal; LO: Local; M: Male; N/A: Data not available; NS: Not statistically significant; SC: Subcutaneous.

Table 6 Studies on therapeutic compounds in models of radiotherapy

Ref.	Compound	Time of administration	Species	Sex	Sample size ¹	Dosage	Route	Test	Test day	Effect ²
Demir <i>et al</i> ^[96]	NAC	Preoperative and postoperative	Rat	M	24	300 ⁵	PO/IP	BPR	4	↑ 126/↑ 182
Ozdemir <i>et al</i> ^[94]	Amifostine	Preoperative	Rat	F	20	200 ⁵	IP	BPR	5	↑ 16
Carroll <i>et al</i> ^[93]	Ribose-cysteine ³	Preoperative	Rat	M	72	2000 ⁵	IP	BPR	7	↑ 50
	Ribose-cysteine ⁴	Preoperative				5000 ⁵	IP			N/A
	Ribose-cysteine ³ + glutamine ³	Preoperative and postoperative				2000 ⁵ + 3 ⁶	IP + PO			NS
	Amifostine ³	Preoperative				250 ⁵	IP			↑ 46
	Amifostine ⁴	Preoperative				250 ⁵	IP			NS
	MgCl ₂ ³ + ATP ³	Preoperative				10 ⁷ + 50 ⁷	<i>iv</i>			↑ 67
Rowe <i>et al</i> ^[97]	Ribose-cysteine	Preoperative	Pig	M	12	1000 ⁵	<i>iv</i>	BPR	9/11	NS
Değer <i>et al</i> ^[27]	Pycnogenol	Preoperative	Rat	M	40	200 ⁵	PO	BPR	3/7	↑ 19/↑ 38
Ozel Turku <i>et al</i> ^[95]	EPO	Preoperative and postoperative	Rat	M	16	500 ⁸	IM	BPR	N/A	NS

¹Total number of animals; ²↑% increase ($P < 0.05$) vs controls; ³40 GY; ⁴70 GY; ⁵mg/kg; ⁶%-solution; ⁷g/kg; ⁸IU/kg. ATP: Adenosine triphosphate; BPR: Bursting pressure; EPO: Erythropoietin; F: Female; IM: Intramuscular; IP: Intraperitoneal; *iv*: Intravenous; M: Male; NAC: N-acetyl cysteine; N/A: Data not available; NS: Not statistically significant; PO: Per os.

group, but not at later time points^[88,89]. Interestingly, iloprost significantly decreased the rate of AL from 30% to 0% in rats receiving chemotherapy^[90]. The positive effects on anastomotic strength in models of chemotherapy were possibly due to increased angiogenesis^[90] and collagen deposition with iloprost^[88,90]. Furthermore, iloprost significantly reduced the severity of intra-abdominal adhesions compared with the chemotherapeutic control group^[90].

A single study on IGF-1 treatment reported normalization of anastomotic BPR and hydroxyproline levels on day 7 in fluorouracil-treated rats^[89]. IGF-1 had no significant effects on AL^[89].

Postoperative HBOT increased BPR on day 7 in one study^[84] but had no significant effect on day 5 in another study, in which the rats received combined chemo- and radiotherapy before surgery^[85].

Interleukin-2 administered postoperatively had no effect on either BPR or BST^[87].

Radiotherapy

None of the eight agents identified and investigated in

radiotherapy models qualified for meta-analysis (Table 6). Animals were irradiated with half-body radiation^[27,93] or abdomino-pelvic radiation^[94-96] in a single dose and as rectosigmoid radiation^[97] 5 d a week for 40-45 d.

NAC is theoretically attractive in preventing oxidative damage after radiotherapy. NAC administered before and after construction of the anastomosis also increased BPR^[96]. In one study, NAC treatment increased the levels of superoxide dismutase and glutathione, but decreased malondialdehyde^[96]. Superoxide dismutase and glutathione are known to neutralize toxic substances in the cell, whereas malondialdehyde is a marker for oxidative stress^[96].

Other compounds found beneficial for the prevention of the deleterious effects of preoperative radiation include amifostine^[93,94] and magnesium chloride in combination with adenosine triphosphate^[93].

Ribose-cysteine^[93] administered before surgery improved anastomotic healing day 7 in rats receiving abdominal radiation with 40 GY, but not in irradiated pig colon days 9-11^[97]. No beneficial effects were reported by Carroll *et al*^[93], who investigated the effects of ribose-

cysteine combined with glutamine.

Pycnogenol administered preoperatively increased BPR on postoperative days 3 and 7 in male rats^[27].

EPO had no significant effect on anastomotic strength^[95].

DISCUSSION

We have previously reviewed therapeutics intended to enhance normal anastomotic repair in the colorectal region^[28]. In this paper we systematically retrieved publications on therapeutic agents intended to promote anastomotic wound healing under the influence of complicating factors, including ischemia, I/R injury, colonic obstruction, obstructive jaundice, peritonitis, chemotherapy and radiotherapy. The majority of the 48 different therapeutic compounds identified were only assessed in one study and/or in one complicated model. Meta-analysis was performed for HBOT and GM-CSF. Postoperative HBOT significantly improved wound healing in a rat model complicated by ischemia in the anastomosis. GM-CSF failed to show a beneficial effect on anastomotic healing in conjunction with chemotherapy. On the other hand, positive effects of GM-CSF were found in models of segmental ischemia^[46] and obstructive jaundice^[17]; these findings make this agent interesting for further investigation. Iloprost was found to be beneficial for early healing of anastomotic wounds in rats with colonic obstruction^[62] and in rats exposed to chemotherapy^[88,90], calling for further studies with this agent. The positive actions of NAC after I/R injury^[53] and radiotherapy^[96] justify further investigations on this antioxidant, as well.

Limitations

Because the 65 pre-clinical studies examined in our review used surrogate outcomes in models mimicking clinical phenomena, the results do not directly translate into clinical AL. Only 12 (25%) of the agents were investigated more than once in the same model. Furthermore, 13 (27%) therapeutic compounds were tested in two or more models of complicated anastomotic wound healing. We were unable to assess publication bias, for example, with Funnel plots, due to the small sample sizes of the included studies^[98].

Further exploration of the therapeutic agents identified in this review may be the next step to reach more robust conclusions regarding whether the agents could be effective in preventing AL in high-risk patients.

COMMENTS

Background

Despite improvements in preoperative management and surgical techniques, anastomotic leakage remains a major complication in gastrointestinal surgery. There are no therapeutic agents with documented prophylactic effect against this serious postoperative surgical complication. A recently published meta-analysis identified seven compounds with the potential to improve anastomotic healing under non-complicated conditions.

Research frontiers

This study is the first to systematically review therapeutic agents that are potentially capable of abolishing or reducing the deleterious effects of various known complicating factors on anastomotic healing.

Innovations and breakthroughs

The search identified 48 different therapeutic agents. A meta-analysis indicated that hyperbaric oxygen therapy improved colonic anastomotic repair in models of ischemia.

Applications

This systematic review identified therapeutic substances from pre-clinical studies on complicated anastomotic wound healing that would be worthwhile exploring further for the prevention of anastomotic leakage.

Terminology

Anastomotic leakage results in contamination of the abdominal cavity with intestinal contents, leading to peritonitis or sepsis, or in worst case mortality.

Peer-review

This systematic review assessed the efficacy of therapeutic agents against anastomotic leakage in animal models. The manuscript is excellent, very well written and educational despite being research-oriented. A widespread prospective multicenter trial would be ideal to follow up on the collected information.

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2016 Laparoscopic Surgery: Global view

Strategies of laparoscopic spleen-preserving splenic hilar lymph node dissection for advanced proximal gastric cancer

Qi-Yue Chen, Chang-Ming Huang, Chao-Hui Zheng, Ping Li, Jian-Wei Xie, Jia-Bin Wang, Jian-Xian Lin, Jun Lu, Long-Long Cao, Mi Lin, Ru-Hong Tu, Zhi-Liang Hong

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Abstract

For advanced proximal gastric cancer (GC), splenic hilar (No. 10) lymph nodes (LN) are crucial links in lymphatic drainage. According to the 14th edition of the Japanese GC treatment guidelines, a D2 lymphadenectomy is the standard surgery for advanced GC, and No. 10 LN should be dissected for advanced proximal GC. In recent years, the preservation of organ function and the use of minimally invasive technology are being accepted by an increasing number of clinicians. Laparoscopic spleen-preserving splenic hilar LN dissection has become more accepted and is gradually being used in operations. However, because of the complexity of splenic hilar anatomy, mastering the strategies for laparoscopic spleen-preserving splenic hilar LN dissection is critical for successfully completing the operation.

Key words: Gastric neoplasm; Laparoscopic; Splenic hilus; Lymphadenectomy; Strategy

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Core tip: According to the 14th edition of the Japanese gastric cancer (GC) treatment guidelines, a D2 lymphadenectomy is the standard surgery for advanced GC and No. 10 lymph nodes (LNs) should be dissected for advanced proximal GC. In recent years, the preservation of organ function and the use of minimally invasive technology are being accepted by an increasing number of clinicians. Laparoscopic spleen-preserving splenic hilar LN dissection has become more accepted. However, because of the complexity of splenic hilar anatomy, mastering the strategies for laparoscopic

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VALUE OF SPLEEN-PRESERVING SPLENIC HILAR (NO. 10) LYMPH NODE DISSECTION FOR ADVANCED PROXIMAL GASTRIC CANCER

Value of No. 10 LN dissection for advanced proximal gastric cancer

The most important purpose of radical operations for gastric cancer (GC) is to increase the long-term survival of patients. The thoroughness of lymph nodes (LNs) dissection during the surgery is directly related to a patient's postoperative survival rate. No. 10 LN dissection is an important but difficult part of a D2 radical resection for advanced proximal GC. The rate of No. 10 LN metastasis has been reported to be 9.8%-27.9%^[1-3]. Shin *et al*^[4] reported that of 319 patients, 41 (12.9%) had No. 10 LN metastasis. No. 10 LN metastasis was not observed in patients with early GC. Data from Japanese patients also revealed that the No. 10 LN metastasis rate in early proximal GC is so low (0.9%) that the No. 10 LN does not need to be dissected. However, in advanced GC, the No. 10 LN metastasis rate is 13.4% in stage T3 and 34.4% in stage T4^[5]. A 346-case analysis of laparoscopic spleen-preserving No. 10 LN dissection for proximal GC conducted by our center indicated that the incidence of No. 10 LN metastasis is 10.1% in advanced proximal GC^[6]. No. 10 LN metastasis is mainly associated with the tumor size, depth of invasion, Borrmann type and histological type. The rate of GC in the upper region is significantly higher than that in the lower third of the stomach^[7]. Koga *et al*^[8] reported that No. 10 LN metastasis frequently appears in Borrmann type IV cancer or when the primary tumor involves the serosa or the entire stomach. Okajima *et al*^[9] reported a higher No. 10 LN metastasis rate (26.7%) in GC involving the entire stomach. Moreover, the survival rate is significantly associated with No. 10 LN metastasis. Shin *et al*^[4] reported that the 5-year survival rate was significantly lower for a No. 10 LN metastasis group (11.04%) than for a non-metastasis group (51.57%) ($P < 0.05$). Chikara *et al*^[10] reported that the 5-year survival rate of patients with No. 10 LN metastasis was 23.8%, whereas the rate in patients without No. 10 LN

metastasis was 41.4% ($P < 0.05$). Thus, the No. 10 LN metastasis status is a significant prognostic factor for GC. No. 10 LN dissection is necessary in advanced upper GC because the radical excision of a tumor seems to be insufficient. Kosuga *et al*^[11] reported on 280 patients who underwent curative total gastrectomy with simultaneous splenectomy. No significant difference was found in the 5-year survival rates between patients with and without No. 10 LN metastasis (51.3% and 42.1%, respectively). Ikeguchi *et al*^[12] reported a study of patients who underwent curative total gastrectomy with simultaneous No. 10 LN dissection. This study also revealed that the 5-year survival curves of No. 10 LN-positive patients did not differ from those of No. 10 LN-negative patients. Therefore, the value of LN dissection in this area is significant. No. 10 LN dissection is becoming more accepted by an increasing number of clinicians.

Value of spleen-preserving No. 10 LN dissection for advanced proximal GC

Before the 1990s, a pancreateosplenectomy was performed to completely excise No. 10 LNs. The prophylactic dissection of No. 10 LNs using this surgical method increases the risk of distal pancreatectomy-associated complications^[13,14]. Currently, this surgical method is only performed when direct invasion of the spleen or of the body and tail of the pancreas is observed. Many subsequent studies have reported that pancreas-preserving splenectomy with No. 10 LN dissection has a similar survival rate and morbidity but significantly lower incidence of complications and mortality compared with pancreateosplenectomy. Therefore, pancreas-preserving splenectomy with No. 10 LN dissection has been recommended as a curative procedure for standard D2 dissection in place of pancreateosplenectomy^[9,15,16]. However, Yang *et al*^[17] reported a meta-analysis of 466 patients showing that gastrectomy with splenectomy was not associated with a significantly different 5-year overall survival rate relative to splenic preservation, with an RR of 1.17 (95%CI: 0.97-1.41, $P < 0.05$). Splenectomy did not prolong survival. The RR of splenectomy did not significantly influence postoperative morbidity and mortality based on a 5-year overall survival rate outcome compared to splenic preservation for proximal and whole GC (RR = 1.14, 1.76 and 1.58, respectively). In recent years, many subsequent studies have shown that the spleen is the largest peripheral immune organ in the human body. The spleen can participate in normal operation of the circulatory system for immune regulation and also has roles in the immune and endocrine systems; additionally, it contains numerous immune cells, which play important roles in anti-tumor immunity. Some researchers have applied immunotherapy postoperatively in cases of advanced GC and determined that natural killer (NK) cell activity and the IL-2 concentration were significantly higher in a spleen-preserving group than a splenectomy group. They concluded that spleen preservation in a radical

operation enables immunotherapy for patients with advanced GC^[18,19]. The Dutch scholar H.H. Hartgrink performed a multicenter randomized controlled trial that followed up 1078 patients for more than 10 years and found that morbidity and mortality were significantly increased if splenectomy was performed. In contrast, pancreas- and spleen-preserving LN dissection (D2) improved patient prognosis^[20]. Schwarz^[21] reported that with the development of surgical techniques, spleen-preserving No. 10 LN dissection is technically feasible. Therefore, spleen-preserving No. 10 LN dissection is becoming more accepted by an increasing number of clinicians.

VALUE AND PROCEDURE OF LAPAROSCOPIC SPLEEN-PRESERVING NO. 10 LN DISSECTION

Value of laparoscopic spleen-preserving No. 10 LN dissection

This operation tends to reduce surgical trauma, increase safety, and protect organ function. With further study of the disease, surgical instruments and technology have been continuously developed. Traditional open operations do not meet patients' needs. Laparoscopic D2 LN dissections are conducted by many surgeons who demonstrate a mature grasp of laparoscopic technology. The first report of laparoscopic spleen-preserving No. 10 LN dissection regarding the treatment of GC in the upper third of the stomach was published by Hyung *et al.*^[22] in 2008. In our study, the average number of LNs retrieved using laparoscopic surgery was 3.6 per patient, and no patients required an open conversion resulting from an injury to the spleen or its vessels. No complications such as hemorrhage, splenic ischemia or splenic necrosis associated with dissection of the splenic hilar region were observed postoperatively, indicating favorable short-term outcomes^[23]. Although to date the prognostic benefit of laparoscopic splenic hilar LN dissection for advanced GC is under debate, a randomized controlled trials on laparoscopic spleen-preserving No. 10 LN dissection for advanced middle or upper third GC (No. NCT02333721) is ongoing in our center. We think it could demonstrate that this procedure has potential benefit for those patients without increase in morbidity in experienced center.

Operative procedure of laparoscopic spleen-preserving No. 10 LN dissection

Regarding the different surgical approach, some experts use a medial approach. Dissection of the No. 11p, 11d, and 10 LNs is then performed with ultrasonic shears from the root of the splenic artery (SpA) toward its distal end. This procedure requires severing of the short gastric vessels (SGVs) prior to LN dissection, which is facilitated when the surgeon stands on the patient's right side. Other experts use a retropancreatic approach in which the surgeon starts

with division of the gastrosplenic ligament and severing of the left gastroepiploic and short gastric vessels. We utilize a left-sided approach in which the LNs are excised from the SLA toward the root of the SpA, and the SGVs are severed at their roots. This approach, which enables the complete removal of No. 10 LNs and the stomach, is consistent with the concept of oncological radical resection. Our center performed laparoscopic spleen-preserving No. 10 LN dissections in January 2010 during more than 500 laparoscopic GC surgeries. We have summarized an effective procedure called Huang's three-step^[24] maneuver for performing laparoscopic spleen-preserving No. 10 lymphadenectomies in clinical practice. We divided the originally complex operation steps into three steps as follows: The first step includes the dissection of LNs in the inferior pole region of the spleen, the second step includes dissection of the LN in the region of the SpA trunk, and the third step includes the dissection of LNs in the superior pole region of the spleen.

STRATEGIES OF LAPAROSCOPIC SPLEEN-PRESERVING NO. 10 LN DISSECTION

To safely and effectively perform laparoscopic spleen-preserving No. 10 LN dissection, the following points should be considered.

Importance of teamwork

At our center, we realized that stable and automatic teamwork plays an important role in laparoscopic spleen-preserving No. 10 LN dissection. Above, we not only introduced the concrete operative steps taken by each participant but also indicated the scope and methodology of each technique to simplify the complicated No. 10 LN dissection procedure and to improve the efficiency of the operation. By presenting this information, we hope to promote laparoscopic spleen-preserving No. 10 LN dissection, and we hope that this technique will become more popular.

Step over the learning curve

Similar to other laparoscopic surgeries, performing laparoscopic spleen-preserving No. 10 LN dissection requires an initial learning phase to allow the surgeon to develop adequate and stable skills. Thus, when a certain number of surgeries are performed, the surgeon's operative technique significantly improves, typically reaching a plateau over time. With respect to achieving proficiency in laparoscopic GC surgical techniques, a surgeon can be considered to have stable skills after he has performed 40 surgical training procedures^[25]. To shorten the learning curve, the surgeon should perform the procedure on patients in good condition who are younger and have fewer complications, smaller tumors, or leaner figures. These criteria facilitate a reduction in surgical risk while

increasing the surgeon's confidence, helping him to eventually achieve proficiency. An adequate ability to summarize one's experiences and lessons and to explore the operative position and anatomical approach that are most suitable for oneself will help the surgeon to gradually establish relatively stable surgical abilities.

Be familiar with the complex anatomy in this region

Because of the deep location of the splenic hilar, the narrow operative space, the fragile texture of the spleen, the tortuosity of splenic vessels and the complicated branching of the SLA, adequate exposure of the splenic hilar area is difficult. There is a high risk of injury to the splenic parenchyma or to adjacent organs such as the pancreas and adrenal gland in a No. 10 LN dissection. In addition, the splenic vessels exhibit a tortuous course, and their branches are complex. This configuration may lead to a high risk of vessel injury and result in uncontrollable hemorrhage during laparoscopic dissection in this region. Therefore, we hypothesize that 3-dimensional computed tomography (3DCT) reconstruction can be used preoperatively to detect the distribution of the splenic vessels. The research outcomes of our unit also revealed that the operative time and intraoperative blood loss were significantly decreased in the 3DCT group compared with the non-3DCT group^[26].

PROSPECT OF LAPAROSCOPIC SPLEEN-PRESERVING NO. 10 LN DISSECTION

Presently, although the long-term curative effect of laparoscopic spleen-preserving No. 10 LN dissection for advanced proximal GC is still not fully supported by evidence-based medical research, the development of minimally invasive technology, represented here by laparoscopic technology, is an inevitable trend in GC surgery. Therefore, a randomized controlled trial for spleen-preserving No. 10 LN dissection for advanced proximal GC should be conducted to further confirm the efficacy of laparoscopic spleen-preserving No. 10 LN dissection.

Moreover, not all centers can presently complete independent laparoscopic spleen-preserving No. 10 LN dissection. Surgeons at these centers must first master techniques for laparoscopic spleen-preserving No. 10 LN dissection despite the substantial learning curve. Mastery of these techniques is the key to successfully completing the operation. Providing professional training for GC surgeons, establishing an active, hands-on training program and employing experienced and senior surgeons who can convey their knowledge and experience to young doctors are critical. Improving the level of integration of laparoscopic spleen-preserving No. 10 LN dissection is also challenging. Therefore, laparoscopic spleen-preserving No. 10 LN dissection will likely become one of the standard treatments for advanced proximal GC following improvement of the

standardized operation training system and laparoscopic technology and the promotion of Huang's three-step technique.

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Parenchymal-sparing liver surgery in patients with colorectal carcinoma liver metastases

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Abstract

Liver resection is the treatment of choice for patients with colorectal liver metastases (CLM). However, major resections are often required to achieve R0 resection,

which are associated with substantial rates of morbidity and mortality. Maximizing the amount of residual liver gained increasing significance in modern liver surgery due to the high incidence of chemotherapy-associated parenchymal injury. This fact, along with the progressive expansion of resectability criteria, has led to the development of a surgical philosophy known as "parenchymal-sparing liver surgery" (PSLS). This philosophy includes a variety of resection strategies, either performed alone or in combination with ablative therapies. A profound knowledge of liver anatomy and expert intraoperative ultrasound skills are required to perform PSLS appropriately and safely. There is a clear trend toward PSLS in hepatobiliary centers worldwide as current evidence indicates that tumor biology is the most important predictor of intrahepatic recurrence and survival, rather than the extent of a negative resection margin. Tumor removal avoiding the unnecessary sacrifice of functional parenchyma has been associated with less surgical stress, fewer postoperative complications, uncompromised cancer-related outcomes and higher feasibility of future resections. The increasing evidence supporting PSLS prompts its consideration as the gold-standard surgical approach for CLM.

Key words: Colorectal liver metastases; Parenchymal-sparing hepatectomy; Ultrasound; Liver failure; Resection margins; Complications; Ablative therapies

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Core tip: This review provides a profound insight into parenchymal-sparing liver surgery, including the oncological rationality for this approach, the different anatomical and technical aspects as well as its present role and future perspective in modern liver surgery.

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INTRODUCTION

Colorectal carcinoma is the third most frequent cancer in the world, with nearly 1.23 million new cases diagnosed each year^[1,2]. About half of these patients will develop liver metastases during the course of the disease, causing two thirds of deaths^[3]. In terms of treatment, liver resection is the treatment of choice to prolong survival and offer a chance of cure to patients with colorectal liver metastases (CLM)^[3,4]. However, resection is not always feasible due to tumor location, contact with major vascular elements, bilaterality, insufficient liver remnant or patient comorbidities. Although not long ago the majority of patients with CLM (70%-80%) were considered unsuitable for resection at diagnosis, nowadays a greater number of patients finally undergo surgery thanks to the significant improvements in imaging modalities, surgical techniques, anesthesia, chemotherapy regimens and the expansion of resectability criteria among surgeons^[4].

Over the years, hepatobiliary surgeons have been constantly pushing the frontiers of resectability in patients with malignant liver tumors. The paradigm of resectability in modern liver surgery has shifted from "what is resected" to "what remains after resection"^[5]. Surgeons performing oncological liver surgery must balance two conflicting objectives that might jeopardize each other whenever extensive disease is present: (1) to achieve a complete tumor resection with curative intent (negative margins); and (2) to preserve as much liver parenchyma as possible to avoid liver failure. However, major hepatectomies are often required to achieve an R0 resection and these are associated with substantial rates of morbidity and mortality^[6]. Posthepatectomy liver failure (PLF) is the main cause of death after major hepatectomy and it is strictly related to the volume and quality of the future liver remnant (FLR)^[7]. Several strategies have been developed to minimize the risk of PLF and expand resectability. These strategies could be grouped into those that tend to reduce the tumor size (*e.g.*, conversion chemotherapy, endovascular procedures) and those that tend to preserve or increase the amount of liver remnant (*e.g.*, local ablation techniques, preoperative portal vein embolization, two-stage procedures). These developments led to the successful removal of multiple, often bilateral, liver lesions otherwise considered unresectable. Yet, when using classical approaches of portal vein occlusion (either ligation or embolization) to increase the amount of FLR, up to 40% of patients never become eligible for tumor resection either because of insufficient hypertrophy or disease progression during the long interval periods

(6-12 wk) usually required to achieve hypertrophy^[8,9]. Moreover, patients who fail to complete the second stage have worse survival than those treated with chemotherapy alone^[10].

Although maximizing the amount of residual liver parenchyma has always been a matter of concern among surgeons, it has become a major issue to modern liver surgery due to the high incidence of parenchymal injury associated with downsizing chemotherapy (*i.e.*, steatohepatitis, sinusoidal obstruction syndrome), where the extent of resection critically determines postoperative risk. The need of preserving non-tumor parenchyma as well as the progressive expansion of resectability criteria for CLM, mainly related to the significant reduction of what was considered a sufficient tumor margin, has led to the development of a surgical concept known as "parenchymal-sparing liver surgery" (PSLS). This philosophy gathers various surgical strategies aiming to offer the minimum sufficient margins in order to preserve as much liver parenchyma as possible, where preoperative planning and intraoperative ultrasound (US) are key factors for success. PSLS, which intends to avoid major liver resections and eventually the need of using techniques to induce FLR hypertrophy, has recently been associated with equal or better perioperative and long-term outcomes than non-PSLS^[11-13].

This review aims to critically analyze the literature available to date regarding PSLS in the treatment of patients with CLM.

HISTORICAL PERSPECTIVE AND ONCOLOGICAL BASIS

Over the years, there has been an increasing trend towards PSLS for patients with stage IV colorectal cancer in most specialized centers around the world. This has been clearly reflected by the group from Memorial Sloan-Kettering Cancer Center (MSKCC), demonstrating that the techniques used to deal with bilateral CLM changed uniformly over a 20-year period in favor of wedge resections and ablations to spare uninvolved surrounding liver instead of major hepatectomies^[12]. From an oncological perspective, there are mainly two factors closely associated with this phenomenon: (1) The evolution of the concept of resectability; and (2) The increased knowledge on tumor biology.

Tumor resectability

The concept of tumor resectability in CLM has evolved greatly in the past three decades. In the 1970s, most surgeons considered resection only in patients with single liver metastasis. In 1984, Adson *et al.*^[14] reported similar 5-year survival rates between patients with solitary metastases and those with multiple lesions (25% and 18%, respectively). Two years later, Ekberg *et al.*^[15] identified a series of poor prognostic factors associated with surgical resection and proposed to

contraindicate surgery in patients with any of the following characteristics: More than four lesions, bilobar compromise, impossibility to achieve a margin of at least 1 cm and presence of extrahepatic disease. These were known as the "Ekberg criteria" and were welcomed by various authors up to the late 1980s. During the 1990s, this concept evolved again due to the increased use of chemotherapy and more aggressive surgical treatments with favorable outcomes were performed in patients presenting the characteristics traditionally considered contraindications^[16]. Probably the most important breakthrough with regards to tumor margins was accomplished by Pawlik *et al*^[17] in 2005, who demonstrated that the width of a negative surgical margin did not affect survival, recurrence risk, or site of recurrence. In this study, which included 557 patients undergoing liver resection for CLM, negative margins had similar overall recurrence rates (1-4 mm: 38.7%; 5-9 mm: 41.2%; ≥ 10 mm: 39.2%, $P = 0.32$) and 5-year overall survival (OS) rates (1-4 mm: 62.3%; 5-9 mm: 71.1%; ≥ 10 mm: 63.0%, $P = 0.63$). This was later supported by many authors, including a recent propensity score-matched analysis in 2715 patients demonstrating that the disease-free survival (DFS) was not significantly different between patients with more than 1 mm margin (1-4.9 mm vs 5-9.9 mm vs ≥ 10 mm), and showed that a 1 mm cancer-free margin was sufficient to achieve 33% 5-year DFS^[18]. Moreover, unfortunately around 70%-80% of patients with bilateral CLM recur within five years of surgery, most of them with disease at an extrahepatic site as a component of a recurrence pattern in which a wide resection margin would not really make any difference^[12,19,20].

Along with the finding that the width of surgical margin did not correlate with liver recurrence, several surgeons started favoring limited liver resections over major hepatectomies. This laid the foundations for the development of sophisticated techniques to spare liver parenchyma. However, there are special situations where achieving a negative margin might require sacrificing more parenchyma than expected by preoperative and intraoperative evaluation. Mentha *et al*^[21] found a dangerous halo of re-growing tumor occurring at the periphery of the metastasis when chemotherapy was interrupted before surgery in patients undergoing two-staged liver resections, regardless of previous response. Therefore, a resection margin wider than 1 mm might be especially advisable when chemotherapy is interrupted for a long time before surgery.

Although securing a margin larger than 1 mm should be considered the standard of care, recent evidence suggests that in the era of modern chemotherapy, even patients with microscopic positive margins (R1) may benefit from resection because survival is similar to that of R0 resection and better than chemotherapy alone^[22,23]. Moreover it has been

demonstrated that the negative impact of positive margins is mainly restricted to patients with suboptimal response to preoperative chemotherapy^[24]. Nowadays the paradigm of resectability considers that CLM should be resected regardless of size and number, provided resection is complete (negative margins), the remaining parenchyma is sufficient to prevent PLF and there is no unresectable extrahepatic disease^[25].

Tumor biology

There are two known mechanisms for intrahepatic spread of CLM: Metastasis from the primary site and remetastasis from other existing metastases. Most liver metastases arise from circulating tumor cells that have shed into the bloodstream from the primary tumor^[26,27]. Given that the distribution of such deposits is random, the presence of a high density of micrometastases in the immediate vicinity of the main tumor indicates that the majority of such micrometastases might have derived from the closest main tumor^[27,28]. Contrarily to hepatocellular carcinoma, tumor cells from CLM do not migrate into intrahepatic portal branches to form intrahepatic secondary metastases. Instead, intrahepatic lymphatic invasion is in fact the main responsible for "remetastasis" from liver metastases^[28,29]. The incidence and distribution of intrahepatic micrometastases (IHM), defined as any microscopic lesions separated from the gross tumor by a rim of non-neoplastic parenchyma, remains controversial in the literature. Kokudo *et al*^[27] demonstrated an incidence of histological IHM of 24%. However, the incidence of genetically confirmed IHM in the study was 2% and they were located within 4 mm of the tumor border. In contrast, Wakai *et al*^[28] found in a more recent study an incidence of IHM of 58%, 95% of them located in the close zone (< 1 cm). The differences found in these studies might have been related to different patient populations, IHM detection methods and variable use of chemotherapy, as recent evidence demonstrated that neoadjuvant chemotherapy in CLM reduces the incidence of IHM^[30]. Despite the differences found in terms of IHM incidence and location, both studies recognized a 2 mm margin as the acceptable minimum requirement based on survival analysis and margin recurrence^[27,28]. Moreover, a recent retrospective study evaluating intrahepatic mechanisms of invasion on patients undergoing resection of CLM demonstrated that lymphatic vascular invasion rather than blood vascular, biliary, or sinusoidal invasion is the key prognostic marker of aggressiveness and spread of CLM, and this feature was evident only within 2 mm from the tumor edge^[31].

Segmental resections including tumor-bearing portal branches and the corresponding liver parenchyma in CLM do not appear justified at least from a theoretical point of view. On the other hand, while previous authors have advocated anatomic hepatectomies on the basis of a reduced likelihood of margin involvement, a recent meta-analysis including 1662 patients contradicted

this data demonstrating that the incidence of a positive surgical margin was equal in both anatomic resection (AR) and non-anatomic resection (NAR) groups (OR = 0.64; 95%CI: 0.31-1.32; $P = 0.23$)^[13]. Moreover, most studies evaluating long-term oncological outcomes have demonstrated that there is no benefit of AR over NAR in terms of 5-year OS and DFS in patients with similar tumor characteristics^[13,32]. Other studies have looked specifically at differences between major AR vs restricted NAR in patients with limited resectable disease (one or two lesions). Kokudo *et al*^[33] demonstrated that prophylactic large resections were useless in preventing intra- or extra-hepatic recurrence in the majority of patients, since ipsilateral recurrence developed in only 19.6% of patients undergoing limited NAR and 90% of such recurrences could undergo second hepatectomy, compared to only 20% in the AR group. In this study, equivalent 5-year OS was reported between major AR vs limited NAR (45.7% vs 40.4%). More recently, the MD Anderson group^[11] found that patients with a solitary tumor of less than 30 mm in size who underwent partial wedge resection instead of right hepatectomy, left hepatectomy or left lateral sectionectomy (LLS) had similar liver-only recurrence rates (14% vs 17%, $P = 0.44$) and significantly improved survival due to higher salvageability (68% vs 24%, $P < 0.01$). Taken together, this evidence clearly demonstrates that a combination of a first limited NAR followed by repeated hepatectomy in case of recurrence offers equivalent or even more benefits than major hepatectomy in patients with few unilobar metastases and should probably be considered now on the standard of care approach^[11,33]. Moreover, although the prognostic significance of micrometastases is still controversial, it should be taken into account that the greater the amount of liver parenchyma resected, the more likely to accelerate the growth of occult intra or extrahepatic disease as a response to growth factors and cytokines produced to stimulate liver regeneration^[11,34-36]. This fact might be especially important in patients with aggressive disease behavior. Tanaka *et al*^[37] found that the prognosis of patients having 6 or more metastases was poorer after major resection than after multiple minor resections, perhaps due to a more accelerated growth of micrometastases after a massive hepatectomy. Current evidence indicates that the hypothetical benefit of prophylactically resecting more "at-risk" parenchyma where metastases could seed does not really reduce disease recurrence and is counteracted in the clinical setting by increased patient risk, more tumor stimulation and less chances of future repeated resection. Thus, it seems to be that tumor biology (as expressed by primary tumor stage, preoperative CEA level, number and size of metastatic tumors, time from primary tumor treatment to hepatic metastases, preexisting occult metastases and the presence of extrahepatic disease) rather than the number of millimeters present at a negative surgical margin, is the most important factor determining survival in patients with CLM.

PREOPERATIVE ASSESSMENT AND PATIENT SELECTION

All patients with CLM should be discussed at a multidisciplinary tumor board and considered eligible for surgery with curative intent on a case-by-case basis. Either patients with single or multiple liver metastases are potentially eligible for a parenchymal-sparing type of surgery as has been demonstrated by several authors^[11-13,33,37]. Preoperative staging should include a multislice computed tomographic (CT) scan of the abdomen and chest, as well as an abdominal magnetic resonance imaging (MRI) for a better assessment of patients with small lesions, a fatty liver or preoperative chemotherapy^[38]. Positron emission tomography (PET) scan should be considered in case of tumor recurrence in patients with a previous liver resection or suspected distant metastasis.

Eligibility for surgery should be determined taking into account three aspects: (1) risk perspective; (2) technical resectability; and (3) oncological rationality. With regards to risk perspective, medical fitness for general anesthesia and major abdominal surgery (anesthesiological risk and patient fragility) has to be carefully evaluated preoperatively. In certain cases, this includes the evaluation of the underlying parenchymal status and function. Surgeons should be especially careful with obese patients and those who have undergone long-course chemotherapy regimens, consequently adjusting the volume of the predicted FLR to its respecting quality. For patients with normal hepatic function, a FLR of approximately 25% of total liver volume is considered sufficient to maintain liver function after resection^[39]. On the other hand, in patients with hepatic dysfunction or liver injury (*e.g.*, because of chemotherapy) a FLR of at least 40% of total liver volume is highly recommended^[40]. The surgical indication should therefore be tailored according to the existence of both patient and liver-related operative risks. PLS might be particularly beneficial for patients with a high operative risk for major resection, who would otherwise not be candidates for resection. From a technical perspective, the availability of state-of-the-art abdominal imaging is crucial to define resectability and to plan the optimal surgical procedure. However, given the widely varying concept of resectability among surgeons, as evidenced by the literature^[41], surgical exploration should be undertaken at specialized centers only when the surgical team strongly believes that a potentially curative operation will be feasible. Even though resection with negative margins of every CLM is the preferred treatment option, it has to be remarked that when selecting candidates for PLS, the combination of resection of most lesions with radiofrequency ablation of those unfavorably located could be considered for certain patients in order to offer the best possible survival^[12,42]. From an oncological perspective, evaluation of extrahepatic disease and its resectability, as well as the response to pre-operative

systemic therapy in patients with dismal prognostic factors are main considerations, as they are the most likely to benefit from this approach. Thus, associating an acceptable patient risk with a safe technical proposal and a reasonable oncological indication should be the goal of liver surgeons when selecting candidates for PLS. As in any type of liver resection, unresectable extrahepatic metastases or unresectable primary tumor, prohibitive anesthesiological risk and medical contraindications to hepatectomy still constitute contraindications for resection.

IMAGING TECHNIQUES AND OPERATIVE PLANNING

Operative planning is the key for successful treatment in patients with CLM. As mentioned before, a parenchymal-sparing approach should be preferred whenever possible. Hepatic surgery has evolved greatly in the last 20 years and advances in complementary imaging studies have played a key role in this development.

Imaging techniques

Operative planning is essentially based on imaging techniques, both pre- and intra-operatively, since the type of surgical procedure will be personalized to each patient according to the size, location and number of tumors. In the preoperative setting, multislice CT-scan utilizing tri-phase contrasted acquisitions is still the standard imaging modality for the liver, and while it is principally used for the evaluation of liver tumors, it also provides useful information about the quality of liver parenchyma, vascular distribution, total and partial liver volumes, *etc.*^[43]. Nowadays multislice CT angiography with three-dimensional (3D) reconstruction has replaced hepatic angiography for the preoperative study of vascular liver anatomy. Regarding specifically CLM evaluation, recent evidence suggests that MRI offers superior sensitivity and specificity compared with CT-scan, particularly for the detection of lesions measuring less than 1 cm^[38]. Diffusion-weighted imaging techniques of MRI improves the diagnostic accuracy because of the differences in proton diffusion between benign and malignant tissue, the last showing in general a more restricted diffusion. Furthermore, the recent introduction of new liver-specific MRI contrast agents has further improved the capacity of MRI for detecting and characterizing small lesions^[38].

With regards to the intraoperative scenario, ultrasonography deserves a particular mention since it stands out as the most important imaging aid to the surgeon and PLS is essentially an ultrasonographically-guided surgical approach^[44,45]. After being described by M. Makuuchi in 1977, intraoperative ultrasound (IOUS) exploration of the liver has gained increasing protagonism and is nowadays a fundamental component of modern liver surgery. IOUS guidance is crucial to fulfill the objective of PLS, which is essen-

tially to minimize resection margins while keeping the oncological radicality, reducing the rate of major hepatectomies and whenever possible avoiding the need for strict anatomic approaches. IOUS should be the first step of any liver surgery and has to be always carried out personally by the surgeon in charge rather than an assistant, radiologist or technician. It allows to confirm the findings of preoperative images, evaluate vascular anatomy, study the tumor-vessel relationships, assess the direction of portal flow and to guide the planned type of resection or ablation. Therefore, state-of-the-art color Doppler ultrasonography equipment with standard convex, microconvex and T-shaped probes should be present in the operative room. The liver is usually evaluated at 5 and 7.5 MHz^[44,45]. The preferred probes to obtain the best images without artifacts are those that can be sterilized and then stay in direct contact with the liver surface. If available, contrast-enhanced IOUS (CE-IOUS) may help intraoperative staging and assessment of tumor relation with the liver vascular structures. This seems to be especially important in patients who received preoperative chemotherapy, scenario in which Ruzzenente *et al.*^[46] found that CE-IOUS allowed detecting additional lesions in 14% of patients and changing the operative management in 18% of patients, therefore improving both the sensitivity of IOUS to detect CLM and the R0 resection rate.

Although standard IOUS provides real-time visualization of anatomic structures, limitations may arise from the 2D nature of the images. Recent technological advances have enabled operation planning using 3D image-processing software for both CT and US^[47,48]. Detailed 3D anatomical information could facilitate complete tumor removal while preserving a sufficient amount of functional liver tissue especially in complex liver surgery and interventional treatments. Those who favor navigation in liver surgery argue that this technology is not only useful for guiding surgical instruments during resection or ablation, but also for the treatment of patients who have received chemotherapy prior to liver resection or who have steatosis, where liver parenchyma is often difficult to evaluate with conventional US. However, despite several efforts to make real-time navigation feasible, some limitations continue to hamper its clinical application. Lack of millimetric accuracy, deformation of the liver parenchyma during resection, and breathing movements are some of the most important criticisms of this method. Recent preliminary studies using navigation systems that integrate IOUS, preoperative CT imaging and 3D anatomic models on a single display have shown promising results^[49]. Real-time navigation systems might become in the near future an important adjunct for safe liver resections, although its actual applicability for PLS has not been consistently proven yet.

Operative planning

The final technical strategy should be decided upon

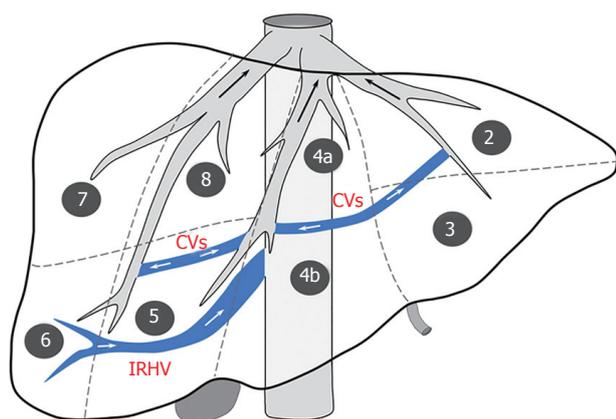


Figure 1 Diagram of liver segmentation and the anatomical variations of hepatic outflow important for parenchymal-sparing liver resections. CVs: Communicating hepatic veins; IRHV: Inferior right hepatic vein.

completion of IOUS assessment, based on the following: Unexpected discovery of new lesions or invasion of vascular structures, FLR volume, chemo-related liver toxicity and the need to perform simultaneous resection of the primary tumor or adjacent organs. Atypical resections can be used for peripheral lesions, but some tumors might require larger and eventually anatomical resections only because they are located centrally or in the vicinity of major portal pedicles or hepatic veins (HVs). With specific regards to the feasibility of PSLS related to vascular proximity, Torzilli *et al.*^[50] proposed certain criteria to define operative strategy. Whenever a tumor is near a HV close to the hepato-caval confluence and either of the following is present: (1) the tumor is not separated by a thin layer of liver parenchyma; (2) there is vessel wall discontinuation; or (3) the contact exceeds 1/3 of the vessel diameter; the vessel has to be sacrificed and AR of the segment/s (S) is many times necessary to avoid the risk of congestion if certain vascular variations are not present. In this scenario, after HV resection, the drained liver can't be spared and if the FLR is not sufficient to allow major resection, HV reconstruction could represent the only surgical option^[51]. Similarly, when a tumor is near a Glissonian pedicle and contact exceeds 2/3 of the diameter or a distal bile duct dilatation is present, it is mandatory to sacrifice the corresponding anatomic territory^[52].

Anatomical principles

The vascular anatomy of the liver should be thoroughly assessed with imaging methods before PSLS. Hepatic venous variants, as well as the pattern of venous drainage into the inferior vena cava (IVC) need to be specially investigated^[53]. This is particularly important when en-block resection of a HV and part or the entire adjacent liver segment/s needs to be performed for tumors involving HVs at the hepato-caval confluence.

More frequently, the right HV (RHV) drains S5, 6, 7 and 8; the middle HV (MHV) drains S4, 5 and 8; and the left HV (LHV) drains S2, 3 and 4. However, S6 may have an independent drainage directly into the IVC^[53].

Although this accessory HV is present in most patients (86%-100%), it is larger than 0.5 cm in less than a quarter of them, representing a variant known as inferior right HV (IRHV)^[53,54]. Another important anatomical variation is the presence of communicating veins (CVs), which connect adjacent HVs, and have been demonstrated using IOUS in up to 80% of patients with CLM at the hepato-caval confluence^[55]. The detection of the IRHV or CVs between adjacent HVs in cases with hepato-caval confluence compromise may enable safe conservative hepatectomies instead of major resections or complex vascular reconstructions (Figure 1)^[45,51]. However, to guarantee the safety of the procedure, a HV should be resected only after intraoperatively testing the proper function of these variants. As proposed by Torzilli^[52], the feeding portal branch of the segment to be spared must preserve hepatopetal blood flow (rather than hepatofugal) on Doppler US when the HV/s is occluded by using a clamp or just the fingers. Systematically using this method, these authors observed that only 2 out of 22 patients with involvement of HVs needed a major hepatectomy, and none underwent vessel reconstruction^[45].

SURGICAL TECHNIQUES

Once the feasibility of PSLS has been determined pre- and intra-operatively, resection can be carried out. Different kinds of resections have been proposed in order to maximize the amount of liver parenchyma after resection. The consideration of a certain technique as parenchymal-sparing depends on each patient. Almost any type of hepatic resection could be considered as sparing whenever it involves the willing of performing a certain procedure over another that compromises more liver parenchyma (e.g., a major central hepatectomy may be excessive for a peripheral lesion involving both S5 and 4b, but it becomes a parenchymal-sparing approach if used instead of a hemi-hepatectomy right or left for a patient with a large centrally located tumor).

From a technical point of view and for the purpose of this review, PSLS could be considered as every type of liver resection not conforming an AR of a hemiliver or extended resections as defined by the standardized Brisbane 2000 nomenclature, proposed by the International Hepato-Pancreato-Biliary Association^[56]. The sole exception to these rule would be LLS, because the left lateral liver accounts for more than 20% of total liver volume in one out of every four patients, and its preservation is always desired to increase future salvageability^[11,57]. PSLS includes both segment-oriented and non-segment-oriented variants, either as isolated procedures or in combination. The different proposals reported in the literature are summarized in Table 1. In general, segment-oriented resections are reserved for patients with multiple tumors within a single anatomic segment or those in whom the tumor is located centrally and invading the major portal pedicle or HV to an anatomic segment/s^[58]. In these cases transection

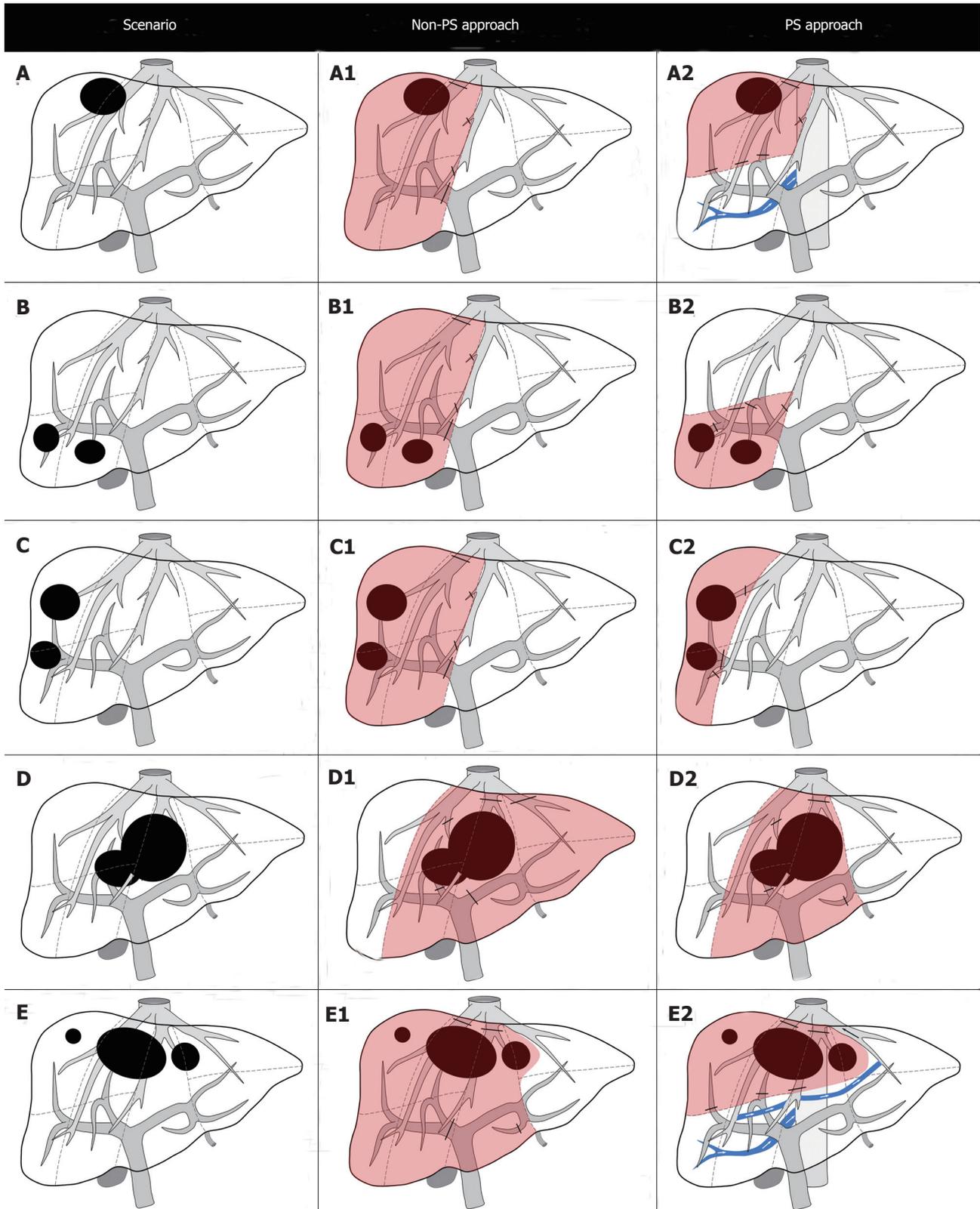


Figure 2 Diagram of segment-oriented parenchymal-sparing resections according to different surgical scenarios. A: Metastatic lesion infiltrating the RHV; A1: Right hepatectomy; A2: Bisegmentectomy 7-8 is possible due to the presence of an IRHV; B: Metastatic lesions located in S5-6; B1: Right hepatectomy; B2: Bisegmentectomy 5-6; C: Metastatic lesions in right posterior section; C1: Right hepatectomy; C2: Right posterior sectionectomy; D: Large central tumors invading the MHV; D1: Left trisectionectomy; D2: Central hepatectomy; E: Metastatic lesions invading the RHV and the MHV; E1: Right trisectionectomy extended to S2; E2: Upper transversal hepatectomy is possible due to the presence of an IRHV and communicating hepatic veins. PS: Parenchymal-sparing; RHV: Right hepatic vein; IRHV: Inferior right hepatic vein; MHV: Middle hepatic vein.

lines are based on the combination of external anatomic landmarks, selective devascularization by clamping

Table 1 Different parenchymal-sparing operative procedures

Type of resection	Segment/s resected
Segment-oriented	
Monosegmentectomy	Any isolated segment
Bisegmentectomy	Two contiguous segments
Right posterior sectionectomy	S6 and 7
Right anterior sectionectomy	S5 and 8
Right inferior bisegmentectomy	S5 and 6
Right superior bisegmentectomy	S7 and 8
Central anterior bisegmentectomy	S4b and 5
Central posterior bisegmentectomy	S4a and 8
Left medial sectionectomy	S4a and 4b
Central hepatectomy	S4, 5 and 8
Upper Transversal Hepatectomy	S7, 8, 4a and 2 + RHV and MHV
Non-segment-oriented	
Corkscrew technique	Any segment
Mini-mesohepatectomy	Partial S8 and 4a + MHV
Mini upper-transversal hepatectomy	Partial S7, 8 + RHV
Hepatic Vein-Sparing Hepatectomy	Partial S7, 8, and 4a ± 1 paracaval
Systematic extended right posterior sectionectomy	Complete S6-7 + partial S5 and/or S8 (en-block)
Liver tunnel	Partial S4a, 8 and 1
Lower inferior hepatectomy	S3, 4b, 5, 6 and 7
Local ablation ¹	Any

¹Combined with other surgical resection. MHV: Middle hepatic vein; RHV: Right hepatic vein.

to create ischemic margins and intraoperative US. Segment-oriented operative procedures for PSLS are depicted in Figure 2. Non-segment-oriented resections (also referred as atypical or wedge resections) are usually applied for lesions smaller than 5 cm and located near the liver surface. Since anatomical boundaries are not respected, the use IOUS to guide this type of resection is paramount to clearly identify all the bile ducts and vascular branches. For non-large atypical resections, the “corkscrew technique” proposed by de Santibañes *et al.*^[59] is especially useful. In this particular technique, the liver surface is marked with electrocautery and stiches are placed surrounding the lesion in order to easily achieve traction and countertraction of the liver, thus facilitating the identification of biliary ducts and vascular branches. Non-segment-oriented operative procedures for PSLS are depicted in Figure 3.

Even though most patients treated by PSLS are usually approached by a J-shaped or bilateral subcostal incision with upper midline extension, Torzilli *et al.*^[44] recommends a J-shaped thoracophrenolaparotomy for cases with tumors involving S1, 4a, 7, and 8 close to the HV confluence into the IVC. Regarding parenchymal transection, no study has consistently demonstrated significant differences among the various existing techniques up to date. However, it is strongly recommend to use the cavitron ultrasonic surgical aspirator (CUSA) for PSLS since it facilitates a meticulous transection and provides an additional margin beyond that examined by the pathologist. This has been recently associated with an advantage in case of limited margins^[18,60,61].

There are some especially sophisticated IOUS-guided variants of PSLS that deserve to be addressed independently.

Bisegmentectomy 7-8 or right superior bisegmentectomy

Metastatic lesions located in S7-8 that infiltrate the RHV have been traditionally treated with a right hepatectomy given that the right hemiliver is theoretically drained totally (S6, 7) or partially (S5, 8) by the RHV (Figure 2A). The presence of an IRHV, allowed Makuuchi *et al.*^[62] in 1987 to report the first resection of S7-8 en-block with the RHV sparing S5 and S6 without congestion. Although the presence of IRHV is paramount when considering the possibility of sacrificing the RHV, Machado *et al.*^[63] and Capussotti *et al.*^[54] described the feasibility of resecting S7-8 and the RHV without an IRHV. These experiences were based on the anatomical assumption that S6 has several venous anastomoses with S5 and the latter drains into the MHV. The presence of these CVs was later confirmed by Torzilli *et al.*^[55] using high-frequency IOUS. In summary, a 7-8 bisegmentectomy with RHV resection can be performed safely when: (1) an IRHV is present; (2) CVs connecting the RHV with MHV are recognized; and/or (3) hepatopetal rather than hepatofugal blood flow is maintained in the feeding portal branch by color Doppler IOUS after clamping the RHV.

Mesohepatectomy or central hepatectomy

When a tumor invades the MHV at the confluence with the IVC or large central tumors are present, formal anatomic extended hepatectomies are performed by most surgeons (Figure 2D). The resection of central hepatic segments (Couinaud’s S4, 5, and 8), was first proposed by McBride *et al.*^[64] in 1972 and later validated by others as a conservative alternative, preserving more functioning liver tissue than either left or right trisectionectomy^[65,66]. Central resection could also be less extensive; either including S4b and S5 (anterior central) or S4a and S8 (posterior central). Despite being a technically demanding major resection, mesohepatectomy represents a valuable alternative to extended hepatectomy since its complication rate, postoperative recovery, and preserved liver tissue compare favorably with extended hepatic resections.

Mini-mesohepatectomy

In order to avoid major resection, mini-mesohepatectomy (MMH) has been designed by Torzilli *et al.*^[67] specifically for non-large tumors (< 5 cm) invading more than 2/3 of the circumference of the MHV close to the hepato-caval confluence (within 4 cm) (Figure 3B). It is defined as the partial removal of S8 and/or S4a including the involved tract of MHV^[68]. To carry out this technique, as for RHV ligation, at least one of these 3 criteria must be present when the surgeon fingertips compress the MHV: (1) reversed flow direction in the peripheral portion of the MHV, which suggests drainage through collateral circulation in adjacent HVs or IVC;

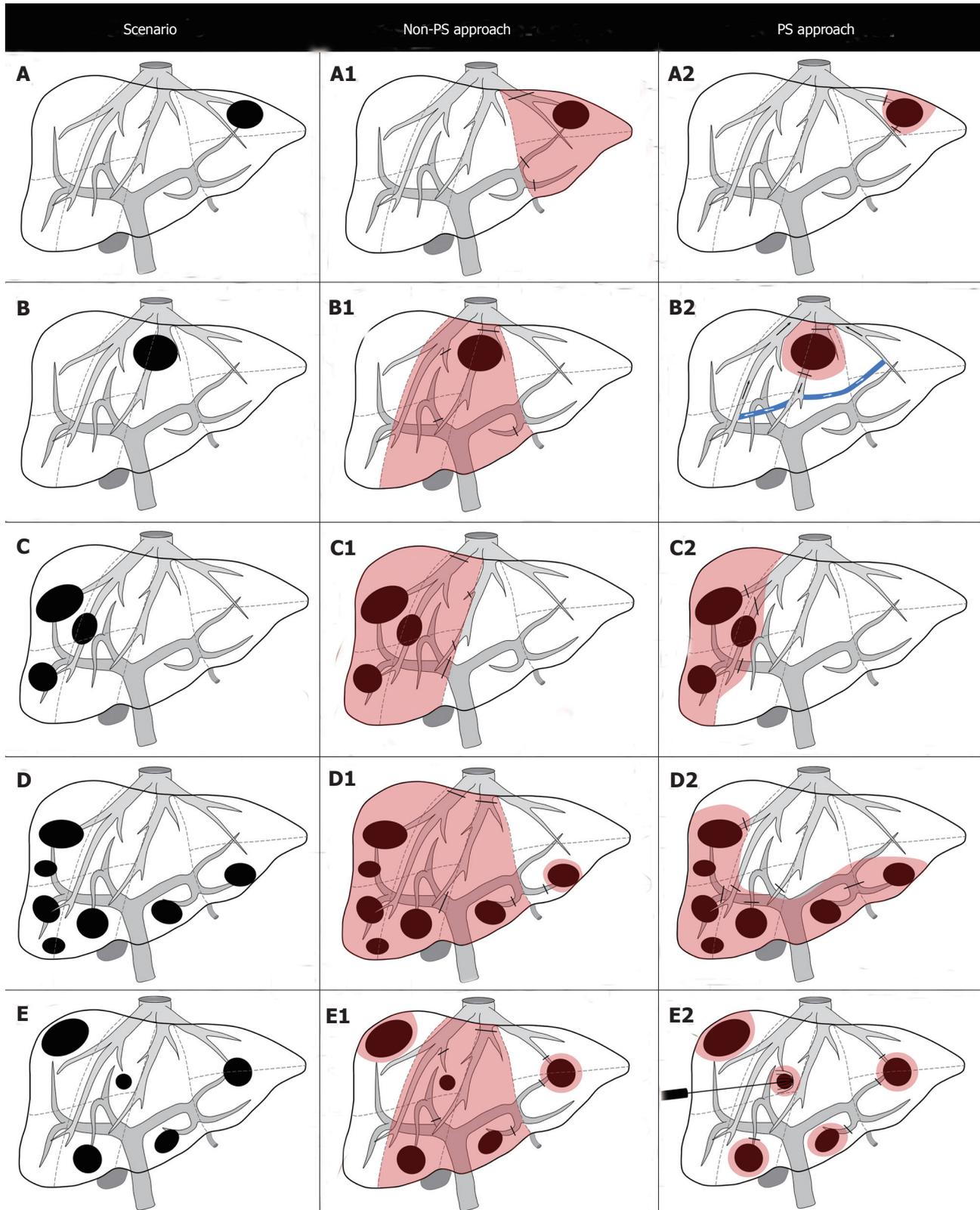


Figure 3 Diagram of non-segment-oriented parenchymal-sparing resections according to different surgical scenarios. A: Metastatic lesion in S2; A1: Left lateral sectionectomy; A2: Atypical resection of S2; B: Metastatic lesion infiltrating the MHV close to the hepato-caval confluence; B1: Central hepatectomy; B2: Mini-mesohepatectomy is possible due to the presence of communicating hepatic veins; C: Metastatic lesions in right posterior section invading the RHV and tumor in proximity of right anterior portal branch; C1: Right hepatectomy; C2: Systematic extended right posterior sectionectomy; D: Liver metastases peripherally located in S3, 4b, 5, 6 and 7; D1: Right trisectionectomy; D2: Lower inferior hepatectomy; E: Multiple bilateral metastases; E1: Atypical resections combined with central hepatectomy; E2: Multiple atypical resections combined with radiofrequency ablation. PS: Parenchymal-sparing; RHV: Right hepatic vein; MHV: Middle hepatic vein.

(2) detectable shunting collaterals between MHV and RHV or LHV; and (3) hepatopetal flow in S5, 8 and/or

S4b portal branches. The posterior wall of the MHV or of the tumor itself is used as the deepest landmark of the resection area. A crucial point is to delineate a transection plane that does not interrupt CVs. This is obtained by dividing the MHV the closest possible to its point of infiltration using IOUS guidance, preserving its distal portion for collateral circulation. Even though this interesting surgical proposal provides an alternative to limit the use or even replace central hepatectomy in certain cases, further validation of its efficacy and safety is awaited before expanding its application.

Upper transversal hepatectomy

This type of parenchymal-sparing resection, proposed by Torzilli *et al.*^[69], is specifically useful for tumors involving the RHV and MHV, or even all HVs at the hepato-caval confluence (Figure 2E). These cases are considered irresectable by most surgeons. However, a major hepatectomy with vascular reconstruction represents the only option offered by others. This last can be avoided when CVs between adjacent HVs are detected intraoperatively with US^[69]. Upper transversal hepatectomy involves total or partial resection of the superior liver segments (S7, 8, 4a and 2) accompanied by the RHV and MHV or even all HVs. It can be performed only when an IRHV is present simultaneously with CVs connecting the IRHV with the MHV and the MHV with the LHV. After checking the function of the complete inter-venous circuit by IOUS and certifying the absence of macroscopic congestion, resection is IOUS-guided preserving the CVs. More recently, an even more conservative variant of this approach has been proposed also by Torzilli *et al.*^[70], denominated "mini upper-transversal hepatectomy".

HV-sparing hepatectomy

This approach has been recently introduced by Torzilli *et al.*^[71] for metastases located in S8, 4a involving both the RHV and MHV at the hepato-caval confluence but neither the IRHV nor CVs are present at imaging. In such cases, when vascular invasion comprises 1/3 of their circumference or less, partial resection of S7, 8, and 4a \pm 1 paracaval can be performed sparing both RHV and MHV by partial resection and reconstruction by running suture. This approach has been proposed as an effective alternative to major resection performed immediately or in a staged perspective^[71].

Systematic extended right posterior sectionectomy

In case of vascular invasion of the RHV with multiple tumors in the right posterior section, and/or invasion of the right posterior portal branch (P6, 7) with tumor in close adjacency (< 5 mm) with right anterior portal branch (P5, 8), right hepatectomy is traditionally performed (Figure 3C). Systematic extended right posterior sectionectomy (SERPS) has been proposed by Torzilli *et al.*^[72] as an alternative approach, performing a right posterior sectionectomy with a tailored extension

to the right anterior section, either the right part of segment 8 \pm the RHV and/or the right part of S5 exposing but not dividing the pedicle of S5, 8 on the cut surface just enough to guarantee complete tumor removal. In all the aforementioned conditions, portal blood flow at color-Doppler IOUS in the pedicle of S5, 8 (right anterior glissonean sheath) has to be hepatopetal once RHV is clamped for carrying out SERPS. SERPS serves also as an alternative to right hepatectomy when bisegmentectomy 7-8 is not possible (in cases where there is vascular invasion of the RHV but without tumor involving S6) because there is not a proper outflow for S6 once RHV is divided (absence of IRHV and hepatofugal portal blood flow at Doppler IOUS in P6 when RHV is clamped). IOUS-guided SERPS has proven to be feasible, safe and effective^[72]. Preserving the majority of the right anterior section (S5, 8) is utmost important, as the right anterior section of the liver is most relevant in terms of volume^[73,74]. In a previous prospective series including 201 patients, SERPS was performed more frequently than right or extended right hepatectomy (10% vs 9%), avoiding such major resections^[72].

Other types of parenchymal sparing resections

There have been anecdotal reports of exceptional strategies of PSLS^[52]. The so-called "liver tunnel" represents an extension of the MMH in patients with central tumors compromising the MHV but extending from S8 vertically to S1 and the "lower inferior hepatectomy" represents the atypical en-block resection of S3, 4b, 5, 6 and 7 for liver metastases peripherally located in these segments (Figure 3D). These particularly challenging approaches deserve further validation in larger series of patients before expanding its application.

Combination of resection with local ablation

As the indications for surgical treatment of CLM have broadened, the use of multimodal therapies has become more common. Nowadays, the use of interstitial treatments (radiofrequency or microwaves) to compliment resectional strategies has proven to be a useful and rationale approach to treat patients with multiple lesions when complete resection of all metastases is not possible, therefore extending the limits of surgical treatment^[12]. In this combined approach, hepatectomy addresses the main tumor mass and the residual tumor that cannot be resected is treated with local tumor-ablative therapy (Figure 3E). Ideally, lesions treated with RFA should be less than 25 mm in size, since technically successful ablation is possible in more than 90% of the cases^[74]. However, a recent retrospective study evaluating recurrence patterns of CLM treated with ablation, found that ablation was more effective for metastases of size equal to or smaller than 10 mm^[75]. This combined approach has not been associated with a compromise in disease-

specific survival^[112], while demonstrated a reduction in the need of major resections and two-stage procedures, offering the possibility of repeated treatments for recurrences with reduced morbidity^[42,50].

USE OF LAPAROSCOPY IN PARENCHYMAL SPARING RESECTIONS

The advantages of laparoscopic hepatic resection vs open surgery in the perioperative period (*e.g.*, less blood loss, fewer complications, and shorter duration of hospitalization) as well as favorable cosmetic results have been well recognized in the literature^[76]. In addition, there is an increase body of evidence indicating that laparoscopic approach does not compromise oncological principles in selected patients^[76,77]. Traditionally, laparoscopy has been mostly used for small and subcapsular liver lesions located in peripheral liver segments (S2, 3, 4b, and 5). With regards to laparoscopic PSLS, from the beginning of laparoscopic liver surgery a parenchymal-sparing philosophy has been applied and limited NAR of accessible segments dominated the scene. Along with increasing experience in laparoscopic liver surgery, more complex laparoscopic liver resections are being practiced to treat central liver lesions or those ill located in posterior and superior segments. Recent evidence presented by experienced surgical teams demonstrates that segment-oriented parenchymal-sparing variants can be performed safely using laparoscopy^[78]. A recent retrospective study concluded that laparoscopic liver resection with a parenchymal-sparing approach does not worsen oncological outcome, allowing a higher percentage of repeat hepatectomy^[79]. Montalti *et al.*^[80] showed that the laparoscopic parenchyma-preserving approach with the CUSA is possible and that R1 margins are a risk factor for tumor recurrence but not for OS. A major limitation for this technique was the presence of multiple lesions since it was identified as the only independent risk factor for R1 margins^[80]. More recently, robot-assisted liver surgery has been introduced as a minimally invasive alternative to facilitate the parenchymal-sparing treatment of lesions located in the posterosuperior segments or when portal triad dissection is necessary, suggesting the potential of robotics to resemble techniques and outcome of open PSLS^[81]. The routine use of laparoscopic IOUS is as important as in the open approach and have also been highlighted in the literature^[82].

During the 2nd international consensus conference for laparoscopic liver resection held in Morioka (Japan) in 2014^[76], it was noted as a concern that larger procedures resecting more liver parenchyma are sometimes favored if the procedure is done laparoscopically because a smaller parenchyma-sparing operation may be more complex laparoscopically. As well, there has been a tendency towards more LLS instead of atypical resections to facilitate laparoscopic treatment

of single or few small sized metastases located in the left lateral segment. However, recent data in patients with single lesions supports atypical resection over LLS, demonstrating increased future salvageability and survival^[111]. Therefore, in light of this new evidence, LLS should be discouraged from now on, for lesions amenable to atypical resection even when performing laparoscopic surgery.

SHORT AND LONG-TERM OUTCOMES

As mentioned previously, PSLS encompasses a wide variety of surgical alternatives for a heterogeneous population of patients, therefore outcome analysis can be very complex. In terms of comparative studies, Torzilli *et al.*^[72] compared SERPS with right hepatectomy in patients matched for age, tumor size and number. They found that SERPS resulted in significantly less blood loss, less transfusions, less portal pedicle clamping with similar operative length, hospital stay and safety profile. Similarly, Ferrero *et al.*^[83] demonstrated that bisegmentectomy instead of right hepatectomy improves postoperative outcomes, offering similar survival results and increasing the opportunity to re-resection in patients with CLM of ≤ 10 cm located in the right liver lobe. Despite these few reports, for the purpose of the present review, probably the most practical way to evaluate outcomes would be to consider PSLS as the philosophy of saving parenchyma and compare it against a non-saving parenchyma philosophy, rather than each different technical variant evaluated separately. The comparison that most resembles this scenario, and even gave rise to the debate, is that of AR vs NAR in patients with CLM. There have been many studies in the literature aiming to compare the outcomes of these opposite approaches with similar results (Table 2).

Operative results and complications

From the short-term perioperative results perspective, several groups have experienced better perioperative outcomes with the increased use of a parenchymal-sparing policy^[11-13]. This association correlates well with findings from large series demonstrating that the number of segments resected is an important determinant of outcomes^[84,85]. In 2008 the MSKCC group evaluated a series of 440 patients operated on for bilateral CLM from 1992 to 2003, dividing the study in four time-periods with the purpose of determining trends over time^[12]. They found a significant trend away from large resections in favor of multiple smaller resections despite patient and tumor variables did not change over time. A significant drop in 90-d mortality (from 6.3% to 1.2%, $P = 0.02$); operative blood loss (from 950 to 490 mL, $P < 0.001$) and length of hospital stay (from 12 to 9 d, $P < 0.001$) was observed occurring simultaneously with the increased application of parenchymal-sparing techniques^[12]. In a retrospective

Table 2 Overview of the different comparative studies involving non-anatomic resection in patients with colorectal liver metastases

Ref.	Year	Groups (n)	Hospital stay (d)	Morbidity (%)	Mortality (%)	Operative time (min)	Blood loss (mL)	Margin + (%)	5-year DFS (%)	5-year OS (%)	Matching ²
Mise <i>et al</i> ^[11]	2015	AR (144) vs NAR (156)	NA	36 vs 36	1 vs 0	128 vs 150	200 vs 100 ³	5 vs 2	NS	NS	1-8, 10
Von Heesen <i>et al</i> ^[89]	2012	AR (47) vs NAR (61)	NA	NA	NA	In favor of NAR ³	In favor of NAR ³	NA	37 vs 27	37 vs 48	NA
Lalmahomed <i>et al</i> ^[32]	2011	AR (88) vs NAR (113)	8 vs 7 ³	27 vs 23	2 vs 1	NA	NA	9 vs 11	30 vs 32	49 vs 39	1-4, 6-10
Sarpel <i>et al</i> ^[86]	2009	AR 94 vs NAR 89	8 vs 6 ³	NA	3 vs 0	NA	NA	1 vs 6	NS	NS	1, 2, 6, 9
Guzzetti <i>et al</i> ^[88]	2008	AR 102 vs NAR 106	9 vs 8	8.8 vs 16	0 vs 0	300 vs 240 ³	700 vs 500 ³	20 vs 11	NS	27 vs 29	1-8, 10
Finch <i>et al</i> ^[61]	2007	AR 280 vs NAR 96	NA	29 vs 15	4.4 vs 0	NA	NA	25 vs 33	35 vs 24	50 vs 54	1, 2, 8, 9
Zorzi <i>et al</i> ^[87]	2006	AR 181 vs NAR 72	7 vs 7	23 vs 28	1.1 vs 1.4	NA	NA	8.3 vs 8.3	NA	60 vs 61	1-3, 6-9
Kokudo <i>et al</i> ^[33]	2001	AR 96 vs NAR 78	NA	12 vs 6.4	2.1 vs 0	315 vs 259 ³	1489 vs 895 ³	27 vs 20 ¹	NA	46 vs 40	1-4, 6
DeMatteo <i>et al</i> ^[90]	2000	AR 148 vs NAR 119	8 vs 9	20 vs 13	0.8 vs 0.4	198 vs 189	531 vs 456	2 vs 16 ³	NA	49 vs 37 ³	1-3, 6-8

¹Margins < 2 mm; ²Matching: 1 = age; 2 = gender, 3 = number of tumors; 4 = tumor distribution; 5 = tumor size; 6 = primary tumor site; 7 = node positive primary; 8 = preoperative carcinoembryonic antigen level; 9 = synchronous disease; 10 = disease-free interval. ³Statistically significant difference ($P < 0.05$). NAR: Non-anatomic resection; NA: Not-available; NS: Not-stated in the original article because of non-significant difference; DFS: Disease-free survival; OS: Overall survival. AR: Anatomic resection.

study comparing major AR vs minor NAR in 174 patients, Kokudo *et al*^[33] found that the mean operating time and operative blood loss were significantly greater during AR. These findings are in accordance with those of Sarpel *et al*^[86], who reported significantly more blood transfusions in patients who underwent AR compared to NAR (44% vs 16%, $P < 0.001$), despite Pringle time was similar between groups (11 ± 7 min vs 10 ± 7 min, $P = 0.313$). Even though several more recent series have confirmed a significant advantage in terms of operating time and blood loss during NAR^[11], in most studies this was not translated into a significant difference in morbidity or mortality, probably owing to an insufficient number of patients studied and the retrospective nature of the analyses^[32,33,86-88]. A recent meta-analysis of non-randomized studies was designed as an attempt to overcome these limitations^[13]. Among 1662 subjects with CLM, 989 underwent AR and 673 underwent NAR. The meta-analysis demonstrated that NAR reduced the operation time and blood transfusions, whereas it confirmed that overall morbidity (22.1% AR vs 16.6% NAR, $P = 0.32$) and mortality were similar between the two groups (0.9% AR vs 0.7% NAR, $P = 0.68$). However, it has to be taken into account that significant heterogeneity across studies was present for some of these variables. In a recent comparative study of patients matched for clinical characteristics and tumor size, the MD Anderson group found that parenchymal-sparing resection was associated with significantly reduced blood loss but equal morbidity (23% vs 26%, $P = 0.54$), major complications (3% vs 6%, $P = 0.21$) and 90-d mortality (0% vs 1%, $P = 0.23$) compared to non-parenchymal-sparing resection^[11]. Conversely, when analyzing specifically liver-related morbidity, Gold

et al^[12] showed that AR were independently associated with higher liver-related complications as opposed to wedge resections. Moreover, von Heesen *et al*^[89] found that AR had a significant higher incidence of pleural effusions requiring interventional drainage than NAR and combined resections.

Oncological results

In terms of oncological long-term results, one of the main concerns regarding PSLS has been the specimen margin status and the fact of leaving more at-risk liver parenchyma behind where liver metastasis could seed, with their potential negative impact in patient survival. So far, none of these concerns has found a solid scientific background in the current clinical field.

Among the few authors who advocated non-parenchymal-sparing resections for CLM during the 1990s, DeMatteo *et al*^[90] presented one of the most controversial evidence in 2000. In their series of 267 patients, AR resection had a significantly lower rate of positive margins compared to NAR (2% vs 16%, $P < 0.001$) resulting in longer survival for AR on univariate analysis (53 mo vs 38 mo, $P = 0.015$). In a larger study published 8 years later, the same group found that although the width of negative margin using wedge resection was significantly less than when wedge resection was not used (mean 0.5 cm vs 0.8 cm, $P = 0.02$), margin positivity did not correlate with the use of a wedge resection ($P = 0.40$)^[12]. More recent studies involving modern approaches reported that the incidence of a positive surgical margin was equal for AR and NAR either with single or multiple liver lesions^[11,32,61,86-88]. A recent meta-analysis confirmed these results^[13].

With regards to recurrence and survival, the majority of reports have found no significant differences according to the type of hepatectomy performed. The study published in 2009 from the Mount Sinai Medical Center found that the type of resection was not associated with significant differences in recurrence or survival even when adjusted for differences in preoperative risk^[86]. Another study by Lalmahomed *et al.*^[32] reported comparable median time to recurrence between AR and NAR (9 mo vs 10 mo, $P = 0.802$) in 201 patients with single or multiple liver metastases. In addition, the pattern of recurrence in terms of location and 3-year intrahepatic recurrence rate did not differ between the two groups^[32]. The 5-year DFS and OS were also similar for AR and NAR (30% vs 32%, $P = 0.599$; 49% vs 39%, $P = 0.989$). These findings were later confirmed by the meta-analysis by Sui *et al.*^[13], where 5-year OS was not significantly different between the two groups (OR = 1.13; 95%CI: 0.92-1.39, $P = 0.24$). Regarding 5-year DFS, even though no significant difference was shown between the groups, the marked heterogeneity between studies raises questions about the validity of this data. In order to overcome the effects of differences in the number of liver tumors that might influence patient survival between types of resections, some authors individualized patients with multiple metastases and analyzed them separately. In this regard, in the study presented by Tanaka *et al.*^[37], from Yokohama city in 2008, among the subgroup of patients with six or more metastases, the overall survival of those who had a major resection was significantly poorer than those who had minor resections ($P = 0.028$), although the clinical characteristics were comparable between the two groups. On the other hand, in the MSKCC study from the same year regarding the unique subgroup of patients with multiple bilateral lesions, the use of wedge resection independently correlated with worse liver recurrence-free survival but not disease-specific survival^[12]. Additionally, they found that in the era of modern multimodal tactics, disease-specific survival or liver recurrence-free survival did not change over time despite modifying the technical approach.

It has been hypothesized that in the specific subgroup of patients with multiple CLM, local failure in the liver after wedge resection may not be as critical to survival as for patients with solitary metastases. Thus suggesting that patients with a less aggressive disease behavior should probably not undergo parenchymal-sparing procedures. However, different studies have not supported this proposal. In a retrospective study by Kokudo *et al.*^[33] a subset analysis of patients with unilobar single or double tumors demonstrated that intrahepatic recurrence did not differ significantly between those who underwent major AR vs minor NAR (31.3% vs 41.2%, $P > 0.05$), and nor did patient survival. Interestingly, only 19.6% of patients in the NAR group developed ipsilateral recurrence and 90% were resected, compared to 20% of recurrences resected in the AR group^[33]. Almost fifteen years later a similar study from the MD Anderson

group^[11], but focused in patients matched for clinical characteristics and with solitary metastases equal or less than 3 cm, reported even more interesting results in the era of modern chemotherapy. They retrospectively compared 156 patients who underwent a parenchymal-sparing hepatectomy (excluding concomitant RFA) with 144 patients who underwent non-parenchymal-sparing hepatectomy, and found that no significant differences were found in OS, recurrence-free survival, and liver-only recurrence-free survival^[11]. However, a subanalysis of patients who had liver-only recurrence revealed a significantly improved 5-year OS from initial hepatectomy (72.4% vs 47.2%, $P = 0.047$) and from liver recurrence (73.6% vs 30.1%, $P = 0.018$) in the parenchymal-sparing hepatectomy group^[11]. This was explained by the fact that salvage hepatectomy for liver-only recurrence was performed significantly more often in the parenchymal-sparing hepatectomy group compared to the non-parenchymal-sparing hepatectomy group (68% vs 24%, $P < 0.01$). In this study, multivariate analysis revealed that non-PSH was a risk of noncandidacy for repeat hepatectomy^[11].

All reports addressing PSLs are retrospective in nature and most compare heterogeneous groups of patients, thus making the interpretation of data problematic. Given that results may be biased by different patient selection criteria for either approach among centers and surgeons, definitive conclusions in terms of oncological results cannot be drawn. However, the presence of an increasing body of evidence with consistent data among different centers, strongly suggests that PSLs does not compromise oncological outcome and in certain occasions long-term survival might be even better than non-parenchymal approaches in current days. Randomized controlled data is best desired to confirm these findings. However, such a study seems unfeasible from a practical and ethical point of view, given that surgical risk of anatomical major resection is greater and surgeons would be unwilling to choose an unnecessary major hepatectomy for small single tumors near the liver surface.

CONCLUSION

There is a clear trend toward a parenchymal-sparing philosophy in HPB centers worldwide. Parenchymal-sparing strategies, either by resection alone or complemented with ablative therapies, have become an essential part of modern liver surgery and every liver surgeon should be aware of their existence and feasibility. A profound knowledge of liver anatomy as well as expert IOUS skills are necessary to perform PSLs appropriately and safely. Current evidence indicates that tumor biology is the most important predictor for intrahepatic recurrence and survival rather than the amount of millimeters at a negative resection margin. Complete tumor removal avoiding the unnecessary sacrifice of functional parenchyma has been associated with less surgical stress, fewer

postoperative complications, uncompromised cancer-related outcomes and higher feasibility of future resections. The increasing evidence supporting PSLs prompts its consideration as the gold-standard surgical approach for patients bearing liver metastases from colorectal cancer.

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Gao's double-way approach for laparoscopic D2 radical surgery for gastric cancer

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Abstract

Laparoscopic D2 radical surgery for gastric cancer is minimally invasive but complex. In this path: (1) Repeated operation of lesser curvature side; (2) The gastrohepatic ligament is relatively fixed. Hence, it is not easy to expose the suprapancreatic area; and (3) It is not easy to dissect No. 1, 12 lymph nodes. This area may not be sufficiently cleaned or surrounding vessels may be injured during a resection. So it is critical to choose position fixing, and a clear, fast and convenient operation path. The author, based on his experience, has established a set of procedural steps called "Gao's double-way", lesser omentum approach and traditional greater omentum approach, which are described in detail in this article. The path of this first approach is described as a "W" type of dissection. The second way is the traditional greater omentum approach, whose path is described as a "M" type of dissection. This will enable laparoscopic surgeons to select a suitable path. This new approach not only simplifies the surgery but also provides more space for the subsequent operation, thereby making the surgery more simple, safe and easy.

Key words: Laparoscopic; Gastric cancer; Path; Surgery; Operation

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Core tip: This new approach not only simplifies the surgery but also provides more space for the subsequent operation, thereby making the surgery more simple, safe and easy.

Gao YS, Sun JG, Huang JJ, Chen P. Gao's double-way approach for laparoscopic D2 radical surgery for gastric cancer. *World J Gastrointest Surg* 2016; 8(6): 424-426 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/424.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.424>

INTRODUCTION

Clinical vignette

For the traditional laparoscopic D2 radical surgery, the abdominal cavity and lesser curvature side were initially explored. Then the gastrocolic ligament was opened to enter the greater omental bursa. That is: Open the gastrocolic ligament → Splenic hilar lymph node dissection (No. 10, 11d) → Cardial area lymph node dissection (No. 2, 110) → Infrapyloric area lymph node dissection (No. 6) → Suprapancreatic area lymph node dissection (No. 7, 9, 11p, 12p), which can be described as a "W" type of dissection^[1-3]. But the following problems exist in this path: (1) repeated operation of lesser curvature side; (2) the gastrohepatic ligament is relatively fixed. Hence, it is not easy to expose the suprapancreatic area; and (3) it is not easy to dissect No. 1, 12 lymph nodes (LN). This area may not be sufficiently cleaned or surrounding vessels may be injured during a resection. Since the hepatogastric ligament and plica gastropancreatica are anatomically complex and difficult to expose, it will be more difficult for a new surgeon to learn, especially with a less skilled assistant^[4]. So choosing a position fixing, and a clear, fast and convenient surgical path is critical. Based on our experiences of laparoscopic D2 radical surgery in more than 200 gastric cancer patients, we gradually explored a set of procedural steps called "Gao's double-way", that is, the lesser omentum approach and the traditional greater omentum approach. Herein, the detailed procedures are described.

Surgical techniques

The patient is placed in supine position, with right leg abduction, described as a "才" word, that is right leg separated position. The surgical table is declined by 10°-20° into the reverse Trendelenburg position. Therefore, the patient's upper body is elevated. This causes the intestine to move towards the lower abdomen. The surgeon stands on the patient's left side, the assistant on the right side and the camera operator stands between the patient's legs. Audio core tip lists the detailed steps of the procedure [Audio core tip: Detailed surgical steps presented in the video clips (Video core tip)].

The first way (the lesser omentum approach): Cut the hepatogastric ligament at the thinnest area and enter the lesser omentum. The location is fixed with no anatomic variation.

The first step: Assistant's left hand holds the intestinal forceps to push the liver lobe up. Fully expose the hepatogastric ligament. Right hand holds the intestinal forceps to press the liver side of the hepatogastric ligament. The surgeon's left hand provides downward traction of the gastric side of the hepatogastric ligament, so as to produce moderate tension. The right hand holds an ultrasonic knife to cut the hepatogastric ligament at the thinnest area.

The second step: Along the edge of the liver, clean left to the front of cardia, and complete the dissection of No. 1, 2 LN. When separating, be close to the liver. This area can be thoroughly cleaned, which makes it easy to separate the organization. Do not damage the inferior vena cava. Assistant's left hand holds the intestinal forceps to fully reveal the front of cardia. The surgeon dissects No. 1, 2 LN from right to left along the esophageal hiatus, from right diaphragmatic angle of esophageal gastric junction to left diaphragmatic angle.

The third step: Along the edge of the liver, clean right to hepatoduodenal ligament, and complete the dissection of No. 12 a, p LN. Assistant's left hand holds the intestinal forceps to push the liver lobe up to fully expose the hepatoduodenal ligament. Right hand holds the intestinal forceps to press the liver side of the hepatoduodenal ligament. The surgeon's left hand provides downward traction of the gastric side of the hepatoduodenal ligament, so as to produce moderate tension. The right hand holds an ultrasonic knife to dissect this area from the liver side to tumor side. Protect the hepatic artery and left portal vein.

The path of this first approach is described as a "W" type of dissection. The second way is the traditional greater omentum approach, whose path is described as a "M" type of dissection.

DISCUSSION

At present laparoscopic D2 radical surgery is a simple, greater omentum approach. However, the author's path combined the lesser omentum and the traditional greater omentum approaches. The lesser omentum approach (the first way) is as follows: Open the lesser omentum, left to cardial area lymph node dissection (No. 1, 2 LN), right to hepatoduodenal ligament lymph node dissection (No. 12a, p LN), which can be described as "M" type of dissection (Video core tip). The advantages of this approach include: (1) Due to the rapid development of modern medical imaging, the pre-surgical evaluation is quite explicit^[5], so exploration of the local lesions can be prevented. Typically, surgeons would push the liver up and explore the lesser omentum, then release the liver and continue other steps. However, the author combined the exploration and dissection to avoid repeat surgery of lesser curvature side; (2) It could also provide a convenient way of cardial area lymph node dissection (No. 1, 2, 110 LN) and hepatoduodenal ligament lymph node dissection (No. 12a, p LN); (3) When cleaning the infrapyloric area lymph node (No. 6 LN) and the suprapancreatic area (No. 7, 9, 11p, 12p LN), the area can be easily exposed thereby making the dissection more safe and convenient; (4) Open the lesser omentum, so the stomach can be lifted, which can provide larger space for dissection; (5) It can provide a larger space for the dissection of infrapyloric area LN and suprapancreatic area, thereby saving time by not changing the patient's posture; (6) The lesser side

has high incidence of gastric cancer, so after opening the lesser omentum, chemotherapy drugs could be poured into it. So the lesion area of tumor and exfoliated cells (especially gastric juice) was soaking in drugs, thereby preventing tumor spread caused by surgery; and (7) Due to the first path, the cleaning of greater omentum approach could be easier thereby making the operation more safe. For example, the dissection of hepatoduodenal ligament LN can be simplified (No. 12a, p LN). Besides, with the first approach, the space is enough for cleaning cardial area LN (No. 110 LN).

CONCLUSION

Based on the author's experiences with laparoscopic D2 radical surgery in more than 200 gastric cancer patients, this approach was summarized as "W + M".

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Retrospective Study

Impact of previous cyst-enterostomy on patients' outcome following resection of bile duct cysts

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Institutional review board statement: A multicenter retrospective study was conducted under the auspices of the Association Française de Chirurgie among their members, surgeons coming mainly from European countries. The patients' medical records were included on a website database (<http://www.chirurgie-viscerale.org>) using an online computerized standardized questionnaire.

Informed consent statement: A multicenter retrospective study was conducted under the auspices of the Association Française de Chirurgie among their members, surgeons coming mainly from European countries.

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Abstract

AIM: To analyze the impact of previous cyst-enterostomy of patients underwent congenital bile duct cysts (BDC) resection.

METHODS: A multicenter European retrospective study between 1974 and 2011 were conducted by the French Surgical Association. Only Todani subtypes I and IVb were included. Diagnostic imaging studies and operative and pathology reports underwent central revision. Patients with and without a previous history of cyst-enterostomy (CE) were compared.

RESULTS: Among 243 patients with Todani types I and IVb BDC, 16 had undergone previous CE (6.5%). Patients with a prior history of CE experienced a greater incidence of preoperative cholangitis (75% *vs* 22.9%, $P < 0.0001$), had more complicated presentations (75% *vs* 40.5%, $P = 0.007$), and were more likely to have synchronous biliary cancer (31.3% *vs* 6.2%, $P = 0.004$) than patients without a prior CE. Overall morbidity (75% *vs* 33.5%; $P < 0.0008$), severe complications (43.8% *vs* 11.9%; $P = 0.0026$) and reoperation rates (37.5% *vs* 8.8%; $P = 0.0032$) were also significantly greater in patients with previous CE, and their Mayo Risk Score, during a median follow-up of 37.5 mo (range: 4-372 mo) indicated significantly more patients with fair and poor results (46.1% *vs* 15.6%; $P = 0.0136$).

CONCLUSION: This is the large series to show that previous CE is associated with poorer short- and long-term results after Todani types I and IVb BDC resection.

Key words: Bile duct cyst; Congenital; Biliary disease; Cyst-enterostomy; Long-term outcome

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Core tip: Previous cyst-enterostomy is associated with more severe clinical presentation, including increased incidence of synchronous cancer, as well as poorer short- and long-term results in patients undergoing operations for Todani types I and IVb bile duct cysts.

Ouaissi M, Kianmanesh R, Ragot E, Belghiti J, Majno P, Nuzzo G, Dubois R, Revillon Y, Cherqui D, Azoulay D, Letoublon C, Pruvot FR, Paye F, Rat P, Boudjema K, Roux A, Mabrut JY, Gigot JF. Impact of previous cyst-enterostomy on patients' outcome following resection of bile duct cysts. *World J Gastrointest Surg* 2016; 8(6): 427-435 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/427.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.427>

INTRODUCTION

In contrast to Asian countries^[1], congenital bile duct cysts (BDC) are rare in the United States and in Europe^[2], with an incidence between 1 in 13000 and 1 in 2 million live births^[3], respectively. whereas the incidences vary from 1 in 1000 in Japan^[4], to 1 in 13500 in United States^[5] and 1 in 15000 in Australia^[6]. For this reason, there are few published series concerning the Western experience with this disease process^[7]. The optimal surgical procedure for the management of BDC is still debated with cyst-enterostomy (CE) having been preferred in the past owing to its technical simplicity^[8,9]. However, CE has been reported to be associated with increased morbidity (especially biliary complications) and higher reoperation rates during short- and long-term follow-up in comparison to primary BDC resection^[9-11]. Additionally, a few series have emphasized the negative impact of previous CE on results of secondary BDC resection^[2]. Lastly, CE has been shown to be associated with an increased risk of cholangiocarcinoma^[12,13]. Consequently, primary resection has been considered as the treatment of choice for BDC^[9,14,15]. The purpose of the present study was to investigate the role of a previous CE on short and long-term outcomes after secondary cyst resection in a large European multicenter cohort of patients.

MATERIALS AND METHODS

Study population and patients' data collection

A multicenter retrospective study was conducted under the auspices of the Association Française de Chirurgie. During a 37 years period (between 1974 and 2011), 33 centers (including 24 academic centers) from 6 different European countries have included a total of 505 patients operated from Todani type I, IVb, II, III, IVA BDC.

The patients' medical records were included on a website database (<http://www.chirurgie-viscerale.org>) using an online computerized standardized questionnaire. Patients' demographic data, previous history of surgical and/or endoscopic interventions for hepatobiliary and pancreatic (HBP) disease, clinical symptoms, biochemical and imaging studies, details of surgical procedures, pathological data, duration of follow-up and short- and long-term postoperative outcome were collected.

Table 1 Patients' demographic data, todani bile duct cyst subtypes and imaging studies

	Patient with previous CE	Patient without previous CE	Total	P value
Patients	16	227	243	-
Median age (yr) at the time of BDC resection	47.8 (26-60)	29.2 (0-81)	30.8 (0-81)	0.0074
Sex ratio F/M	7	3.73	3.8	0.5359
Adults/children	16/0	148/79	164/79	0.0041
ASA score ¹				
1 or 2	15 (93.75%)	217 (95.6%)	232 (95.0%)	0.5350
≥ 3	1 (6.3%)	10 (4.4%)	11 (4.5%)	
Types of imaging studies				
None (incidental detection)	1 (6.3%)	2 (0.9%)	3 (1.2%)	0.1855
Percutaneous ultrasound	8 (50.0%)	188 (82.8%)	196 (80.7%)	0.0042
Computed tomography	7 (43.8%)	119 (52.4%)	126 (51.9%)	0.5022
MR-cholangiography	9 (56.3%)	138 (60.8%)	147 (60.5%)	0.7194
ERCP	7 (43.8%)	40 (17.6%)	47 (19.3%)	0.0186
Endoscopic ultrasound	8 (50.0%)	36 (15.9%)	44 (18.1%)	0.0026
Percutaneous cholangiography	0	17 (7.5%)	17 (7.0%)	0.6115
Intravenous cholangiography	2 (12.5%)	13 (5.7%)	15 (6.2%)	0.2583
Intraoperative cholangiography	0	6 (2.6%)	6 (2.5%)	1.0000
Todani bile duct cyst types				
Type I	16	221	237	
Type IVB	0	6	6	1.0000
MBC adequately analyzed	12 (75%)	196 (86%)	208 (85.5%)	
Cyst involvement of MBC	5/12 (41.6%)	47/196 (24.0%)	52 (21.4%)	0.3173
MBC-1	3	39	42	
MBC-2	2	8	10	0.2420
Presence of PBM adequately explored	10	180	190	
Presence of anomalous PBM	8 (80.0%)	141 (78.3%)	149 (78.4%)	1.0000

¹The American Society of Anesthesiology physical status score; CE: Cyst-enterostomy; ERCP: Endoscopic retrograde cholangio-pancreatography; PBM: Pancreato-biliary malunion; MBC: Main biliary confluence.

Additional data were obtained from e-mail exchanges or phone calls with the referral centers. Operative reports, pathology reports and imaging studies were systematically reviewed by the 3 senior authors (Jean-Yves Mabrut, Reza Kianmanesh and Jean François Gigot) in order to establish homogeneous disease classifications. Patients' operative risk was evaluated by using the American Society of Anesthesiology physical status score (ASA)^[16]. A pediatric patient was defined as under 15 years of age.

Complicated clinical presentation was defined by the presence of severe episodes of cholangitis or pancreatitis, portal hypertension, biliary peritonitis or

coexistent synchronous carcinoma. Disease involvement of the main biliary confluence (MBC) was also classified according to the classification reported by two of the co-authors^[17]. Postoperative morbidity and mortality were defined at 3 mo or during hospital stay. Postoperative morbidity was graded according to Dindo-Clavien' classification^[18]. Long-term outcome was evaluated according to the dedicated evaluation score reported by the Mayo Clinic^[2]. Complete cyst excision was defined as without macroscopic dilatation of bile duct after resection.

BDC subtypes were defined based on imaging studies in accordance with the Todani classification^[14]. Todani BDC subtypes included type I in 47.3% ($n = 239$), type II in 3.7% ($n = 19$), type III in 2.5% ($n = 13$), type IVa in 14.4% ($n = 73$), type IVb in 1.2% ($n = 6$) and type V in 30.7% ($n = 155$). Only patient with isolated, extrahepatic BDC disease (Type I and IVb) were included ($n = 245$). Two additional patients that did not undergo resection were excluded and thus 243 were ultimately analyzed.

A pediatric patient was defined as being aged under 15 years of age. Patients' operative risk was evaluated by using the ASA^[16]. Complicated clinical presentation was defined by the presence of severe episodes of cholangitis or pancreatitis, portal hypertension, biliary peritonitis or coexistent synchronous carcinoma. Disease involvement of the MBC was also classified according to the classification reported by two of the co-authors^[17]. Postoperative morbidity and mortality were defined at 3 mo or during hospital stay. Postoperative morbidity was graded according to Dindo-Clavien' classification^[18]. Long-term outcome was evaluated according to the dedicated evaluation score reported by the Mayo Clinic^[2].

Statistical analysis

Comparisons between patient with and without CE were performed using the χ^2 test (or the Fisher's exact test when conditions for the χ^2 test were not fulfilled) for categorical variables and using the Student t test (or the Mann-Whitney nonparametric rank sum test in case of non-normality) for continuous variables. Predictive factors of poor or fair result during long-term follow-up were analyzed by multivariate statistical analysis. Significant variables at the 0.15 level in univariate analysis were introduced in the multivariate logistic regression model. Kaplan-Meier analysis was used to predict the postoperative survival rate at 1 year and at 3 years. The log-rank test was used to compare subgroups of patients at 1 year and at 3 years. Statistical analysis was performed using SAS[®] version 9.2 (SAS Institute Inc, Cary, North Carolina, United States).

RESULTS

Patients were stratified based on a history of a previous CE. Demographic data, Todani BDC subtypes, types

Table 2 Patients' clinical presentation

	Patients with previous CE <i>n</i> = 16	Patients without previous CE <i>n</i> = 227	Total <i>n</i> = 243	<i>P</i> value
Median delay between symptoms and diagnosis (mo) (range)	2 (0-486)	2 (0-360)	2 (0-486)	0.8848
Type of symptoms and signs				
Asymptomatic	2 (12.5%)	31 (13.7%)	33 (13.6%)	1.0000
Isolated pain	2 (12.5%)	104 (45.8%)	106 (43.6%)	0.0094
Cholangitis	12 (75%)	52 (22.9%)	64 (26.3%)	< 0.0001
Pancreatitis	2 (12.5%)	49 (21.6%)	51 (21.0%)	0.5344
Abdominal mass	2 (12.5%)	22 (9.7%)	24 (9.9%)	0.6631
Jaundice ¹	6 (37.5%)	59 (26.0%)	65 (27.2%)	0.3843
Pruritus	1 (6.2%)	2 (0.9%)	3 (1.2%)	0.1855
Weight loss	2 (12.5%)	6 (2.6%)	8 (3.2%)	0.0903
Complicated presentation	12 (75%)	92 (40.5%)	104 (42.8%)	0.0071
Number of patients with > 2 symptoms	9 (56.25%)	92 (40.5%)	102 (42.0%)	0.2942

CE: Cyst-enterostomy; ¹without fever.

Table 3 Coexistent hepato-biliary and pancreatic diseases

	Patients with previous CE <i>n</i> = 16	Patients without previous CE <i>n</i> = 227	Total <i>n</i> = 243	<i>P</i> value
Biliary disease	9 (56.2%)	52 (22.9%)	61 (25.1%)	0.0059
Common biliary atresia	0	1 (0.4%)	1 (0.4%)	1.0000
Stones	4 (25%)	37 (16.3%)	41 (16.9%)	0.3216
Gallbladder	0	16 (7.0%)	16 (6.6%)	-
Cyst	3 (18.8%)	9 (4.0%)	12 (4.9%)	-
Common bile duct	1 (6.3%)	22 (9.7%)	23 (9.5%)	-
Intra hepatic duct	0	4 (1.8%)	4 (1.6%)	-
Synchronous cancer	5 (31.3%)	14 (6.2%)	19 (7.8%)	0.0043

CE: Cyst-enterostomy.

of imaging studies (Table 1), clinical presentations (Table 2), coexistent HBP diseases (Table 3), types of surgical procedures (Table 4), and short- and long-term postoperative outcomes (Table 5) were then compared between the two cohorts. Finally, predictive variables of poor/fair long-term outcome are reported in Table 6.

Patients' demographic data, todani BDC subtypes and types of imaging studies

During a 37-year period (1974-2011), 243 patients underwent resections for Todani types I and IVb congenital BDC at 33 centers (including 24 academic centers). The patients' gender ratio was largely female (193/50, *i.e.*, 3.86%). Median age was 30.8 years old (range: 0.1-81 years) and 79 patients were classified at pediatric. Patients' characteristics are detailed in Table 1. Sixteen patients had undergone previous CE (16/243, *i.e.*, 6.58%), they were all adults (100% vs

Table 4 Preoperative treatment and types of surgery

	Patients with previous CE <i>n</i> = 16	Patients without previous CE <i>n</i> = 227	Total <i>n</i> = 243	<i>P</i> value
Preoperative biliary drainage	2 (12.5%)	14 (6.2%)	16 (6.6%)	0.2842
Types of surgical procedures				
Absence of resection	1 (6.3%)	5 (2.2%)	6 (2.5%)	0.3384
Elective surgery	14 (87.5%)	214 (94.3%)	228 (93.8%)	0.2583
Emergency surgery	1 (6.2%)	9 (4.0%)	10 (4.1%)	0.5007
Complete cyst excision	13 (81.2%)	199 (87.6%)	212 (87.2%)	0.6631
Incomplete cyst excision	2 (12.5%)	23 (10.1%)	25 (10.3%)	-
Superior excision	1 (6.3%)	13 (5.7%)	14 (5.8%)	-
Inferior excision	1 (6.3%)	9 (4.0%)	10 (4.1%)	-
Unknown	0	1 (0.4%)	1 (0.4%)	-
Associated procedures				
Hepatectomy	2 (12.5%)	4 (1.8%)	6 (2.5%)	0.0523
Pancreaticoduodenectomy	4 (25.0%)	4 (1.8%)	8 (3.3%)	0.0008
Stone extraction	2 (12.5%)	10 (4.4%)	12 (4.9%)	0.2072
Synchronous cancer excision	5 (31.3%)	13 (5.7%) ¹	18 (7.8%)	0.0043
Biliary reconstruction				
Hepatico-jejunostomy	13 (81.2%)	208 (91.6%)	221 (90.9%)	0.1658
Hepatico-duodenostomy	2 (12.5%)	7 (3.1%)	9 (3.7%)	0.1116
Choledoco-duodenostomy	0	1 (0.4%)	1 (0.4%)	1.0000
MBC anastomosis	8/14 (57.1%)	96/180 (53.3%)	104/194 (53.6%)	0.7831

CE: Cyst-enterostomy; MBC: Main biliary convergence; ¹secondary central hepatectomy was performed after good response of chemotherapy.

65.2%; *P* = 0.0041) and significantly older (47.8-year-old vs 29.2-year-old; *P* = 0.0074) than those without a history of CE. Imaging studies used for the diagnosis of BDC were different between the 2 groups: Patients without previous history of CE were offered more non-invasive studies, whereas those patients with previous CE had been submitted to significantly more endoscopic techniques. There was no difference concerning the BDC sub-types, the MBC involvement and the presence of an anomalous pancreato-biliary malunion (PBM) (Table 1).

Clinical presentation

The median delay between the disease's first symptoms and the diagnosis of BDC was 2 mo (0-486) and was similar between the 2 groups of patients. Abdominal pain was the most common presenting symptom (43.6%) for the whole population and significantly more frequent in patients without previous CE (12.5% vs 45.8%; *P* = 0.009). The group of patients with previous CE was observed to have a significantly increased prevalence of cholangitis (75.0% vs 22.9%; *P* < 0.0001) and complicated presentation (75.0% vs 40.5%; *P* = 0.007) (Table 2).

Coexistent HBP diseases

Coexistent biliary disease (liver disease, pancreatic disease, and biliary disease) occurred in 25.1% of the present cohort and was significantly more frequent in

Table 5 Early postoperative and long term outcome of patients

	Patients with previous CE <i>n</i> = 16	Patients without previous CE <i>n</i> = 227	Total <i>n</i> = 243	<i>P</i> value
Median postoperative hospital stay (d) (range)	16 (9-110)	10 (2-150)	10 (2-150)	0.0014
Mortality rate	0 (0.0%)	1 (0.4%)	1 (0.4%)	1.0000
Overall complications	12 (75.0%)	75 (33%)	87 (35.8%)	0.0018
Grade I-II	5 (31.3%)	47 (20.9%)	52 (21.4%)	0.3454
Grade III-IV	7 (43.8%)	28 (12.3%)	35 (15.4%)	0.0031
Surgical complications	7 (43.8%)	45 (19.8%)	52 (21.4%)	0.0509
Biliary	0 (0.0%)	20 (8.8%)	20 (8.2%)	0.3750
Mixed pancreatic and biliary fistula	1 (6.3%)	5 (2.2%)	6 (2.5%)	0.3384
Pancreatic	1 (6.3%)	17 (7.5%)	18 (7.4%)	1.0000
Bleeding	5 (31.3%)	3 (1.3%)	8 (3.3%)	< 0.0001
Reoperation rate	6 (37.5%)	20 (8.8%)	26 (10.7%)	0.0032
Long-term outcome of patients				
	Patients with previous CE <i>n</i> = 13	Patients without previous CE <i>n</i> = 185	<i>n</i> = 198	
Median follow-up (mo) (range)	59 (12-175)	36 (4-372)	37.5 (4-372)	0.2482
Mayo clinic score				
Excellent	5 (38.5%)	138 (74.6%)	143 (72.2%)	
Good	2 (15.4%)	18 (9.7%)	20 (10.1%)	0.0099
Fair	0	5 (2.7%)	5 (2.5%)	
Poor	6 (46.2%)	24 (13.0%)	30 (15.1%)	
Mayo clinic score				
Excellent + good	7 (53.8%)	156 (84.3%)	163 (82.3%)	0.0136
Fair + poor	6 (46.2%)	29 (15.7%)	35 (17.7%)	

CE: Cyst-enterostomy.

patients with previous CE (56.2% vs 22.9%; *P* = 0.006). The occurrence of associated calculus disease (16.9%) was similar between the two groups. Synchronous biliary cancer occurred in 7.8% of the total cohort and was significantly more frequent in patients with previous CE (31.3% vs 6.2%; *P* = 0.004) (Table 3).

Preoperative treatment and type of surgery

Preoperative biliary drainage was performed in 6.6% of the whole cohort. All patients underwent surgical exploration. However, 5 adult patients without CE did not undergo BDC resection, one for no specified reason, the others respectively for locally advanced gallbladder cancer, peritoneal carcinomatosis, severe inflammation of the hepatic pedicle, performance of simple cholecystectomy. Only one patient with previous CE had severe hepatic pedicle inflammation prohibiting cyst resection. Associated bile duct stone extraction rates were similar between the two subgroups. Complete cyst excision was accomplished in 93.8% of all patients and there was no significant difference between the two groups of patients. Associated hepatectomy was more frequently performed in patients with previous CE but

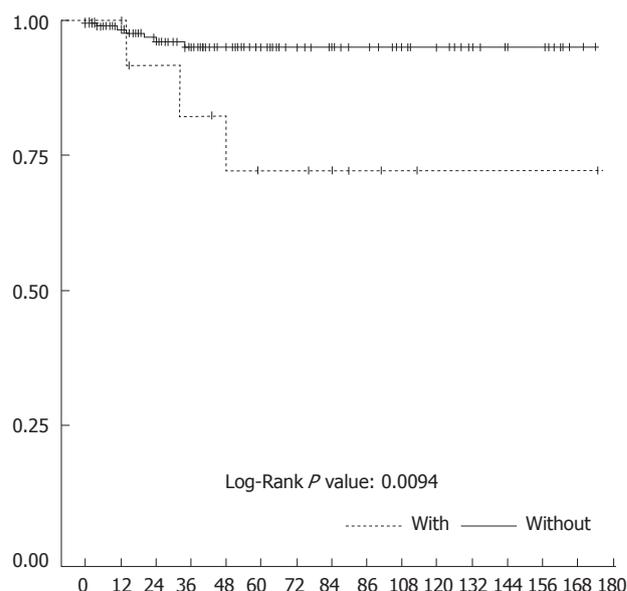


Figure 1 Comparison of overall survival between patients operated from bile duct cysts with and without previous history of cyst-enterostomy.

the difference was not significant (12.5% vs 1.8%; *P* = 0.0523). Associated pancreaticoduodenectomy was significantly more frequent in patients with previous CE (25% vs 1.8%; *P* = 0.008) (Table 4).

Postoperative mortality, morbidity and early postoperative outcome (within 3 mo)

Postoperative death due to cardiac arrhythmia, occurred in 1 patient (0.4%). Overall morbidity and severe complications rates were 36.2% and 14%, respectively. Patients with previous CE had significantly higher morbidity rates (75.0% vs 33.5%; *P* < 0.0008), more severe complications (Grade III-IV) (43.8% vs 11.9%; *P* = 0.003), more hemorrhagic complications (31.3% vs 1.3%; *P* < 0.0001), a greater reoperation rate (37.5% vs 8.8%; *P* = 0.003) and a longer median length of stay (16 vs 10 d; *P* < 0.001) than those without previous CE (Table 5).

Postoperative long-term outcome

A total of 44 patients were lost for follow-up at 3 mo, only 3 of whom belonged to the subgroup of patients with previous CE. The median follow-up in the 198 remaining patients was 37.5 mo (range: 4 to 732 mo) for the whole cohort, without any difference between both subgroups. According to the dedicated Mayo Clinic Risk score evaluating long-term results, there were significantly more patients with fair and poor results in the subgroup of patients with previous CE (*P* = 0.001). The overall 3-year survival rate was significantly lower in patients with prior CE (82.5% vs 95.9%; *P* = 0.01) (Figure 1) (Table 5).

Univariate and multivariate analysis

Predictive variables of poor and fair long-term results (according to the Mayo Clinic clinical score) were

Table 6 Predictive factors of poor and fair long-term outcome according to Mayo clinic score in 198 patients with a follow-up > 3 mo, including patients suffering from synchronous cancer

Covariate	Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value
Adult patient <i>vs</i> child	3.587	1.322-9.735	0.0084	-	-	-
Previous cyst-enterostomy; Yes <i>vs</i> No	4.611	1.445-14.712	0.0136	3.165	0.829-12.077	0.0918
Synchronous cancer; Yes <i>vs</i> No	18.462	4.687-72.71	< 0.0001	16.612	3.999-69.013	0.0001
Post-operative complications; Yes <i>vs</i> No	2.397	1.143-5.028	0.0186	-	-	-
Postoperative biliary complications; Yes <i>vs</i> No	4.356	1.669-11.367	0.0038	4.597	1.635-12.925	0.0038

OR: Odds ratio.

evaluated in the 198 patients surviving surgery and with a follow-up over 3 mo. Univariate statistical analysis indicated that predictive variables of poor or fair long-term results were to be an adult patient, with prior CE, postoperative complications, postoperative biliary complications and coexistent synchronous cancer. By multivariate analysis, predictive variables of poor or fair long-term results were previous CE, synchronous cancer and postoperative biliary complications (Table 6).

DISCUSSION

The present retrospective series shows that patients submitted to secondary resection of congenital BDC following a previous cyst-enterostomy suffered more complications before, during and after surgery with poorer results during long-term follow-up. Strengths of the present series include the relatively large cohort of patients issued from a multicentric European series, and the central revision of radiological, operative and pathological data, thereby ensuring a homogeneous classification of patients and their symptoms and signs both prior and after surgery, with the use of a dedicated clinical score for long-term results. Furthermore, the analysis was performed in a homogeneous group of BDC with only extrahepatic biliary involvement, namely patients suffering from Todani types I and IVb BDC. Indeed, patients with Todani type IVA were excluded from the present series so that poor results could not be due to residual non-resected intrahepatic biliary disease.

According to the results of the present study, primary complete excision of BDC, with the construction of a wide bilio-digestive anastomosis to a healthy proximal bile duct should be the "gold standard" surgical management of patients suffering from BDC^[2,14,19]. Cyst-enterostomy must definitively be abandoned as a treatment option. Limitations of the study include its retrospective design, its long period (37 years) of patients inclusion and the number of patients without available long-term follow-up. The comparison between patients with previous cyst-enterostomy and the control group should also be considered with caution due to the small number of patients in the CE group.

However, despite cyst-enterostomy being no longer the primary approach for the surgical management of BDC, its prevalence was 17.2% in 186 patients operated

on after 1980^[2,7,20-22] and previous cyst-enterostomy was still observed in 7.3% of 354 patients operated on after 1990^[23-26]. Practically, this means that previous CE still remains a challenge during the management of BDC.

Indeed, the consequences of having undergone a cyst-enterostomy, regardless of the technique used, easily explain the more complicated clinical presentation of previously operated patients encountered in the present series: Possible mechanisms include reflux of digestive juice through the entire biliary tract, activation of pancreatic juice by enterokinases linked to pancreatico-biliary malunion^[27] or even anastomotic stricture of the CE on diseased cystic biliary tissue^[19,28,29]. Any of these can lead to severe biliary inflammation^[15], cholangitis, hepatolithiasis^[10,19,30,31] and increase the risk of carcinogenesis^[12,13,19,27]. The latter is estimated to be over 50% by Todani *et al.*^[27]. Indeed, malignant degeneration of BDC occurs more than 15 years earlier in patients with previous CE than in patients with primary carcinomas, with a median delay of 4 years in a series by Flanigan *et al.*^[13] to 10 years (range: 1-53 years of delay) in yet another by Todani *et al.*^[27] and, overall, is associated with a very poor prognosis. Finally, the reoperation rate after previous CE is high, ranging from 15.7% to 87.5%^[1,9,30,32].

The present series also shows that more complex surgical procedures had to be used for patients with a previous CE, mainly due to an increased need for a pancreaticoduodenectomy. Such an extensive procedure was linked, for half of these patients, with the presence of coexistent carcinoma, thereby, requiring tumor resection with a wide tumor-free margin. The other pancreaticoduodenectomies were mainly performed because of severe inflammation within the hepatic pedicle, probably as a result of repeated episodes of cholangitis. This feature observed during secondary BDC resection in patients with previous CE has not been reported until now.

According to several surgical series which compared primary CE with primary BDC resection with Roux-en-Y hepaticojejunostomy have reported an increased mortality rate (range: 8.3%-10% *vs* 0%-7%), morbidity rate (range: 17%-93% *vs* 0%-17%) and reoperation rate (range: 29.7%-87.5% *vs* 0%) in patients with primary CE^[9,10,30]. At the time of writing, there are only

3 studies that compared the morbidity and mortality rates between primary BDC resection and secondary BDC resection with previous CE, and these concerned series with only small numbers of patients^[2,15,19]. For patients with previous CE, Chijiwa *et al.*^[19] and Gigot *et al.*^[2] observed significantly more early postoperative complications, whilst Kaneko *et al.*^[15] reported significantly increased operative blood losses, operative time, early postoperative complications and wound infections. The present series demonstrates similar findings of an increased rate of overall and severe postoperative complications as well as hemorrhagic complications and reoperation rates for patients operated following previous CE.

The key-messages of this first large European multicenter study are that BDC patients who have undergone previous CE have more complications including carcinoma, that long-term results and survival rate are worse and that the reoperation rate is greater. It should be emphasized that these results cannot be attributed to intrahepatic disease alone as only Todani type I and IVb lesions were studied in this analysis. Late complications were also increased in the series reported by Kaneko *et al.*^[15], especially regarding late development of hepatolithiasis and pancreatic stones, though this was not reported in the series by Chijiwa *et al.*^[19]. Finally, multivariate statistical analysis confirmed in the present series that previous CE was representing an independent predictive factor of fair or poor prognosis after secondary BDC resection. Weaknesses of the present study include its retrospective nature, the number of patients excluded from long-term follow-up after 3 mo (18.1% of the whole series), the limited median follow-up duration of 37.5 mo and the small numbers of patients with previous CE.

In conclusion, this European retrospective series showed that previous CE was associated with a more complicated presentation, more coexistent HPB diseases including synchronous cancer, more complex surgery and worse early and long-term postoperative outcomes. These features confirmed the abandonment of cyst-enterostomy for the surgical management of congenital bile duct cysts.

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COMMENTS

Background

Congenital bile duct cysts (BDC) are rare in the United States and in Europe. Cyst-enterostomy has been reported to be associated with increased morbidity (especially biliary complications) and higher reoperation rates during short- and

long-term follow-up in comparison to primary BDC resection. Consequently, primary resection has been considered as the treatment of choice for BDC. The purpose of the present study was to investigate the role of a previous cyst-enterostomy (CE) on short and long-term outcomes after secondary cyst resection in a large European multicenter cohort of patients.

Research frontiers

Limitation of the study includes its retrospective design, its long period (37 years), included patients and the number of patients without available long-term follow-up. The comparison between patients with previous cyst-enterostomy and the control group should also be considered with caution due to the small number of patients in the CE group. However, despite cyst-enterostomy being no longer the primary approach for the surgical management of BDC, its prevalence was 17.2% in 186 patients operated on after 1980 and previous cyst-enterostomy was still observed in 7.3% of 354 patients operated on after 1990. Practically, this means that previous CE still remains a challenge during the management of BDC.

Innovations and breakthroughs

This European retrospective series showed that previous CE was associated with a more complicated presentation, more coexistent HPB diseases including synchronous cancer, more complex surgery and worse early and long-term postoperative outcomes. These features confirmed the abandonment of cyst-enterostomy for the surgical management of congenital bile duct cysts.

Applications

These features confirmed the abandonment of cyst-enterostomy for the surgical management of congenital bile duct cysts.

Peer-review

The results of this European multicenter study are very interesting and the manuscript is well-written.

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Retrospective Study

Predictors of long term survival after hepatic resection for hilar cholangiocarcinoma: A retrospective study of 5-year survivors

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Abstract

AIM: To determine predictors of long term survival after resection of hilar cholangiocarcinoma (HC) by comparing patients surviving > 5 years with those who survived < 5 years.

METHODS: This is a retrospective study of patients with pathologically proven HC who underwent surgical resection at the Gastroenterology Surgical Center, Mansoura University, Egypt between January 2002 and April 2013. All data of the patients were collected from the medical records. Patients were divided into two groups according to their survival: Patients surviving less than 5 years and those who survived > 5 years.

RESULTS: There were 34 (14%) long term survivors (5 year survivors) among the 243 patients. Five-year survivors were younger at diagnosis than those surviving less than 5 years (mean age, 50.47 ± 4.45 vs 54.59 ± 4.98 , $P = 0.001$). Gender, clinical presentation, preoperative drainage, preoperative serum bilirubin, albumin and serum glutamic-pyruvic transaminase were similar between the two groups. The level of CA 19-9 was significantly higher in patients surviving < 5 years (395.71 ± 31.43 vs 254.06 ± 42.19 , $P = 0.0001$). Univariate analysis demonstrated nine variables to be significantly associated with survival > 5 year, including

young age ($P = 0.001$), serum CA19-9 ($P = 0.0001$), non-cirrhotic liver ($P = 0.02$), major hepatic resection ($P = 0.001$), caudate lobe resection ($P = 0.006$), well differentiated tumour ($P = 0.03$), lymph node status (0.008), R0 resection margin ($P = 0.0001$) and early postoperative liver cell failure ($P = 0.02$).

CONCLUSION: Liver status, resection of caudate lobe, lymph node status, R0 resection and CA19-9 were demonstrated to be independent risk factors for long term survival.

Key words: Hilar cholangiocarcinoma; Hepatic resection; Caudate lobe resection; CA19-9; Liver cell failure

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Core tip: Hilar cholangiocarcinoma is an uncommon malignancy with a relatively poor prognosis. Surgery remains the only line of treatment offering the possibility of cure. The central location of the tumor and its close relationship to vascular structures at the hepatic hilum have resulted in a low resectability rate. Five year survivors were younger at diagnosis than those surviving less than 5 years. Major hepatic resection and caudate lobe resection achieved better R0 resection rate. Liver status, resection of caudate lobe, lymph node status, R0 resection and CA19-9 were demonstrated to be independent risk factors for long term survival.

Abd ElWahab M, El Nakeeb A, El Hanafy E, Sultan AM, Elghawalby A, Askr W, Ali M, Abd El Gawad M, Salah T. Predictors of long term survival after hepatic resection for hilar cholangiocarcinoma: A retrospective study of 5-year survivors. *World J Gastrointest Surg* 2016; 8(6): 436-443 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/436.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.436>

INTRODUCTION

Hilar cholangiocarcinoma (HC) is the most common type of biliary tract malignancy, arising at the confluence of the right and left hepatic ducts, and comprises 40% to 60% of all cholangiocarcinomas^[1-3]. It is a complex and aggressive disease with a poor prognosis^[2-6]. The resectability rate varies from 25% to 58% of patients who are surgically explored due to locally advanced tumour or liver metastasis. The central location of the tumor and its close relationship to vascular structures at the hepatic hilum have resulted in a low resectability rate and high morbidity and mortality^[3-7].

Although the results of surgical treatment for HC were dismal, recent studies have reported improved outcomes using aggressive surgical approaches: Postoperative morbidity generally ranges from 30% to 50% and mortality is 10% or less^[5-10]. However,

the actual 5-year survival after radical resection of HC ranges from 10% to 28 % with the majority of studies reporting 20% or higher. The median survival after curative resection is about 19 to 35 mo^[10-13].

Few studies of HC have long enough followed patients to report a survival beyond 5 years^[7-10]. It has long been recognized that radical resection offers the only hope for cure and improves long term survival. Many studies have confirmed that hepatic resection combined with caudate lobe resection can achieve high rates of margin-free resection (R0) and significantly improve the overall survival^[4-6,11-15].

The aim of this study was to determine variables that are predictors of long term survival after resection of HC by comparing patients surviving 5 years after resection of HC with those who survived less than 5 years.

MATERIALS AND METHODS

This is a retrospective study of patients with pathologically proven HC who underwent surgical resection at the Gastroenterology Surgical Center, Mansoura University, Egypt between January 2002 and April 2013. Data were collected from the patient records in April 2015. Follow-up was held regularly at the outpatient clinic. The patients were treated in accordance with the center policy, with patients with liver metastasis, lymph node metastasis far beyond regional lymph nodes, and local invasion of the major vessels of the contralateral site considered to have an unresectable tumour.

Informed consent was obtained from all patients after a careful explanation of the nature of the disease and possible treatment with its complications. The study was approved by the Institution Review Board.

Patients were divided into two groups according to their survival: Patients who survived < 5 years and those surviving > 5 years.

Preoperative assessment

All patients underwent full laboratory investigations, abdominal contrast enhanced CT and/or magnetic resonance cholangiopancreatography. Upper gastrointestinal tract endoscopy was performed routinely to exclude esophageal and fundic varices. Preoperative biliary drainage (PBD) was done by endoscopic retrograde cholangiopancreatography or by ultrasound (US) guided percutaneous transhepatic drainage to improve the general condition of the patients before surgery especially if there was cholangitis. The state of the liver and the extent of cirrhosis were assessed by the modified Child-Turcotte-Pugh classification^[16].

Surgical procedure

Exploration was done through a bilateral subcostal incision with midline extension of the incision in some cases. Evaluation of the tumour, liver condition and the extent of lymphatic spread were done at first.

The choice of surgical procedure depended on tumour extension and the general condition of patients. The tumours extension was classified according to the Bismuth-Corlette classification system^[17]. All hepatobiliary resections were performed with the intent of achieving free safety margin (R0). Proximal and distal margins were assessed on frozen sections during the operation in some cases. If safety margin was proved to be positive, addition hepatobiliary resection was done as far as technically feasible until R0 was obtained if possible.

All cases underwent extrahepatic biliary resection and lymphadenectomy of locoregional lymph nodes starting from the celiac trunk up to the hilum *en bloc* with the mass. Hepatic resection was variable from minor resection, which included three or less segments to major resection, which included four or more segments according to Couinaud nomenclature. Hepatic resection was done using a harmonic scalpel with or without Pringle's maneuver to control bleeding. Biliary anastomosis was done by hepaticojejunostomy with or without stenting.

Localized resection (minimal central hepatectomy segment 4) was performed in patients with type I HC without any evidence of hepatic infiltration, lymph node metastases, cirrhotic liver, or poor general condition. Hemihepatectomy was selected in cases of single lobe atrophy, invasion of the portal or hepatic branches or extension of the tumor up to the parenchyma of that lobe. Caudate lobe resection was also done in the majority of cases within the last five years.

Postoperative management

After surgery, patients were admitted to the intensive care unit in the early postoperative days to receive the usual postoperative care by the same surgical team.

Liver function tests were performed in the postoperative period regularly on the first, third day and on the day of discharge. Abdominal ultrasonography was done routinely in all patients and repeated when there were complications. Tube drainage was carried out in cases of any significant abdominal collections.

All pathological reports were reviewed to determine the extent of the tumour, differentiation, lymph node infiltration and positive resection margin. R0 resection was defined as cases in which no gross or microscopic tumour residue was left behind, R1 resections had microscopically positive margins and R2 resections still contained some gross tumor matter^[18]. Hospital mortality was defined as death during the first 30 postoperative days.

Follow-up

Follow-up was done in the outpatient clinic at 1 mo, 6 mo, and then every year. Clinical examinations, routine laboratory investigations (complete liver function, complete blood picture and tumour markers CEA and CA 19-9), abdominal sonography and CT scans were

done at each visit.

Data collection

Preoperative clinical data, intraoperative and postoperative data were collected. Postoperative complications, survival rates and recurrence rates were recorded.

Statistical analysis

Statistical analyses of the data in this study were performed with SPSS software, version 17 (Chicago, IL, United States). Descriptive data are expressed as the mean with standard deviation. Categorical variables are described using frequency distributions. Independent sample *t* test was used to detect differences in the means of continuous variables and χ^2 test was used in cases with low expected frequencies. *P* values < 0.05 were considered significant. Variables with *P* < 0.05 were entered into the Cox regression model to determine independent factors for 5-year survival. The independent factors are expressed as odds ratios (ORs) with their 95% CIs. Survival curves were done using Kaplan-Meier method and differences in survival curves were compared by a Cox-regression analysis.

RESULTS

Between January 2002 and April 2013, surgical interventions with curative intent were performed on 278 patients who had HC. Eventually, 243 patients underwent hepatobiliary resection and 35 did not undergo any resection because of advanced disease (liver metastasis in 11 cases and local vascular infiltration in 24 cases). Of these, 34 (14%) patients were long term survivors (> 5 years) and 209 (86%) were short term survivors (< 5 years). In this study, the 1, 3 and 5 year survival rates were 53%, 35% and 22%, respectively, and the median survival was 24 mo.

Five-year survivors were younger at diagnosis than those surviving less than 5 years (mean age, 50.47 ± 4.45 vs 54.59 ± 4.98, *P* = 0.001). Gender, clinical presentation, preoperative drainage, preoperative serum bilirubin, albumin and serum glutamic-pyruvic transaminase were similar between the two groups. The level of CA19-9 was significantly higher in patients surviving < 5 years (395.71 ± 31.43 vs 254.06 ± 42.19, *P* = 0.0001) (Table 1).

Intraoperative data are shown in Table 2. Major hepatectomy, including right or left hepatectomy, was carried out in 173 (71.19%) of 243 patients besides 70 (28.8%) patients who underwent localized resection. The extent of hepatic resection had a significant impact on the survival rate. Major hepatobiliary resection was performed in 30 (88.23%) patients surviving > 5 years and in 143 (68.42%) surviving < 5 years. Segment 1 resection was done in 23 (67.64%) patients surviving > 5 years and it represented a significant factor for long term survival (*P* = 0.006). Liver status showed a

Table 1 Baseline characteristics *n* (%)

	< 5-yr survival (<i>n</i> = 209)	> 5-yr survival (<i>n</i> = 34)	<i>P</i> value
Age	54.59 ± 4.98	50.47 ± 4.45	0.001
Sex			
Male	124 (59.3)	23 (67.6)	0.09
Female	85 (40.7)	11 (32.4)	
Symptoms			
Pain	73 (34.9)	12 (35.3)	0.97
Jaundice	206 (98.6)	34 (100)	0.95
Weight loss	97 (46.4)	13 (38.2)	0.349
Serum albumin	3.7 (± 0.46)	3.82 (± 0.31)	0.162
Total serum bilirubin	15.29 (± 9.74)	15.13 (± 9.41)	0.928
Serum alkaline phosphatase	29.92 (± 41.62)	38.74 (± 24.12)	0.231
SGPT	97.33 (± 112.84)	89.18 (± 52.74)	0.68
CA19-9	395.71 ± 31.43	254.06 ± 42.19	< 0.0001
HCV	86 (41.1)	10 (29.4)	0.18
Preoperative biliary drainage	90 (43.06)	18 (52.9)	0.38
No preoperative biliary drainage	119 (66.94)	16 (47.1)	
ERCP	25 (11.96)	9 (26.5)	0.025
PTD	65 (31.1)	9 (26.5)	0.564

HCV: Hepatitis C virus; ERCP: Endoscopic retrograde cholangiopancreatography; SGPT: Serum glutamic-pyruvic transaminase; PTD: Preoperative biliary drainage.

Table 2 Operative data *n* (%)

	< 5-yr survival	> 5-yr survival	<i>P</i> value
Liver status			0.02
Cirrhotic (<i>n</i> = 102)	97 (46.41)	5 (14.7)	
Non-cirrhotic (<i>n</i> = 141)	112 (53.58)	29 (85.29)	
Bismuth corlette classification			0.68
Types I and II	63 (30.14)	11 (32.35)	
Type III	146 (69.85)	23 (67.64)	
Type IV	0	0	
Extent of hepatic resection			
Type of resection			0.001
Localized resection (<i>n</i> = 70)	66 (31.57)	4 (11.76)	
Major resection (<i>n</i> = 173)	143 (68.42)	30 (88.23)	
Type of major resection			0.07
Lt hepatectomy (<i>n</i> = 102)	81 (38.75)	21 (61.76)	
Rt hepatectomy (<i>n</i> = 71)	62 (29.66)	9 (26.47)	
Segment 1 resection	79 (37.79)	23 (67.64)	0.006
Number of anastomosis			0.85
Single	86 (41.14)	18 (52.9)	
Multiple	123 (58.85)	16 (47.1)	
Blood transfusion			0.91
< 3 units	149 (71.3)	24 (70.58)	
≥ 3 units	60 (28.7)	10 (29.41)	
Operative time	4.28	4.28	0.75

significant difference in both groups. Five-year survivors had a less cirrhotic liver than those surviving less than 5 years (*P* = 0.02).

The postoperative data are shown in Table 3. Five-year survivors had well differentiated tumors than those surviving less than 5 years [18 (52.4%) vs 78 (37.32%), *P* = 0.033]. In addition, 5-year survivors were less likely to have positive lymph nodes [6 (17.6%) vs 81

Table 3 Postoperative data *n* (%)

	< 5-yr survival	> 5-yr survival	<i>P</i> value
Hospital stay	13	11.78	0.33
Bile leakage	75 (35.88)	7 (20.0)	0.08
Wound infection	50 (23.9)	6 (17.6)	0.39
Early LCF	38 (18.18)	1 (2.9)	0.023
Collection	38 (18.18)	6 (17.6)	0.94
Bleeding and fistula	13 (6.2)	1 (2.9)	0.42
Lymph node metastasis	81 (41.8)	6 (17.6)	0.008
Histological grade			0.033
Well differentiated	78 (37.32)	20 (58.82)	
Moderately differentiated	83 (39.71)	11 (32.35)	
Poorly differentiated	48 (23.0)	3 (8.82)	
Safety margin			< 0.0001
R0	93 (44.5%)	28 (82.35)	
R1	116 (55.5)	6 (17.6)	
Recurrence			0.88
Hepatic recurrence	51 (24.4)	8 (23.52)	
Local recurrence	27 (12.9)	6 (17.64)	
Late LCF	51 (51.5)	8 (33.3)	0.11

LCF: Liver cell failure.

Table 4 Multivariate cox regression after resection of hilar cholangiocarcinoma

Variable	<i>P</i> value	Oddis ratio	95%CI for Exp (B)	
			Lower	Upper
Liver status	0.000	11.78	5.271	26.327
Safety margin	0.000	4.937	2.251	10.826
Type of resection	0.984	1.006	0.564	1.795
Caudate lobe resection	0.000	3.808	1.878	7.725
Lymph node status	0.000	0.08	0.029	0.217
Tumour differentiation	0.265	0.819	0.577	1.164
Age	0.055	1.04	0.999	1.084
Early LCF	0.367	1.415	0.666	3.003
CA19-9	0.000	1.01	1.005	1.015

LCF: Liver cell failure.

(41.8%), *P* < 0.008] and positive resection margin (R1) [6 (17.6%) vs 116 (56.7%), *P* = 0.0001] (Figure 1).

Hepatic recurrence occurred in 51 (24.4%) patients surviving < 5 years, 40 of them (78.4%) had R1, while hepatic recurrence occurred in 8 (23.52%) patients surviving > 5 years, 4 of them (50%) had R1.

Univariate analysis demonstrated nine variables (young age, serum CA19-9, non cirrhotic liver, major hepatic resection, resection of caudate lobe, well differentiated tumour, lymph node status, R0 resection margin and early postoperative LCF) to be significantly associated with survival > 5 years. These nine factors identified in univariate analysis were further analyzed in multivariate analysis. Liver status, resection of caudate lobe, lymph node status, R0 resection and serum CA19-9 were demonstrated to be independent risk factors for long term survival (Table 4).

DISCUSSION

Cholangiocarcinoma is an uncommon malignancy with a relatively poor prognosis, providing a major therapeutic

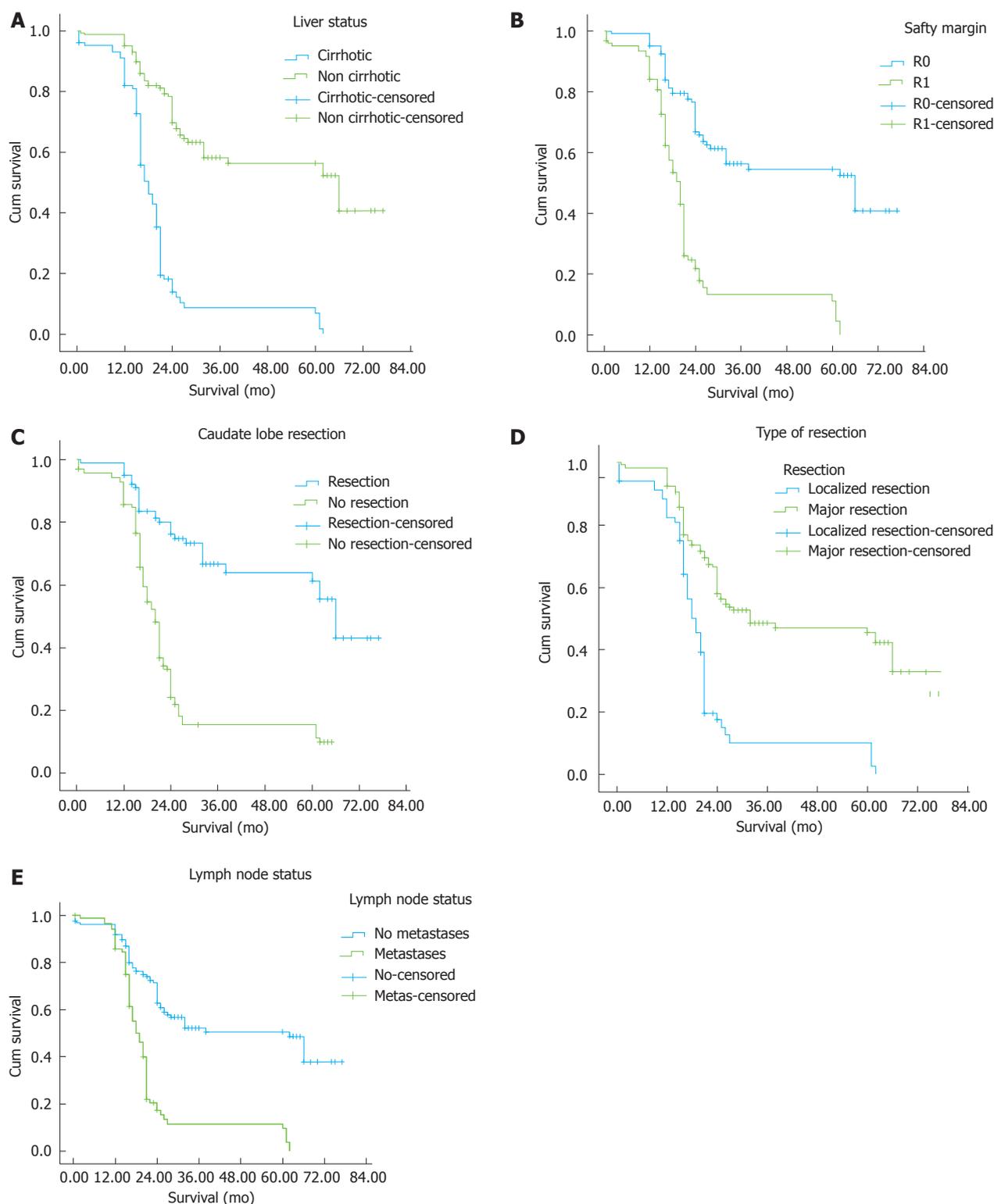


Figure 1 Actuarial survival (Kaplan Meier analysis) after resection of hilar cholangiocarcinoma. Influence of liver status (A), safety margin (B), caudate lobe resection (C), type of resection (D), and lymph node status (E).

challenge. Surgery remains the only line of treatment offering the possibility of cure, but it remains difficult because of their proximity to and possible local invasion of the portal vein, hepatic artery and the surrounding liver parenchyma and caudate lobe^[4-7,19-22]. The surgical approach for HC has changed in the last two decades

from primarily minor surgery to major hepatectomy with CBD resection and portal vein resection. Now all experienced hepatic surgeons agree to do hepatic resection with resection of the extrahepatic biliary tree when treating HC^[20-26].

The resectability rate of HC varies in different studies

from 20% to 80%. The actual 5-year survival after radical resection of HC ranges from 10 to 28% with the majority of studies reporting 20% or higher^[10-15,20-26]. In this study, the 1-, 3- and 5-year survival rates were 53%, 35% and 22%, respectively. The median survival for these cases was 24 mo. Thirty-four (14%) patients were long term survivors (> 5 years) and 209 (86%) were short term survivors (< 5 years). Five-year survivors were younger at diagnosis than those surviving less than 5 years (mean age, 50.47 ± 4.45 vs 54.59 ± 4.98, $P = 0.001$).

The role of PBD in the management of HC remains controversial. However, no evidence demonstrates that routine PBD facilitates resection, decreases postoperative morbidity or increases survival rate^[27,28]. Although PBD does not represent a significant factor affecting long term survival, it is mandatory in cases of preoperative cholangitis or bad general condition and improves the postoperative course of patients with a serum bilirubin level > 20 mg/dL^[15,26].

Curative surgery for patients with HC often necessitates hepatic resection to achieve a R0 resection and improve the long term survival because the characteristics of its growth pattern include longitudinal intraductal extension, perineural, lymphatic, and direct liver invasion^[6-9,20-26]. Major hepatic resection is considered the curative treatment for HC, but it is not always safe because postoperative liver cell failure is a common cause of death after major resection in patients with compromised liver function. However, the dilemma between major hepatic resection with potential postoperative hepatic cell failure and localized resection with potential R1 and R2 resection margins might be solved by advances in preoperative and intraoperative assessments^[15]. Recent advances in perioperative and operative techniques, instruments and care have led to a marked improvement in short and long term outcomes after major hepatic resection^[15]. Major hepatobiliary resection for HC provides R0 resection and improves survival. In this study, 88.23% of 5-year survivors underwent major hepatic resection.

As the caudate lobe is infiltrated by HC either directly due to the close anatomic relationship or by invading the biliary branches, routine caudate lobe resection should be performed for curative treatment of HC^[15,29-31]. Better R0 resection rate and long term survival have been achieved by caudate lobe resection in treating cases of HC^[15,29-34]. Nimura *et al.*^[33] found that 98% of cases of caudate lobe resection were pathologically confirmed to be tumour positive in cases of HC. However, other authors showed that the caudate lobe was infiltrated by HC in 25%-40% of cases^[15,33-35]. Segment 1 resection represents a significant factor affecting survival ($P = 0.006$) in our study. In the initial period of the study, caudate lobe resection was performed only when the caudate lobe was infiltrated, but now it is performed routinely in all cases of HC.

Safety margins after hepatic resection for cholangiocarcinoma represented a highly significant factor

affecting long term survival. Many authors have reported that negative surgical margin (R0) is an important prognostic variable. R0 resection rate in the literature varies from 14% to 80 % and overall 5-year survival rate for R0 resection from 22% to 45%^[4-7,15-17,26-30]. The frequency of R0 resection depends on the extent of hepatic resection. To obtain R0 resection, removal of the caudate lobe is required because of the high rate of infiltration (30%-39%)^[15,29-33]. In the current study five-year survivors were less likely to have a positive safety margin [6 (17.6%) vs 116 (56.7%), $P = 0.0001$]. Surgical treatment of HC with localized resection has been shown to result in early recurrence after surgery due to positive surgical margins at the hepatic edge of the bile duct with low long term survival^[4-8,15,26-30,32,36-40].

Lymph node metastasis was present in 20%-50% of cases of cholangiocarcinoma in the previous literature^[5-12,20-25,32,35-41]. When no lymph node metastasis was detected, the 5-year survival was more than 60%. In contrast, in patients with lymph node metastasis, the 5-year survival was only 21%^[25,26]. Lymph node metastasis beyond the hepatoduodenal ligament (celiac, mesenteric, or paraaortic lymph nodes) has a poor prognosis with a 5-year survival less than 12%, so it is considered a contraindication to resection.

Cirrhosis is expected to be associated with increased blood loss, need for blood transfusion and increased post-hepatectomy LCF. The treatment of HC needs careful patient selection, good perioperative assessment and care, and good decision on the extent of hepatobiliary resection. This is why to carry out the localized resection in cirrhosis and so the achievement of R0 is less in cirrhotic patients with HC^[4-7,32,38-42]. In the current study, 5-year survivors had a less cirrhotic liver than those surviving less than 5 years. This result in cirrhotic patients is attributed to more aggressive HC, localized resection without caudate lobe resection, and poor liver reserve. This can explain the worse 5-year survival in cirrhotic patients in comparison to non-cirrhotic patients^[5,30,39,42].

In conclusion, there were 34 (14%) 5-year survivors with resected HC in this study. Five-year survivors were younger at diagnosis than those surviving less than 5 years. The majority of long term survivors after resection of HC underwent major hepatic resection and caudate lobe resection. Well differentiated HC tumour, negative surgical margins and negative nodal metastasis have an impact on long term survival after hepatic resection for cholangiocarcinoma.

COMMENTS

Background

Hilar cholangiocarcinoma (HC) is an uncommon malignancy with a relatively poor prognosis. HC is the most common type of biliary tract malignancy, arising at the confluence of the right and left hepatic ducts, and comprises 40% to 60% of all cholangiocarcinomas. Surgery remains the only line of treatment offering the possibility of cure, but it remains difficult. The actual 5-year survival after radical resection of HC ranges from 10% to 28%. The median survival after curative resection is about 19 to 35 mo.

Research frontiers

Few studies of HC have long enough followed patients to report a survival beyond 5 years. It has long been recognized that radical resection offers the only hope for cure and improves long term survival. Many studies have confirmed that hepatic resection combined with caudate lobe resection can achieve high rates of margin-free resection (R0) and significantly improve the overall survival.

Innovations and breakthroughs

The surgical approach for HC has changed in the last two decades. Now all experienced hepatic surgeons agree to do hepatic resection with resection of the extrahepatic biliary tree when treating HC. Curative surgery for patients with HC often necessitates hepatic resection to achieve a R0 resection and improve the long term survival because the characteristics of its growth pattern include longitudinal intraductal extension, perineural, lymphatic and direct liver invasion.

Applications

The data in this study suggested that major hepatobiliary resection and caudate lobe resection provide R0 resection and improve survival rate for HC. As the caudate lobe is infiltrated by HC either directly due to the close anatomic relationship or by invading the biliary branches, routine caudate lobe resection should be performed for curative treatment of HC. Furthermore, this study also provided readers with important information regarding the HC treatment and variables that increase survival rate.

Terminology

HC is an uncommon malignancy with a relatively poor prognosis. HC is the most common type of biliary tract malignancy, arising at the confluence of the right and left hepatic ducts.

Peer-review

This is an interesting manuscript with a significant number of patients treating an important topic, and the aim of this study was to determine predictors of long term survival after resection of HC.

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Retrospective Study

How does epidemiological and clinicopathological features affect survival after gastrectomy for gastric cancer patients-single Egyptian center experience

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Abstract

AIM: To investigate the clinicopathological features and the significance of different prognostic factors which predict surgical overall survival in patients with gastric carcinoma.

METHODS: This retrospective study includes 80 patients diagnosed and treated at gastroenterology surgical center, Mansoura University, Egypt between February 2009 to February 2013. Prognostic factors were assessed by cox proportional hazard model.

RESULTS: There were 57 male and 23 female. The median age was 57 years (24-83). One, 3 and 5 years survival rates were 71%, 69% and 46% respectively. The median survival was 69.96 mo. During the follow-up period, 13 patients died (16%). Hospital morbidity was reported in 10 patients (12.5%). The median number of lymph nodes removed was 22 (4-41). Lymph node (LN) involvement was found in 91% of cases. After R0 resection, depth of wall invasion, LN involvement and the number (> 15) of retrieved LN, LN ratio and tumor differentiation predict survival. In multivariable analysis, tumor differentiation, curability of resection and a number of resected LN superior to 15 were found to be

independent prognostic factors.

CONCLUSION: Surgery remains the cornerstone of treatment. Tumor differentiation, curability of resection and a number of resected LN superior to 15 were found to be independent prognostic factors. Extended LN dissection does not increase the morbidity or mortality rate but markedly improves long term survival.

Key words: Cancer stomach; Prognostic factors; Lymph node metastasis; Recurrence after gastrectomy; Lymph node ratio

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Core tip: The epidemiology and the surgical outcomes for patients with carcinoma of the stomach vary significantly from one part of the world to another. Surgery remains the cornerstone of treatment. Tumor differentiation, curability of resection and a number of resected lymph node (LN) superior to 15 were found to be independent prognostic factors. Extended LN dissection does not increase the morbidity or mortality rate but markedly improves long term survival.

El Hanafy E, El Nakeeb A, Ezzat H, Hamdy E, Atif E, Kandil T, Fouad A, Wahab MA, Monier A. How does epidemiological and clinicopathological features affect survival after gastrectomy for gastric cancer patients-single Egyptian center experience. *World J Gastrointest Surg* 2016; 8(6): 444-451 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/444.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.444>

INTRODUCTION

Cancer of the stomach is the fifth most common cancer in the world and it is also the third leading cause of cancer death of both sexes worldwide^[1]. Prognosis is poor perhaps due to late diagnosis and frequent local-regional recurrences^[2]. It still one of the common health problems in Egypt. This requires investigation of the possible reasons for the worsening of survival and searching for prognostic factors of better survival.

Whenever possible, complete resection of the tumor with satisfactory safety margins is the standard treatment providing hope for cure^[3,4]. Many prognostic factors have been investigated to assess their significance in predicting patients' outcome. The number of metastatic lymph nodes (N stage) and the depth of the primary tumor (T stage) are currently considered the most reliable prognostic factors for patients with radically resected gastric cancer^[5-7]. Lymph node (LN) clearance remains the most challenging part of the operation, the extent of LNs dissection is classically termed D0, D1, and D2^[8,9]. The UICC/AJCC classification, suggests that at least 15 LNs should be examined for a correct assessment of N stage^[10,11].

Therefore, the surgeon experience toward more radical resection with LN removal is the most important non-TNM prognostic factors in gastric cancer. However, prognosis varies among patients with a similar tumor stage; therefore, disease staging alone cannot accurately predict the outcome for individual patients^[12].

The aim of this study was to evaluate the Clinicopathological features and the significance of different prognostic factors in patients undergoing resection for gastric cancer.

MATERIALS AND METHODS

This is a retrospective study of patients underwent gastrectomy for gastric cancer from February 2009 to February 2013, in gastroenterology surgical center, Mansoura University, Egypt. A total of 80 patients diagnosed with gastric cancer underwent gastrectomy during this period. R0 resection was defined by the complete tumor excision after surgical treatment proved by pathologic examination of the resected margins. Clinicopathological parameters, including gender and age of patients; location of the tumor; depth of invasion; LN metastasis status; operative details; morbidity and mortality; and survival and recurrence were collected. Patients with synchronous malignancies, and those who were diagnosed others than adenocarcinoma was excluded from the study. We did not use endoscopic ultrasound in our center. During the study period, the median survival for patients who did not undergo surgery and only had palliative management was 6 mo. All patients did not receive a preoperative adjuvant or neoadjuvant therapy.

Cancer staging was as described in the seventh edition of the International Union Against Cancer TNM Classification^[9].

All of the surgical procedures were performed by experienced gastric surgeons of our single institute with a definitive treatment guideline for gastric cancer. Two types of gastrectomy were performed: Subtotal gastrectomy (STG) or total gastrectomy (TG).

STG was performed for tumors located in the lower and middle third of the stomach when a 3-6 cm tumor proximal free safety margin can be achieved. All the other patients underwent TG. STG includes the removal of the greater and lesser omentum. The first portion of the duodenum was mobilized and divided at least 2 cm distal to the pylorus with at least 2 cm distal safety margin. The left gastric artery was ligated at its origin. A roux-en-Y reconstruction was done for 18 patients who left with small gastric pouches (< 20% of the stomach), while 32 patients had a loop gastrojejunostomy as they had a large remnant gastric pouches. For TG, the resection included removal of the spleen if there was a suspected LN involvement at splenic hilum. Esophagojejunostomy roux-en-Y is the most common type of reconstruction with a Roux limb is at least 45 cm long. In all patients, an extended lymphadenectomy, was used as the standard surgical procedure. All patients

Table 1 Co-morbidity and possible risk factors

Symptoms	n (%)
Abdominal pain	80 (100)
Dyspepsia	65 (81)
Heart burn	29 (36)
Dysphagia	17 (21)
Palpable mass	7 (9)
Co-morbidity	
<i>Helicobacter pylori</i>	66 (83)
Smokers	56 (70)
Diabetes mellitus	16 (20)
Hypertension	16 (20)
Total	80 (100)

Table 2 Preoperative endoscopic evaluation

Item	n (%)
Site of tumor:	
Antrum	51 (64)
Body	19 (24)
Cardia	10 (12)
Macroscopic feature:	
Exophytic growth	46 (58)
Ulcerative form	34 (42)
Diffuse form	0
Total	80 (100)

did not receive adjuvant or neoadjuvant therapy.

Statistical analysis

The χ^2 or Fisher's exact test was used to compare categorical variables. Survival was calculated using the Kaplan Meyer method and groups were compared using the Log-Rank test. Factors that were deemed of potential importance on univariate analysis were included in the multivariate analysis. A probability (*P*) of less than 0.05 (two sided) was considered statistically significant. Overall mortality represented all deaths during follow-up. Cox multivariate proportional hazards regression models were used to assess the overall survival power of these parameters. All analyses were done using SPSS® software program version 21 (Chicago, United States).

RESULTS

From February 2009 to February 2013, eighty patients with gastric carcinoma were managed in our Gastroenterology Surgical Center. Their age ranged from 24 to 83 years with a mean age 55.4 ± 11.8 years (median age 57 years). Fifty seven were male (71%) and 23 female (29%), with male to female ratio (2.5:1).

Table 1 shows the co-morbidity and possible risk factors in our patients, 66 of patients (83%) had *Helicobacter pylori*, 56 (70%) of them were heavy smokers. Variable symptoms were experienced by our patients; epigastric pain was the main complaint in all patients (100%). The antrum was the most common tumor location within the stomach in 51 patients

Table 3 Complications after gastrectomy

	n (%)
Anastomotic leakage	3 (4)
Internal hemorrhage	1 (1)
Splenic bed collection	2 (3)
Pleural effusion	2 (3)
Wound infection	2 (3)
Total	10 (13)

Table 4 Pattern of recurrence

Item	n (%)
Local recurrence	9 (11)
Lymph nodes metastasis	2 (3)
Liver metastasis	2 (3)
Total	13 (16)

(64%), and the polypoid growth was the most common macroscopic feature and was found in 46 patients (58%) (Table 2).

Operative data

Total gastrectomy was performed in 30 patients (38%) and subtotal gastrectomy in 50 patients (62%). The radicality of the operation necessitates extension of the resection to the tail of the pancreas and to the spleen in 5 patients, to the colon in 2 patients and to the left liver lobe in one patient. The mean blood transfusion required for TG and STG was (1.29 ± 0.53 unit) and (0.41 ± 0.50 unit).

There is no hospital mortality. Postoperative hospital morbidity was reported in 10 patients (12.5%) (Table 3). Three patients (4%) had anastomotic leakage and were managed conservatively (2 patients after TG and 1 patient after STG). Recurrence was shown in Table 4 whereas local and gastric stump was the commonest site (11%). The median period of hospital stay was 8 d (5 to 36 d).

Table 5 shows the demographic and clinicopathological features predicting overall survival. One, 3 and 5 years survival rates were respectively 71%, 69% and 46%. The median survival was 69.96 mo (Figure 1). During the follow-up period, 13 patients died (16%). The median number of LNs removed was 22 (4-41). LN metastasis was found in 91% of cases. Survival was superior in case of negative LN resected (61 mo vs 31 mo, $P < 0.0001$). Survival also varied according to the number of removed LN. The median survival was 54.48 mo when more than 15 LN were removed vs 14.5 mo when fewer LN were resected ($P < 0.0001$) (Figure 2A). There was no statistical significance between both groups as regard the effect of extended LN dissection on morbidity ($P = 0.34$). The ratio of the number of positive nodes to the total number of nodes retrieved, *i.e.*, the LN ratio, was significantly associated with worse overall survival, it was 62 ± 2.5 mo when LN ration was ≤ 0.2 , 62 ± 2.1 mo when LN ration was between 0.2

Table 5 Demographic and clinicopathological features predicting overall survival

Characteristics	Number of patients <i>n</i> (%)	Months after surgery (mean \pm SD)	<i>P</i> value
Sex			
Male	57 (71)	50.2 \pm 3.1	
Female	23 (29)	47.8 \pm 4.6	<i>P</i> = 0.830
Age			
Below 60	49 (61)	47.3 \pm 3.5	
Above 60	31 (39)	53.6 \pm 3.6	<i>P</i> = 0.259
Site			
Antrum	51 (64)	47 \pm 3.5	
Body	19 (24)	57.2 \pm 3.5	
Fundus and cardia	10 (12)	40.3 \pm 6	<i>P</i> = 0.315
Type of surgery			
Total gastrectomy	30	65 \pm 7	
Subtotal gastrectomy	50	60	<i>P</i> = 0.548
Tumor differentiation			
Well	37 (46)	65.6 \pm 0.3	
Moderate	20 (25)	50.8 \pm 5.3	
Poor	23 (29)	20.8 \pm 4	<i>P</i> = 0.001
T stage			
T1	10 (13)	60 \pm 3.2	
T2	25 (31)	60 \pm 2.4	
T3	29 (36)	61 \pm 3	
T4	16 (20)	12 \pm 2.3	<i>P</i> = 0.001
LN ratio			
0	7 (9)	61	
\leq 0.2	20 (25)	62 \pm 2.5	
0.2-0.4	26 (32)	62 \pm 2.1	
$>$ 0.4	27 (34)	22 \pm 4.5	<i>P</i> $<$ 0.001
LN status			
Negative	7 (9)	61 \pm 3.5	
Positive	73 (91)	31 \pm 2.3	<i>P</i> = 0.03
Number of examined LN			
$>$ 15	65 (81)	54.48 \pm 2.6	
\leq 15	15 (19)	14.5 \pm 1	<i>P</i> $<$ 0.001
Surgical margin			
Negative	73 (91)	53.8 \pm 2.4	
Positive	7 (9)	9.5 \pm 1	<i>P</i> $<$ 0.001
Recurrence			
No	67 (84)	57.3 \pm 2.3	
Yes	13 (16)	12.3 \pm 1.2	<i>P</i> $<$ 0.001

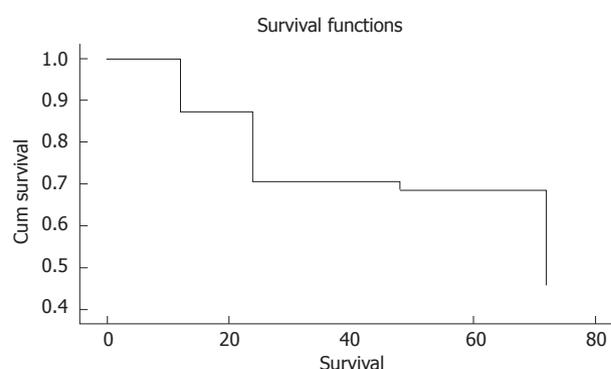
to 0.4 and 22 \pm 4.5 mo when LN ration was $>$ 0.4; *P* $<$ 0.001 (Figure 2B).

The median survival of T1 and T2 tumors was significantly superior to T4 tumors (60 mo vs 12 mo, *P* = 0.0001) (Figure 2C). Survival was significantly higher in case of well and moderate differentiated tumor to poorly differentiated tumor (65.7 mo vs 20.8 mo, *P* $<$ 0.0001) (Figure 2D). Seventy three patients (91%) had a radical resection which is associated with prolonged survival compared to 7 patients (9%) who had a palliative one (53.8 mo vs 9.5 mo, *P* $<$ 0.0001) (Figure 2E). Patients developed a recurrent tumor (13 patients 16%) had a significant poor survival compared to the others (67 patients 84%) (12.3 mo vs 57.3 mo, *P* $<$ 0.0001).

There is no significant difference in survival rate according to age, gender, tumor location, the type of gastrectomy. On multivariable analysis (Table 6), tumor differentiation, curability of resection and a

Table 6 Multivariate analysis

Factors	Odds ratio	CI lower-upper	<i>P</i> value
Tumor differentiation	0.142	0.045-1.092	0.044
Radicality of resection	2.57	1.4-5.1	0.001
Number of resected lymph node $>$ 15	2.04	1.3-3.75	0.001

**Figure 1** Overall survival.

number of resected LN superior to 15 were found to be independent prognostic factors.

DISCUSSION

The epidemiology, surgical management and outcomes for patients with carcinoma of the stomach differ significantly from one area of the world to another. We have a published data and experience from Western, Eastern and European countries. However, we have a little data from Middle East countries, and here we represent our work from a large gastroenterology and transplantation center in Egypt. Complete tumor excision with satisfactory safety margins (*i.e.*, an R0 resection according to the UICC classification) have been accepted as a major significant factor for reduction of tumor recurrences and improvement of survival time in patients with gastric cancer^[13-19]. This radical resection is the most important step to have better survival in our patients (53.8 mo vs 9.5 mo, *P* $<$ 0.0001). In our series, after R0 resection and DII lymphadenectomy, depth of wall invasion, LN metastasis, the number of resected LN, LN ratio and tumor differentiation were the independent prognostic factors.

The extent of regional lymphadenectomy required has been a matter of considerable debate. The number of LN metastases has a higher prognostic value compared to their location^[8,20] and the staging system was updated in the 2010 UICC/TNM 7th edition^[21]. The definition of LN dissections: Has been updated considering the number of removed LN rather than their location, it is as follows: D0 when less than 15 nodes are reported, D1 when 15 to 25 nodes are removed, and D2 when more than 25 nodes are reported in the pathological findings^[8,9].

There has been much argument about the mini-

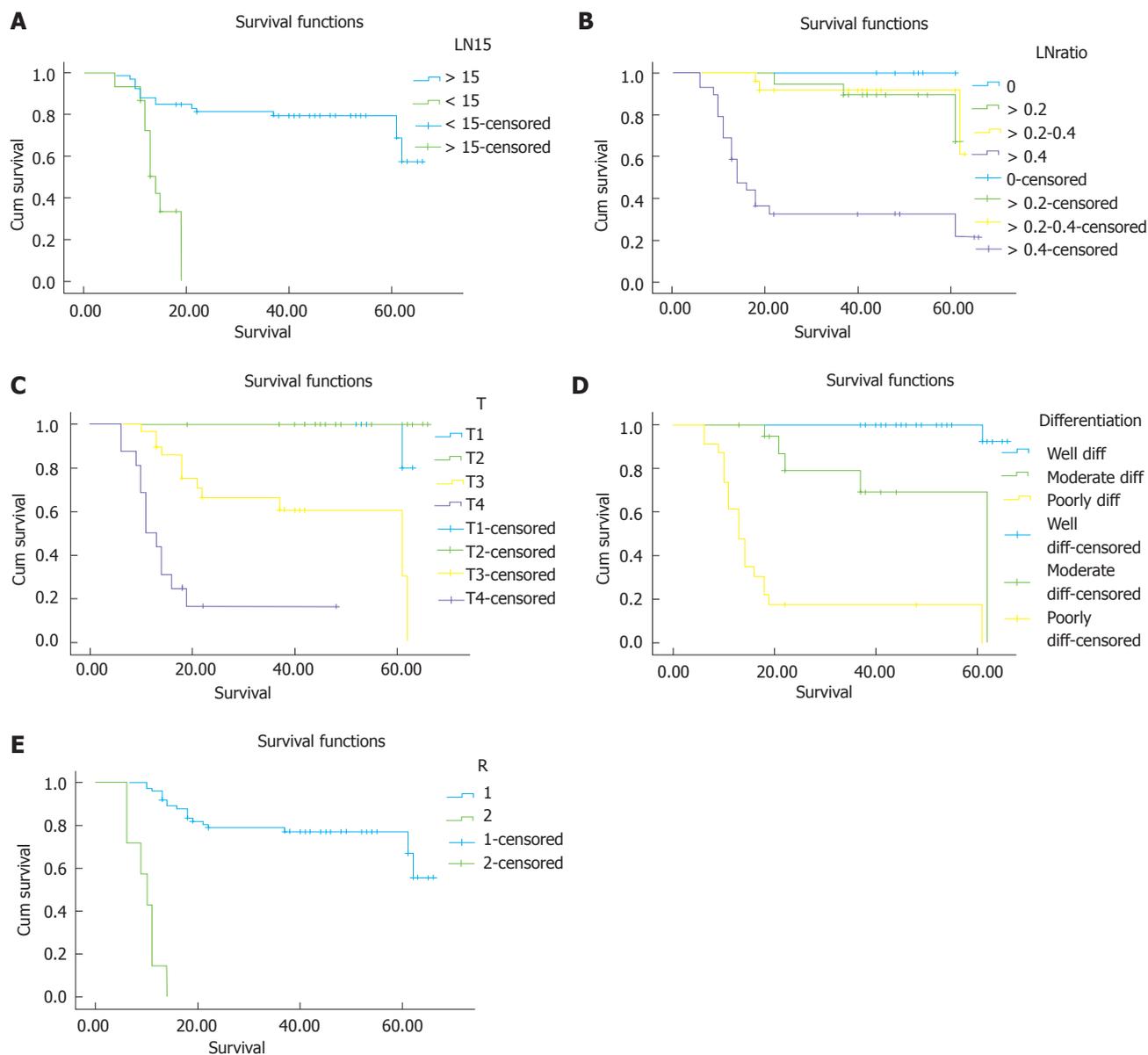


Figure 2 Actuarial survival (Kaplan Meier analysis) after resection of gastric carcinoma. A: Influence of number of affected LN; B: Influence of LN ratio; C: Influence of tumor stage; D: Influence of tumor grade; E: Influence of radicality of resection. LN: Lymph node.

imum number of LNs removed for proper staging. The Union Internationale Contre Le Cancer (UICC), has standardized the operative management of gastric cancer and propose that for proper staging, at least 15 LNs should be removed and pathologically examined^[22]. This recommendation highlights the significance of the total number of LNs removed over their relationship to the primary tumor (N1 or N2). Karpeh *et al*^[8], three years later, made a comparison between different staging systems to show their impact on the long term survival (UICC 1988 that used the location of LN vs UICC 1997 that used the number of LN). They reported that, there is superior significant value of the number of metastatic LNs more than their location.

The number of metastatic LNs increases with the depth of tumor invasion through the gastric wall layers and this had a direct relationship to long term

survival^[23-25]. In our series, the T and N stage had the highest significant prognostic factors especially after R0 resection. Survival was 54.48 mo when more than 15 LN were resected vs 14.5 mo when fewer LN were removed ($P < 0.0001$). In experienced centers, Extended LN dissection does not increase the morbidity or mortality rate but markedly improves long term survival.

The independent prognostic value of LN ratio in our monoinstitutional study was significantly associated with worse overall survival, it was 62 ± 2.5 mo when LN ratio was ≤ 0.2 , and 22 ± 4.5 mo when LN ratio was > 0.4 ; $P < 0.001$. In various Western series, the LN ratio has been considered as an effective prognostic tool after D2 lymphadenectomy^[26-32]. Bando *et al*^[27] reported that, at multivariate analysis the LN ratio was the only independent prognostic factor when the number

Table 7 Published series on prognostic factors after resection for gastric carcinoma

Ref.	Period	No.	Gender	Age	Location	No. excised LN	LN ratio	T stage	Histologic type	N stage	Curative resection
Adachi <i>et al</i> ^[45]	1977-1987	479	NS	NS	$P < 0.01$	$P < 0.01$	NR	$P < 0.01$	$P < 0.01$	$P < 0.01$	NR
Bando <i>et al</i> ^[27]	1974-1995	650	NR	NR	NR	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NR	NR
Yokota <i>et al</i> ^[46]	1985-1995	926	NS	NS	$P < 0.0001$	NR	NR	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	NR
			0.347	0.099							
Angelov <i>et al</i> ^[47]	2005-2013	101	NS	NS	NS	NR	NR	NR	NR	$P = 0.003$	$P < 0.001$
			0.587	0.67	0.54				0.169		
Basaran <i>et al</i> ^[48]	2006-2014	228	NS	0	$P < 0.001$	NR	NR	NS	$P < 0.015$	$P < 0.002$	$P = 0.000$
								0.137			
Present study	2009-2013	80	NS	NS	NS	$P < 0.001$	$P < 0.001$	$P = 0.001$	$P = 0.001$	NR	$P < 0.001$
			0.83	0.259	0.315						

NS: Non-significant; NR : Not reported; LN: Lymph node.

and the side of metastatic LNs were considered in the analysis. Kunisaki *et al*^[33] reported the same result and that the LN ratio independently influenced the prognosis of a radically resected 758 patients.

The median survival of T1 and T2 tumors was significantly superior to T4 tumors (60 mo vs 12 mo, $P = 0.0001$) this is also reported by others^[4,34]. Grade refers to the degree of differentiation of tumor cells and has been shown to correlate with the neoplasm aggressiveness. The prognostic impact in gastric cancer remains to be elucidated, because several retrospective studies have failed to identify grade as an independent prognostic factor^[7]. In our study, Survival was superior in case of well and moderate differentiated tumor to poorly differentiated tumor (65.7 mo vs 20.8 mo, $P < 0.0001$) others reported the same result^[4,34]. On multivariable analysis, tumor differentiation curability of resection and a number of resected LN superior to 15 were found to be independent prognostic factors.

The recurrence after surgical excision of gastric carcinoma shows a different pattern between Eastern and Western countries. However, there are still some disputes. In Eastern countries, the hematogenous recurrence and peritoneal dissemination were the most common recurrence patterns^[35-37]. Wu *et al*^[38] reported that the peritoneal recurrence was 38.4% and the hematogenous recurrence was 32.5% of patients. Our results show that local recurrence is the most common one and account for 11%. This result is consistent with an Italian study that showed that the loco-regional recurrence was the most common recurrence pattern and account for 45% of all recurrent cases^[38]. This difference in recurrence pattern may be explained by that the low incidence of local recurrence in Eastern series is due to a different surgical strategy toward extensive LNs dissection^[39].

In this study, the 3 and 5 years survival rates were 69% and 46%, respectively. Our survival rates are similarly to those reported in Memorial Sloan-Kettering cancer center in New York^[23] and the German gastric cancer study^[3] and some other western centers^[29,34,40,41]. However, our survival results are better than a reported

study from Poland^[42]. We have a lower survival rates than those reported in Japan^[43,44]. Table 7 shows some published series on prognostic factors after resection for gastric carcinoma. Epidemiology, late discovery of the disease, differences in the staging systems and the operative strategy with extensive lymphadenectomy in Japan may explain these differences.

In conclusion, the epidemiology, surgical management and outcomes differ significantly from one area of the world to another. Surgery stills the gold-stander line of management. There might be a correlation between time to discover the disease, radicality and survival. Our study showed that after R0 resection, depth of wall invasion, LNs involvement and the number (> 15) of resected LN, In ratio and tumor differentiation predict survival. On multivariable analysis, tumor differentiation, curability of resection and a number of removed LN more than 15 were found to be independent prognostic factors. In order to have a better survival in our patients, we recommend frequent use of upper endoscopy for gastrointestinal symptoms for early detection of gastric cancer.

COMMENTS

Background

The epidemiology and the surgical outcomes for patients with carcinoma of the stomach vary significantly from one part of the world to another. However, prognosis varies among patients with a similar tumor stage; therefore, disease staging alone cannot accurately predict the outcome for individual patients. There might be a correlation between time to discover the disease, radicality of resection and survival. The experience of the surgeons toward more radical resection with lymph node (LN) removal is the most important non-TNM prognostic factors in gastric cancer.

Research frontiers

Prognosis is poor perhaps due to late diagnosis and frequent local-regional recurrences. This requires investigation of the possible reasons for the worsening of survival and searching for prognostic factors of better survival. Complete resection of the tumor with satisfactory safety margins is the standard treatment. Many prognostic factors have been investigated to assess their significance in predicting patients' outcome. The number of metastatic LNs (N stage) and the depth of the primary tumor (T stage) are currently considered the most reliable prognostic factors for patients with radically resected gastric cancer. LN clearance remains the most challenging part of the operation, the UICC/AJCC classification,

suggests that at least 15 LNs should be examined for a correct assessment of N stage.

Innovations and breakthroughs

The authors have a published data and experience from Western, Eastern and European countries. However, we have a little data from Middle East countries, and here we represent the authors' work from a large gastroenterology and transplantation center in Egypt. The aim of this study was to evaluate the Clinicopathological features and the significance of different prognostic factors in patients undergoing resection for gastric cancer. Clinicopathological parameters, including gender and age of patients; location of the tumor; depth of invasion; LN metastasis status; operative details; morbidity and mortality; and survival and recurrence were collected. All of the surgical procedures were performed by experienced gastric surgeons of the single institute with a definitive treatment guideline for gastric cancer. In all patients, an extended lymphadenectomy, was used as the standard surgical procedure.

Applications

Epidemiology, late discovery of the disease, differences in the staging systems and the operative strategy with extensive lymphadenectomy may explain the difference between prognostic factors between different parts of the world. The center is a referral tertiary center, most of their patients comes with a relatively advanced tumor stage. Intra-operatively there was much LN involvement. So their policy is to remove of all suspected LN involved with the disease to reach satisfactory radical resections. In order to have a better survival in their patients, they recommend frequent use of upper endoscopy for gastrointestinal symptoms for early detection of gastric cancer.

Terminology

The extent of LNs dissection is classically termed D0, D1, and D2 LN dissection was initially classified as D1 to D4, depending on the extent and removal of each LN station according to the primary tumor location. In distal subtotal gastrectomy, D1 included removal of only LN stations 1, 3, 4, 5, 6 and 7 surrounding the stomach, whereas D2 included D1 LN dissection and station 8a, 12a, 9 and 11. D3 and D4 LN dissections occur when the other LN stations are removed. This system has been revised and now reflects the number of retrieved LNs rather than their location. Hence, it is as follows: D0 when less than 15 nodes are reported, D1 when 15 to 25 nodes are removed, and D2 when more than 25 nodes are reported in the pathological findings.

Peer-review

The authors present their surgical experience in the treatment of gastric cancer in one the Middle East centers. Their study included 80 patients with different clinicopathological characteristics in an attempt to investigate the impact of in study mentioned variables on the patients' survival following surgical management.

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Retrospective Study

Critical appraisal of laparoscopic vs open rectal cancer surgery

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Abstract

AIM: To evaluate the long-term clinical and oncological outcomes of laparoscopic rectal resection (LRR) and the impact of conversion in patients with rectal cancer.

METHODS: An analysis was performed on a prospective database of 633 consecutive patients with rectal cancer who underwent surgical resection. Patients were compared in three groups: Open surgery (OP), laparoscopic surgery, and converted laparoscopic surgery. Short-term outcomes, long-term outcomes, and survival analysis were compared.

RESULTS: Among 633 patients studied, 200 patients had successful laparoscopic resections with a conversion rate of 11.1% (25 out of 225). Factors predictive of survival on univariate analysis include the laparoscopic approach ($P = 0.016$), together with factors such as age, ASA status, stage of disease, tumor grade, presence of perineural invasion and vascular emboli, circumferential resection margin < 2 mm, and postoperative adjuvant chemotherapy. The survival benefit of laparoscopic surgery was no longer significant on multivariate

analysis ($P = 0.148$). Neither 5-year overall survival (70.5% vs 61.8%, $P = 0.217$) nor 5-year cancer free survival (64.3% vs 66.6%, $P = 0.854$) were significantly different between the laparoscopic group and the converted group.

CONCLUSION: LRR has equivalent long-term oncologic outcomes when compared to OP. Laparoscopic conversion does not confer a worse prognosis.

Key words: Rectal cancer; Laparoscopic; Outcomes; Conversion; Prognosis

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Core tip: Laparoscopic rectal resection (LRR) remains controversial in view of concerns over its long term oncological outcome and the adverse impact conversion may have on survival. Our retrospective study has demonstrated that LRR has equivalent long-term oncologic outcomes when compared to open surgery. Conversion was also found not to confer a worse prognosis.

Tan WJ, Chew MH, Dharmawan AR, Singh M, Acharyya S, Loi CTT, Tang CL. Critical appraisal of laparoscopic vs open rectal cancer surgery. *World J Gastrointest Surg* 2016; 8(6): 452-460 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/452.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.452>

INTRODUCTION

Surgical management for rectal cancer remains challenging. With the advent of total mesorectal excision (TME) in rectal cancer surgery, local recurrence rates have improved significantly and there is an increasing rate of sphincter-saving surgery when technically and oncologically feasible. However, despite the use of pre- or post-operative adjuvant chemoradiotherapy, local and distant tumor recurrence remains a concern.

While laparoscopic colectomy has established its oncologic equivalence compared to open surgery (OP) in colon cancer, laparoscopic rectal resection (LRR) for rectal cancer remains controversial. Although LRR has been shown to confer short-term benefits, in terms of blood loss, length of stay, recovery of bowel function, and cosmesis, concerns about the long-term oncologic outcomes persists^[1-5]. The necessity for a TME creates a more difficult learning curve for LRR compared to a laparoscopic colectomy. There is also the need to achieve a balance between sphincter preservation without compromising the adequacy of the distal resection margin^[6]. These challenges induce a higher rate of conversion compared to colonic resection^[2] and a recent Cochrane review has noted that conversion rates in LRR can be as high as 35%^[7]. This is an important concern as it has been suggested

that conversion to OP after attempted LRR not only has higher morbidity, but may also adversely affect long-term oncologic outcomes^[2,8-11]. Several publications have attempted to address this issue but the study populations often consisted of a mixture of patients with colon and rectal cancer^[12-14]. This is suboptimal as the prognosis and recurrence pattern of colon and rectal cancer are distinctly different. There are few publications that address the long-term outcomes of laparoscopic conversion specifically in the context of rectal cancer^[10,15,16].

Therefore, the objective of this study is to evaluate the long-term clinical and oncological outcomes of LRR as well as the impact of laparoscopic conversion on the long-term oncological outcomes of patients with rectal cancer.

MATERIALS AND METHODS

An analysis of a prospectively maintained database of 633 consecutive patients with rectal cancer who underwent surgical resection from January 2005 to December 2009 in the Department of Colorectal Surgery at Singapore General Hospital was performed. Patients who presented with recurrent cancer, Inflammatory Bowel Disease, Familial Adenomatous Polyposis, or other polyposis syndromes were excluded. Data on patient demographics, pre-operative, operative, and post-operative course were collected prospectively and maintained in a database by a research assistant.

All cases were performed by consultant surgeons within the department. The decision for laparoscopic or open approach was left to the discretion of the individual surgeon.

For the laparoscopic approach, we preferred the medial approach with early mobilization, ligation and division of the inferior mesenteric artery at its origin after the ureter has been identified. The inferior mesenteric vein was ligated and divided at the inferior border of the pancreas. This was followed by mobilization of the left colon from the lateral sidewall, with mobilization of the splenic flexure if deemed necessary to achieve a tension free anastomosis. Total meso-rectal excision or wide meso-rectal excision up to at least 2 cm distal to the tumor was performed for all cases when feasible. Distal transection was performed using articulating staplers. The specimen is exteriorized *via* extension of the port sites with proximal transection performed extracorporeally. Pneumoperitoneum is then re-established and intra-corporeal circular stapled anastomosis performed under direct vision.

OP was performed *via* a midline laparotomy or left iliac fossa incision as described in a previous publication^[17].

Patients were compared in three groups: OP, laparoscopic surgery (LS), and converted laparoscopic surgery (CON) with their definitions as follows: (1) OP: Completion of surgical resection and anastomosis *via*

midline laparotomy or left iliac fossa incision; (2) LS: Surgery accomplished using the laparoscopic technique as described above. Patients analyzed under the LS group included patients who underwent laparoscopic-assisted surgery as described in a previous publication by our department^[18]. These were patients who had vascular ligation and the majority of bowel mobilization was accomplished intra-corporeally *via* the laparoscopic approach with the following modifications: (a) extension of one port site wound or the utilization of a new wound to complete colonic mobilization and bowel transection for reasons such as the presence of adhesions, excessive tumor fixation, or uncertain tumor location; (b) extracorporeal rectal anastomosis due to technical difficulties such as a narrow pelvis, bulky tumor, or defective equipment; and (c) extension of wounds to repair the anastomosis due to leaks on testing after completion of a pure laparoscopic resection; (3) CON: The laparoscopic approach is aborted after insertion of ports and initial bowel mobilization. This can be due to the presence of dense adhesions, undiagnosed tumor invasion of surrounding organs, or troubleshooting complications such as uncontrolled bleeding, bowel perforation, or injury of adjacent viscera such as ureters or small bowel. Conversion is also defined if the anastomosis requires a complete takedown and revision.

Pre-operative staging

All cases were evaluated preoperatively by plain chest radiograph/computed tomography (CT) of the thorax and CT of the abdomen and pelvis. T-staging with an endo-rectal ultrasound was performed pre-operatively in clinical T1 and T2, mid and low rectal tumors. Magnetic resonance imaging (MRI) of the pelvis was performed for all lower rectum tumors. Upper rectum is defined as 11-15 cm, middle rectum as 6-10 cm, and lower rectum as 0-5 cm from the anal verge. These measurements were recorded by the consultant surgeon after digital rectal examination and endoscopy. Disease staging according to the American Joint Committee Cancer (AJCC) Cancer Staging Manual 7th Edition was adopted^[19].

Neoadjuvant/adjuvant therapy

In our institution, a selective neoadjuvant chemoradiation policy is adopted based on data from previous publications that have consistently shown low local recurrence rates with oncologically adequate surgery alone^[20-22]. If sphincter preservation with good margins can be performed after initial evaluation, neoadjuvant treatment is usually not routinely recommended in our local population. Neoadjuvant treatment is mainly performed in patients who present with a threatened circumferential resection margin, defined as within 2 mm of the circumferential resection margin based on pre-operative staging.

The neoadjuvant regimen consisted of long-course

preoperative radiotherapy (45-50 Gy in 25-28 daily fractions over 5 wk) combined with 5-fluorouracil or oral capecitabine. Patients proceeded with surgical resection 6 to 8 wk after completion of neoadjuvant chemoradiotherapy. Decision for adjuvant chemotherapy was decided after discussion at a multi-disciplinary tumor board meeting.

Perioperative care for all patients was standardized using existing clinical care pathways.

Follow-up details

Post-operatively, the patients were followed-up at three monthly intervals for the first two years, six monthly for the next three years, and then yearly thereafter. At each consultation, carcinoembryonic antigen (CEA) levels were measured and full history and physical examination (including digital rectal examination) were performed. Colonoscopy was performed within six months of surgery if initial complete evaluation was not possible pre-operatively due to tumor obstruction or stenosis. Those who had an initial complete evaluation underwent colonoscopy at the first year follow up, and again at 3-yearly intervals post-operatively. Patients with suspicious symptoms and signs of rising CEA trend on follow-up will be evaluated earlier with colonoscopy and/or radiological imaging (including computerized tomography of the chest, abdomen, and pelvis, bone scan, and positron emission tomography scans if applicable).

Local recurrence was defined as the first clinical, radiologic, and/or pathologic evident tumor of the same histological type, within the true pelvis, at the anastomosis or in the region of the anastomosis. Distant recurrence was defined as similar evidence of spread outside the primary tumor at sites including but not limited to the liver, lungs, bone, brain, and para-aortic region. Patients who were first diagnosed with local recurrence but later developed distant metastasis were classified under the local recurrence group. Mortality data and the cause of death were obtained from the Singapore Cancer Registry.

Short-term outcomes assessed included wound infections, post-operative ileus, anastomotic leaks, pneumonia, peri-operative cardiac events, duration of hospitalization, and 30-d mortality.

Long-term outcomes assessed included the occurrence of intestinal obstruction, incisional hernias, and the oncologic outcomes of local/distal recurrence.

Survival analysis was performed *via* the comparison of progression free survival and overall survival (OS).

Statistical analysis

All statistical analysis was performed by a qualified biostatistician. Demographic and clinicopathological characteristics of the patients were compared across the 3 groups using χ^2 and *t* tests for categorical and continuous variables respectively. Distribution of selected short- and long-term outcomes among the patients

Table 1 Demographic characteristics of study cohort

Variables		Lap (%) n = 200	Converted (%) n = 25	Open (%) n = 408	P value
Gender	Male	128 (64)	15 (60)	243 (60)	0.570
	Female	72 (36)	10 (40)	165 (40)	
Median age (yr)		59	63	66	< 0.001
Ethnic group	Chinese	172 (86)	22 (88)	352 (86.3)	0.368
	Malay	9 (4.5)	0	19 (4.7)	
	Indian	4 (2)	2 (8)	18 (4.4)	
	Others	15 (7.5)	1 (4)	19 (4.7)	
ASA	1	75 (37.5)	4 (16)	84 (20.6)	0.002
	2	105 (52.5)	20 (80)	267 (65.4)	
	3	20 (10)	1 (4)	55 (13.5)	
	4	0	0	2 (0.4)	
Location of tumor	Lower rectum	68 (34)	8 (32)	131 (32.1)	0.381
	Middle rectum	90 (45)	10 (40)	212 (52)	
	Upper rectum	42 (21)	7 (28)	65 (15.9)	
Type of surgery	HAR	30 (15)	4 (16)	24 (5.9)	0.067
	LAR (w/stoma)	27 (13.5)	4 (16)	82 (20.1)	
	LAR (w/o stoma)	32 (16)	5 (20)	76 (18.6)	
	ULAR	98 (49)	12 (48)	193 (47.3)	
Neo-adjuvant therapy status	APR	13 (6.5)	0	33 (8.1)	< 0.001
	Chemotherapy	5 (2.5)	0	14 (3.4)	
Adjuvant therapy status	Radiotherapy	3 (1.5)	0	12 (2.9)	< 0.001
	Chemotherapy	65 (32.5)	15 (60)	134 (32.8)	
Adjuvant therapy status	Radiotherapy	28 (14)	7 (28)	82 (20.1)	0.271

LAR: Low anterior resection; ULAR: Ultra-low anterior resection; APR: Abdomino-perineal resection.

undergoing surgery was compared using Fisher's exact test. Comparison of the median duration of hospitalization was performed using the Kruskal-Wallis nonparametric test as it deviates from the Normality assumption.

OS was calculated from the date of diagnosis to the date of death or last follow-up. Cancer-free survival (CFS) was calculated from the date of diagnosis to the date of disease progression (local or distant relapse) or last follow-up. The 5-year OS and CFS were estimated using Kaplan Meier method and the survival curves were compared using log-rank tests. Multivariate Cox proportional hazards models, using variables found to be significant on univariate analysis, were used to estimate hazard ratios with their 95%CI. A significance level of 0.05 was chosen throughout. All analyses were performed using R 3.1.1 (2014, Vienna, Austria).

RESULTS

Six hundred and thirty-three patients underwent surgical resection for primary rectal cancers during the

Table 2 Reasons for laparoscopic conversion to open surgery

Reason for conversion	No. of patients (% within converted patients)
Excessive adhesions	12 (48)
Advanced tumor or excessive tumor fixation	3 (12)
Difficult anatomy	3 (12)
Intraoperative complications (e.g., bleeding, ureteric/urinary tract injury, bowel perforation/injury)	4 (16)
Intolerant of tilt and pneumoperitoneum	3 (12)

study duration. The demographic characteristics of the study population are illustrated in Table 1. Two hundred and twenty-five patients (35.5%) underwent attempted laparoscopic resection of the rectal tumor. Among these, 200 patients had successful laparoscopic resection with 77 patients (34.2%) requiring a laparoscopic-assisted approach, predominantly due to anatomic difficulties during the LS (50 out of 77 patients). Patients in the OP group were older [66 years old (OP) vs 59 years (LS), $P < 0.001$] and had slightly higher proportion of patients with ASA 3 and 4 [13.5% (OP) vs 10% (LS), $P = 0.002$]. The proportion of patients who underwent neoadjuvant chemotherapy and radiotherapy was also higher among patients in the OP group compared to LS group [3.4% vs 2.5% (chemotherapy) and 2.9% vs 1.5% (radiotherapy) respectively]. The laparoscopic conversion rate was 11.1% (25 out of 225) with the reasons for conversion illustrated in Table 2. All conversions to OP were unplanned pre-operatively. Close to half (12 out of 25) of the patients were converted due to the presence of excessive adhesions. The oncologic and peri-operative outcomes of the entire study cohort are presented in Table 3. Duration of surgery was significantly longer in the LS compared to the OP group [162 min (LS) vs 119 min (OP), $P < 0.001$]. Length of hospitalization was shorter in the LS group compared to OP group (7 d vs 8 d, $P < 0.001$).

Comparison of short-term and long-term outcomes between the 3 groups is illustrated in Table 4 and there were no significant differences between the 3 groups. The 5-year CFS and OS for the 3 group of patients is illustrated in Figure 1. Results of the univariate and multivariate analyses for predictive factors of survival are summarized in Table 5. Factors found to be predictive of survival on univariate analysis include the laparoscopic approach ($P = 0.016$), together with factors such as age, ASA status, stage of disease, tumor grade, presence of perineural invasion and vascular emboli, CRM < 2 mm, and postoperative adjuvant chemotherapy. The survival benefit of LS was no longer significant on multivariate analysis ($P = 0.148$) and only age, stage of disease, tumor grade, and CRM < 2 mm remained significant. After excluding open cases, neither 5-year OS (70.5% vs 61.8%, $P = 0.217$) nor 5-year CFS (64.3% vs 66.6%, $P = 0.854$) were

Table 3 Oncologic characteristics and perioperative outcomes of study cohort

Variables		Lap (%) n = 200	Converted (%) n = 25	Open (%) n = 408	P value
Tumor grade	Well-differentiated	20 (10)	3 (12)	38 (9.3)	0.339
	Mod-differentiated	173 (86.5)	21 (84)	349 (85.6)	
	Poorly-differentiated	7 (3.5)	1 (4)	21 (5.1)	
Median lesion size (cm)		3.9	4.1	4.3	0.275
T stage	T1	18 (9)	3 (12)	23 (5.6)	0.151
	T2	43 (21.5)	4 (16)	73 (17.9)	
	T3	126 (63)	9 (36)	265 (65)	
	T4	13 (6.5)	9 (36)	47 (11.5)	
Nodal status	N0	95 (47.5)	10 (40)	188 (46.1)	0.77
	N+	105 (52.5)	15 (60)	320 (53.9)	
TNM stage	Stage I	47 (23.5)	3 (12)	69 (16.9)	0.086
	Stage II	51 (25.5)	4 (16)	111 (27.2)	
	Stage III	75 (37.5)	9 (36)	162 (39.7)	
	Stage IV	27 (13.5)	9 (36)	66 (16.2)	
Perineural invasion	+	38 (19)	8 (32)	90 (22.1)	0.652
	-	162 (81)	17 (68)	318 (77.9)	
Vascular invasion	+	61 (30.5)	11 (44)	135 (33.1)	0.617
	-	139 (69.5)	14 (56)	275 (66.9)	
Median lymph nodes harvested (range)		14 (4-90)	15 (4-55)	14 (3-56)	0.447
Proximal margin (cm)		9.9 (0-30)	10 (2-22)	12 (0-39)	0.004
Distal margin (cm)		2.1 (1-15)	1.8 (1-15)	2 (1-14)	0.55
CRM < 2 mm		29 (14.5)	5 (20)	75 (18.4)	0.494
Median duration of surgery (min)		162	147	119	< 0.001
Length of hospitalization		7 (3-159)	7 (5-16)	8 (3-78)	< 0.001

CRM: Circumferential resection margin.

Table 4 Distribution of long-term and short-term outcomes across three surgery groups

	Laparoscopic surgery n = 200	Converted surgery n = 25	Open surgery n = 408	P value
	No. of patients (%)	No. of patients (%)	No. of patients (%)	
Short-term outcomes				
Anastomotic leaks	13 (6.5)	0 (0)	17 (4.2)	0.233
Wound complications	8 (4)	2 (8.0)	31 (7.6)	0.227
Bleeding complications	5 (2.5)	1 (4.0)	9 (2.2)	0.840
Ileus	3 (1.5)	2 (8.0)	18 (4.4)	0.097
Pneumonia	1 (0.5)	0 (0)	8 (2)	0.298
Cardiac events	7 (3.5)	2 (8)	17 (4.2)	0.562
30 d mortality	2 (1)	0 (0)	8 (2.0)	0.545
Long-term				
Intestinal obstruction	23 (11.5)	5 (20)	59 (14.5)	0.396
Incisional hernia	9 (4.5)	1 (4)	33 (8.1)	0.218
Local recurrence	9 (4.5)	1 (4.0)	36 (8.8)	0.126
Distant recurrence	45 (22.5)	6 (24)	106 (26)	0.644

significantly different between the laparoscopic group and the converted group.

DISCUSSION

In our study, the 5-year OS was 70.5% in the LS group vs 52.7% in the OP group. While the laparoscopic technique appeared to confer survival benefit on

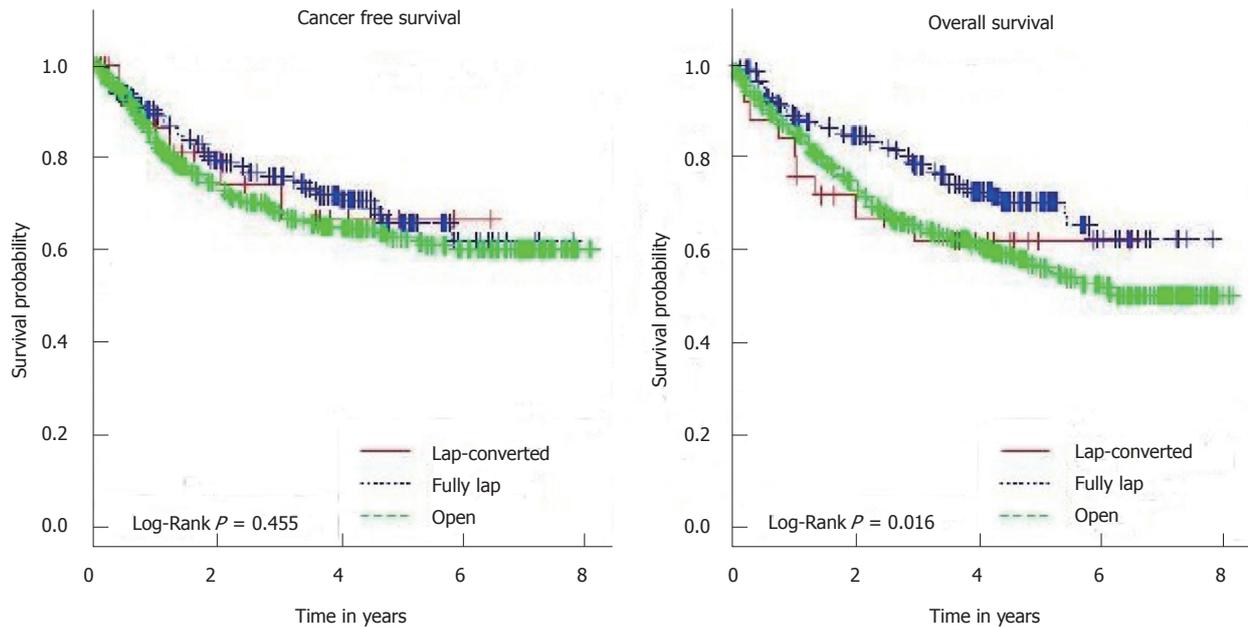
univariate analysis, this is likely attributed to the inherent selection bias in the study as patients chosen for OP tend to be older and with more advanced ASA status. As such, the differences in survival were no longer significant when subjected to multivariate analysis. There was also no difference in the local or systemic recurrence rates between all groups. These results are in line with several published studies comparing at least 5-year survival data of laparoscopic against open rectal resections (Table 6)^[4,6,23-30]. They are also congruent with the findings of two recent randomized trials comparing laparoscopic with open resection in rectal cancer^[31,32]. However, conflicting results were seen when pathologic adequacy of surgical resection was used as the outcome of interest. Both the ALaCaRT and the ACOSOG Z6051 trial failed to demonstrate non inferiority in terms of oncologic adequacy of resection when LS was compared to OP^[33,34]. These results have cast doubt on the role of LS in rectal cancer. Hopefully, the long term follow up data of the above two studies will help shed light on the contentious issue of LS in rectal cancer.

Studies assessing the impact of conversion on oncological outcomes have shown conflicting results and a recent meta-analysis found that conversion was associated with an adverse long-term oncological outcome^[35]. Postulated mechanisms include the increased inflammatory response associated with conversion and requirement for blood transfusion in converted cases that may subsequently increase recurrence risks^[36]. However, both colonic and rectal resections were included in the above meta-analysis,

Table 5 Prognostic factors of overall survival: Univariate and multivariate analysis

Variable	5 yr overall survival (%)	Univariate P value	Overall survival HR (95%CI)	Multivariate P value
Age ≥ 65 vs < 65	50.9 vs 68.3	< 0.001 ¹	1.4557 (1.083-1.9568)	0.003 ²
Gender (male vs female)	60.6 vs 60	0.921	-	-
Lap vs converted vs open	70.5 vs 61.8 vs 52.7	0.016 ¹	-	0.148
ASA 1/2 vs 3/4	62.6 vs 45.7	0.016 ¹	-	0.131
NeoadjChemo (yes vs no)	59.5 vs 60.4	0.36	-	-
NeoadjRT (yes vs no)	66.7 vs 60.2	0.654	-	-
AdjChemo (yes vs no)	40.8 vs 70.5	< 0.001 ¹	-	0.06
AdjRT (yes vs no)	53.2 vs 62.3	0.206	-	-
TNM stage (I-IV)		< 0.001 ¹		< 0.001 ²
Stage I	77.2		Reference	
Stage II	73.8		1.04 (0.58-1.84)	0.907
Stage III	60.3		1.52 (0.89-2.58)	0.124
Stage IV	13.9		5.80 (3.26-10.33)	< 0.001
Tumor grade		0.002 ¹		0.015 ²
Well differentiated	75		Reference	
Moderately differentiated	60.1		2.10 (1.00-4.40)	0.049
Poorly differentiated	39.1		1.18 (0.54-2.54)	0.682
CRM < 2 mm vs > 2 mm	40.1 vs 63.5	< 0.001 ¹	1.66 (1.19-2.32)	0.003 ²
No. of lymph nodes ≥ 12 vs < 12	62.2 vs 56.1	0.08	-	-
Perineural invasion	36.2 vs 67.3	< 0.001 ¹	-	0.276
Vascular emboli	46.2 vs 68.5	< 0.001 ¹	-	0.14
Clinical symptoms of obstruction at presentation (yes vs no)	35.3 vs 64.6	< 0.001 ¹	1.95 (1.39-2.74)	< 0.001 ²

¹Denotes statistically significant results on univariate analysis; ²Denotes statistically significant results on multivariate analysis.



Survival outcomes	Open surgery	Laparoscopic surgery	Conversion	P value
5 year cancer free survival	62.5%	64.3%	66.6%	0.455
5 year overall survival	56.0%	70.5%	66.8%	0.016 ¹

Figure 1 Kaplan-Meier curves comparing the three surgery groups for cancer free survival and overall survival. ¹Cancer free survival and overall survival is compared.

with the former constituting the majority of the pooled patient population. Subset analysis of laparoscopic conversion in our study cohort revealed that conversion did not have an adverse impact on long-term oncologic outcomes in rectal cancer. Several studies have reported

the impact of conversion in LRR for cancer^[6,8,10,15,16,37]. While most studies had similar findings to ours, Rottoli *et al*^[15] concluded that conversion could have a negative impact on long-term overall recurrence rate. It is noted in this study, however, that 8 out of 26 (30.7%) patients

Table 6 Summary of studies reporting at least 5 year survival outcomes of laparoscopic vs open rectal resection

Ref.	Type of study	No. of patients with rectal cancer	5 yr overall survival	Remarks
Lujan <i>et al</i> ^[4]	Randomized Controlled Trial	204 (103 open, 101 lap)	75.3% (open) vs 72.1% (lap) <i>P</i> = 0.980	Middle and low rectal cancers only
Green <i>et al</i> ^[26] , (MRC CLASICC trial)	Randomized Controlled Trial	381 (128 open, 253 lap)	52.9% (open) vs 60.3% (lap) <i>P</i> = 0.132	
Ng <i>et al</i> ^[29]	Pooled Analysis of 3 RCT	278 (142 open, 136 lap)	61.1% (open) vs 63.0% (lap) <i>P</i> = 0.505	10 yr overall survival
Laurent <i>et al</i> ^[6]	Retrospective Comparative Study	471 (233 open, 239 lap)	79% (open) vs 82% (lap) <i>P</i> = 0.52	Cancer free survival main outcome measure
Day <i>et al</i> ^[25]	Retrospective	222 (133 open, 89 lap)	58% (open) vs 75% (lap) <i>P</i> = 0.014	Laparoscopic group had better survival on multivariate analysis as well
Baik <i>et al</i> ^[24]	Case-matched Controlled Analysis	162 (108 open, 54 lap)	88.5% (open) vs 90.8% (lap) <i>P</i> = 0.261	
Li <i>et al</i> ^[28]	Retrospective	238 (123 open, 113 lap)	78.9% (open) vs 77.9% (lap) <i>P</i> = 0.913	Middle and low rectal cancers only
Lim <i>et al</i> ^[21]	Retrospective	191 (91 open, 100 lap)	72.6% (open) vs 74.7% (lap) <i>P</i> = 0.54	
Zhong <i>et al</i> ^[30]	Retrospective	514 (238 open, 186 lap)	61.3% (open) vs 69.4% (lap) <i>P</i> = 0.067	
Agha <i>et al</i> ^[23]	Retrospective	225 (all laparoscopic)	50.5% (lap)	10 yr overall survival

were converted due to advanced tumors and may thus explain poorer survival. In contrast, the majority of our conversions were due to adhesions (> 50%) and not advanced disease (12%) (Table 2). Thus it was not surprising that laparoscopic conversion had no impact on long-term oncologic outcomes.

The major limitation of our study lies in its retrospective nature which makes it susceptible to the effects of confounding and selection bias. While formal matching of the various groups of the study cohort was not performed due to numerical limitations, majority of the clinical demographics and tumor pathological characteristics between groups were similar, allowing for meaningful comparison. While we acknowledge the antecedent limitations of the retrospective nature of our study, it does have several strengths. Firstly, to the best of our knowledge, this is the largest study cohort evaluating the long-term outcomes (5-year survival data) of surgical resection in rectal cancers. Unlike other studies, conversions were clearly defined which facilitates comparison of findings in other institutions. Thus, we believe that this study will add value to the available literature on surgical resection for rectal cancer.

LRR is safe and has equivalent long-term oncologic outcomes when compared to OP. Laparoscopic conversion does not appear to confer an adverse outcome. Further evaluation of long-term data from updated randomized studies comprising of larger number of patients may be required to discern more differences.

COMMENTS

Background

Laparoscopic resection for rectal cancer remains controversial. The authors evaluate the long-term clinical and oncological outcomes of laparoscopic rectal

resection and the impact of conversion in patients with rectal cancer.

Research frontiers

The impact of laparoscopic conversion in rectal cancer remains unknown. This study assesses the impact of laparoscopic conversion in patients with rectal cancer.

Innovations and breakthroughs

Laparoscopic surgery for rectal cancer has equivalent long term oncological outcomes when compared with open surgery. Conversion in rectal cancer was not shown to be associated with an adverse outcome.

Applications

Laparoscopic resection for rectal cancer is feasible with no adverse impact on long term oncological outcomes even in the event of conversion.

Terminology

LRR: Laparoscopic rectal resection; OP: Open surgery; LS: Laparoscopic surgery; CON: Converted laparoscopic surgery.

Peer-review

The paper describes a single-center experience on laparoscopic surgery for rectal cancer. It is well written and references are updated.

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Solitary fibrous tumor of the pancreas: Case report and review of the literature

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Abstract

Solitary fibrous tumor (SFT) is a mesenchymal tumor typically located in the pleura, but can also be found as an asymptomatic mass in other areas, including the liver, peritoneum, kidney and salivary glands. However, SFT rarely locates in the pancreas. We present such a case of pancreatic SFT, along with a review of all reported cases. A 55-year-old man was treated surgically for an asymptomatic pancreatic mass after a rigorous preoperative control. Histologic examination of the resected specimen showed characteristics of an SFT. As only 15 cases of pancreatic SFT have been reported so far, an attempt to compare the cases was considered intriguing. We found that patients with pancreatic SFT were mainly women (81.25%), with a median age of 54 years at the time of diagnosis and a median tumor size of 5.83 cm. Pancreatic SFTs were revealed incidentally in 50% of cases, and all of them showed an enhancement through arterial computed tomography. All tumors were positive for CD34, ten were positive for Bcl-2, and twelve were negative for S100. The diagnosis of this pancreatic tumor is established by a combination of clinical suspicion, imaging procedures and histological findings, and is confirmed by immunohistochemical staining. Although the behavior of SFTs is rather benign, close clinical follow-up is recommended due to a potentially malignant nature.

Key words: Solitary fibrous tumor; Pancreas; Mesenchymal tumors; Differential diagnosis; Solitary fibrous tumor treatment

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Core tip: Solitary fibrous tumor (SFT) is a mesenchymal tumor that rarely locates in the pancreas. We present the case of a 55-year-old man with a pancreatic lesion that proved to be an SFT after thorough pre- and post-operative control. The characteristics of this case and the other fifteen cases of pancreatic SFT reported in the literature are described.

Paramythiotis D, Kofina K, Bangeas P, Tsiompanou F, Karayannopoulou G, Basdanis G. Solitary fibrous tumor of the pancreas: Case report and review of the literature. *World J Gastrointest Surg* 2016; 8(6): 461-466 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/461.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.461>

INTRODUCTION

Solitary fibrous tumor (SFT) was described as a distinct type of mesenchymal tumor for the first time at 1931^[1]. SFT can be benign or malignant and is typically located in the pleura, but the tumor can also be found as an asymptomatic mass in other areas such as the liver, peritoneum, kidney and salivary glands^[2-4]. SFTs often occur in middle age (40-70 years), especially in the fifth decade of life, and metastases can be detected in 10% to 15% of the cases^[4-6]. This type of tumor appears very rarely in the pancreas, as only 15 cases have been reported so far.

CASE REPORT

A 55-year-old man was admitted in our surgical department for further evaluation of an asymptomatic pancreatic mass that had been found incidentally by upper abdomen ultrasonography. No specific symptoms were mentioned except vague abdominal pain. Clinical examination and laboratory results were unremarkable, and the levels of tumor markers (CEA, CA 19-9, CA 15-3) were within normal ranges. The patient's medical history included coronary heart disease (one myocardial infarction and coronary artery bypass surgery seven years ago), open cholecystectomy (27 years ago), choledocholithiasis treated with endoscopic retrograde cholangiopancreatography (5 years ago), dyslipidemia and hypertension under medication.

During ultrasound examination of the abdomen for non-specific pain, a hypoechoic solid mass of 2.8 cm × 3.1 cm on the pancreatic body (Figure 1) and a possible dilation of the common bile duct were found. Further imaging was performed. Computed tomography (CT) scans revealed a 3.9-cm-diameter exophytic mass arising from the pancreatic body that was enhanced from the arterial to portal venous phase (Figure 2). T1-weighted magnetic resonance imaging



Figure 1 Ultrasound echo showing a 2.8 cm × 3.1 cm hypoechoic solid mass located on the pancreatic body.

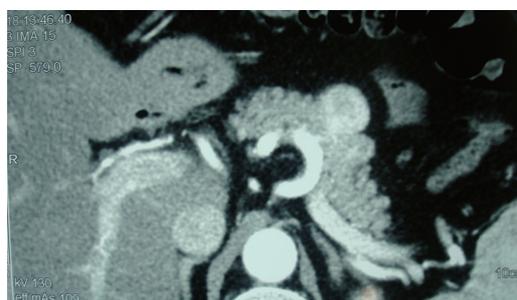


Figure 2 Computed tomography scan revealing a 3.9 cm exophytic mass, arising from the pancreatic body, which was enhanced from the arterial to portal venous phase.

(MRI) scans showed a hypointense mass. Regional lymphadenopathy was not found on the CT or MRI images. Magnetic resonance cholangiopancreatography imaging revealed a pancreatic body cystic portion with heterogeneous internal echogenicities of mixed substantial and necrotic parts. Although the main pancreatic duct was not dilated, the common bile duct displayed a filling deficit. The upper digestive tract endoscopy showed no abnormalities.

Based on the above findings, we considered that the differential diagnosis of the mass should include exophytic non-functioning islet tumor, solid pseudo-papillary mass of the pancreas, gastrointestinal stromal tumor (GIST), neuroendocrine tumor and heman-giopericytoma of the pancreas.

The surgical removal of the mass was considered necessary and the patient underwent a pancreatectomy including body and tail, whereas the spleen was maintained. The resected mass measured 3.6 cm in its greatest diameter and had an ovoid shape with well-capsulated, smooth margins and a yellowish-grey hue (Figures 3 and 4). The abdominal exploration did not show any signs of metastasis or tumor infiltration into neighboring organs.

On histopathological examination, the mass showed characteristics of a neoplasm, including spindle-shaped tumor cells with elongated nuclei. Mitoses were scarce. The neoplasm presented a storiform pattern with

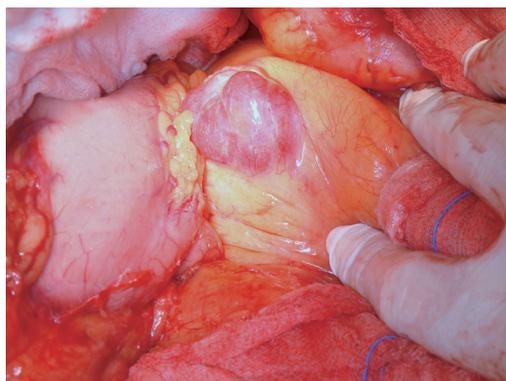


Figure 3 Intra-operative appearance of the pancreatic mass.



Figure 4 Pancreatic mass specimen.

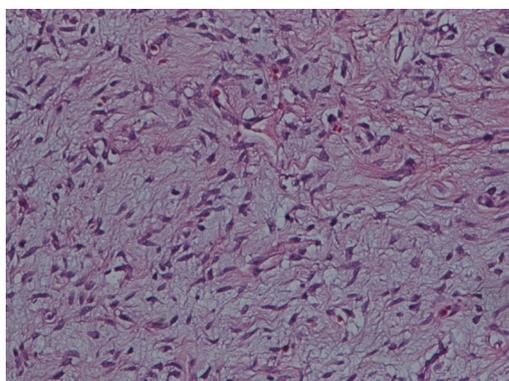


Figure 5 Solitary fibrous tumor with a hyalinized area, HE stain. Magnification: $\times 400$.

alternating hypocellular and hypercellular areas, and some areas showed myxoid degeneration. There were a large number of blood vessels within the stroma (Figure 5).

Immunohistochemically, the tumor cells were positive for CD34, CD99, Bcl-2 (Figure 6) and vimentin, and exhibited focal positivity for S-100 protein. Only a small number of cells were positive for the cell proliferation marker Ki-67/MIB-1. The tumor cells were negative for smooth muscle actin (SMA), keratin, cytokeratin (AE1/AE3), CD117, epithelial membrane antigen and desmin. The final diagnosis was pancreatic

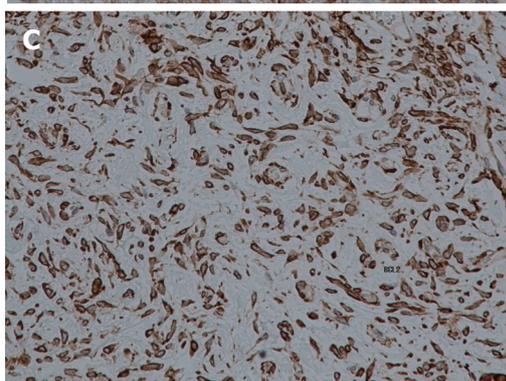
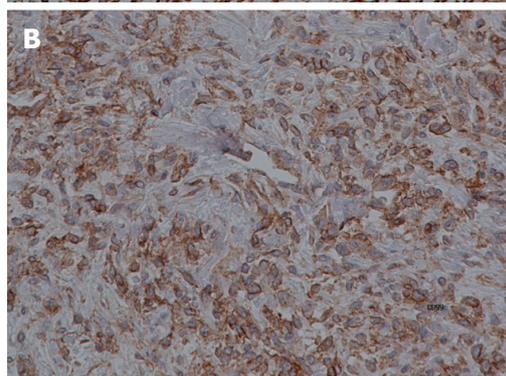
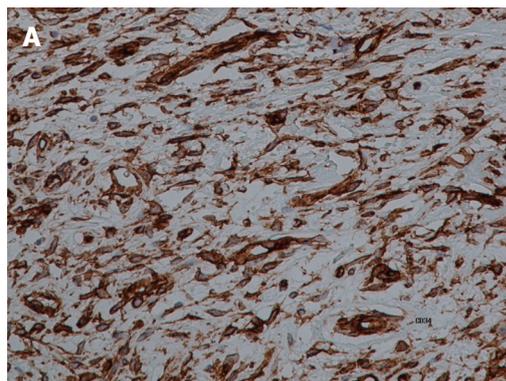


Figure 6 Immunohistochemical staining (brown) for CD34 (A), CD99 (B) and Bcl-2 (C). Magnification: $\times 400$.

SFT with a low grade of malignancy.

After surgery, the patient was led to the intensive care unit. His post-operative course was uneventful and he was discharged on the 9th postoperative day with the recommendation to follow a non-fat diet. Chemotherapy was not considered necessary. In the 6- and 12-mo follow-up periods the patient was asymptomatic and in good health.

DISCUSSION

Mesenchymal tumors of the pancreas include leiomyosarcoma, peripheral nerve tumors, fibro-histiocytic tumors and vascular tumors^[7-9]. Differential diagnosis is based on histology and immunohistochemistry findings and, therefore, diagnosis is often very difficult before surgery.

On the other hand, pancreatic SFTs are very rare, as only 16 cases have been reported in the literature^[1,3-16], including our case. The patients were mainly women

Table 1 Characteristics of patients with solitary fibrous tumor of the pancreas

Ref.	Sex	Age	Symptoms	Size (cm)	Location
Lüttges <i>et al</i> ^[4]	Female	50	Incidental	5.5	Body
Chatti <i>et al</i> ^[8]	Male	41	Pain	13	Body
Gardini <i>et al</i> ^[10]	Female	62	Pain	3	Head
Miyamoto <i>et al</i> ^[9]	Female	41	Pain	2	Head-body
Srinivasan <i>et al</i> ^[5]	Female	78	Pain, weight loss	5	Body
Kwon <i>et al</i> ^[7]	Male	54	Incidental	4.5	Body
Ishiwatari <i>et al</i> ^[11]	Female	58	Incidental	3	Head
Chetty <i>et al</i> ^[3]	Female	67	Incidental	2.6	Body
Sugawara <i>et al</i> ^[6]	Female	55	Incidental	7	Head
Santos <i>et al</i> ^[12]	Female	40	Incidental	3	Body
Tasdemir <i>et al</i> ^[1]	Female	24	Incidental	18.5	Head
van der Vorst <i>et al</i> ^[13]	Female	67	Pain	2.8	Uncinate process
Chen <i>et al</i> ^[14]	Female	49	Pain, distension, appetite loss	13	Head
Hwang <i>et al</i> ^[15]	Female	53	Incidental	5.2	Head
Hee Han <i>et al</i> ^[16]	Female	77	Jaundice	1.5	Head
Paramythiotis	Male	55	Pain	3.6	Body

Table 2 Imaging features of pancreatic Solitary fibrous tumors

Ref.	Arterial CT	Venous CT	MRI T1	MRI T2
Lüttges <i>et al</i> ^[4]	Enhanced	Enhanced		
Chatti <i>et al</i> ^[8]	Enhanced	Enhanced	Hypointense	Hyperintense
Gardini <i>et al</i> ^[10]	Enhanced	Enhanced		
Miyamoto <i>et al</i> ^[9]	Enhanced	Enhanced		
Srinivasan <i>et al</i> ^[5]	Hyper-enhanced	Enhanced		
Kwon <i>et al</i> ^[7]	Enhanced	Enhanced	Hypointense	Hyperintense
Ishiwatari <i>et al</i> ^[11]	Enhanced	Enhanced	Hypointense	Hyperintense
Chetty <i>et al</i> ^[3]	Enhanced	Enhanced		
Sugawara <i>et al</i> ^[6]	Enhanced	Enhanced	Hypointense	Hyperintense
Santos <i>et al</i> ^[12]				
Tasdemir <i>et al</i> ^[1]	Enhanced	Enhanced		
van der Vorst <i>et al</i> ^[13]	Enhanced	Enhanced		
Chen <i>et al</i> ^[14]	Enhanced	Enhanced		
Hwang <i>et al</i> ^[15]	Enhanced	Enhanced	Hypointense	Hyperintense
Hee Han <i>et al</i> ^[16]	Enhanced	Enhanced	Hypointense	Hyperintense
Paramythiotis	Enhanced	Enhanced	Hypointense	Hyperintense

CT: Computed tomography.

(13/16, 81.25%), with a median age of 54 years at the time of diagnosis (range: 24-78 years, median age: 50 years for males, 55.46 years for females) and a median tumor size of 5.83 cm (range: 1.5-18.5 cm). In six cases the tumor was located in the pancreatic body (37%) and in seven cases the tumor was located in the pancreatic head (43.75%) (Table 1). The tumor was revealed incidentally in half the cases; however, in the other half, the main symptom was pain (jaundice was presented in only one case). Regarding imaging, all tumors showed an enhancement through arterial and portal CT. The results of MRI imaging were described for seven cases: These tumors were hypointense in T1-weighted images and hyperintense in T2-weighted images (Table 2).

All cases were treated surgically except for one case which was diagnosed after biopsy. By immunohistochemistry, all tumors were positive for CD34, ten tumors were positive for Bcl-2, and only one tumor was

positive for S100. Many tumors were positive for keratin types. Controls for CD117 (1 positive, 10 negatives), CD19 (11 positives, 1 negative) and SMA (4 positives, 5 negatives) didn't show the same results in all cases (Table 3).

Most pancreatic SFTs presented as well-circumscribed, often partially-encapsulated masses^[9] with a multinodular, whitish and firm appearance. On microscope sections, the tumors showed a patternless architecture characterized by alternating hypocellular and hypercellular areas separated by thick bands of collagen and branching hemangiopericytoma-like vessels^[6]. The tumor cells were round-to-spindle-shaped and the mitoses were scarce. Tumor necrosis and infiltrative margins were observed in malignant neoplasms occurring in other locations.

The differential diagnosis of SFT includes leiomyosarcoma, liposarcoma, fibrosarcoma, fibrous histiocytoma, hemangioendothelioma, hemangiopericytoma, hemangioma, lymphangioma, islet cell tumor, paraganglioma, neuroectodermal tumor, and schwannoma^[12]. The main diagnostic consideration based on imaging findings is thought to be endocrine neoplasms^[3,5]. These are composed of round cells with granular, eosinophilic cytoplasm and are positive for synaptophysin and chromogranin. As leiomyosarcomas are considered to be more frequent than SFTs in the pancreas, the former must be differentiated by their nuclear atypia and increased mitotic activity^[1,5]. Moreover, GISTs are positive for CD34, vimentin and CD117 but SFTs are negative for CD117^[1,5,9].

In our case, preoperative CT and MRI scans strongly showed the typical pattern of SFTs^[15]. Histopathological examination of the resected tumor revealed that it was covered with a fibrous capsule and contained necrotic tissue, favoring the diagnosis of SFT. Immunohistochemistry findings confirmed the diagnosis.

The diagnosis of pancreatic SFT is established from a combination of clinical suspicion (mainly women

Table 3 Treatment and immunohistochemistry findings

Ref.	Surgery	Immunohistochemistry
Lüttges <i>et al</i> ^[4]	Distal pancreatectomy	Positive: CD34, CD99, Bcl-2, vimentin Negative: SMA, S100
Chatti <i>et al</i> ^[8]	Enucleation	Positive: CD34, CD99 (focal), Bcl-2, SMA (focal), CD117 (focal) Negative: EMA, cytokeratin, S100
Gardini <i>et al</i> ^[10]	Traverso-longmire	Positive: CD34, CD99, Bcl-2, vimentin, smooth muscle actin (focal) Negative: Desmin, CD117, S100
Miyamoto <i>et al</i> ^[9]	Head-body junction	Positive: CD34, Bcl-2 Negative: cytokeratin, CAM 5.2, SMA, desmin, S100, CD117
Srinivasan <i>et al</i> ^[5]	Distal pancreatectomy	Positive: CD34 (focal), CD99, Bcl-2, vimentin Negative: CAM 5.2, SMA, desmin, CD117, CD10, chromogranin, S100
Kwon <i>et al</i> ^[7]	Median segmentectomy	Positive: CD34, CD99 Negative: CD117, S100
Ishiwatari <i>et al</i> ^[11]	Pancreaticoduodenectomy	Positive: CD34, Bcl-2 Negative: S100
Chetty <i>et al</i> ^[3]	Whipple	Positive: CD34, CD99, Bcl-2
Sugawara <i>et al</i> ^[6]	Pancreaticoduodenectomy	Positive: CD34 Negative: SMA, S100, CD117, ALK, cytokeratin
Santos <i>et al</i> ^[12]	Partial pancreatectomy	Positive: CD34, b-catenin Negative: C-kit
Tasdemir <i>et al</i> ^[1]	Enucleation	Positive: CD34, vimentin, SMA (focal) Negative: S100, CD117, desmin, cytokeratin
van der Vorst <i>et al</i> ^[13]	Enucleation	Positive: CD34, CD99, Bcl-2 Negative: CD117, b-catenin
Chen <i>et al</i> ^[14]	Whipple/child	Positive: CD34, CD68, MSA, Bcl-2, Ki-67 Negative: SMA, cytokeratin, desmin, CD117, CD99, S100
Hwang <i>et al</i> ^[15]	Partial head resection	Positive: CD34, CD99, Bcl-2, SMA, CD10, ER, PR Negative: CD117, DOG-1, caldesmon, desmin, EMA, S100, cytokeratin
Hee Han <i>et al</i> ^[16]	Echo-guided needle biopsy	Positive: CD34, CD99 Negative: C-kit, S100
Paramythiotis	Distal pancreatectomy	Positive: CD34, CD99, Bcl-2, vimentin, S100 (focal) Negative: SMA, keratin, cytokeratin, CD117, EMA and desmin

SMA: Smooth muscle actin; EMA: Epithelial membrane antigen; CAM: Anti-cytokeratin mouse monoclonal primary antibody; ALK: Anaplastic lymphoma kinase; MSA: Muscle specific actin; DOG-1: Anoctamin-1.

of middle age, with abdominal pain and nonspecific symptoms), imaging procedures (ultrasound, CT and MRI) and histological findings, and is confirmed by immunohistochemistry. Although SFTs are usually benign, clinical follow-up is recommended because

these tumors can become malignant^[1,5].

COMMENTS

Case characteristics

Asymptomatic 55-year-old male.

Clinical diagnosis

Abdominal pain.

Differential diagnosis

Upper abdomen tumors.

Imaging diagnosis

Exophytic mass of the pancreatic body.

Pathologic diagnosis

Pancreatic solitary fibrous tumor (SFT).

Treatment

Pancreatectomy (body and tail).

Related reports

Fifteen case reports of this rare condition.

Term explanation

Mesenchymal tumors arise from mesodermally-derived tissues, and can be either benign or malignant.

Experiences and lessons

This report discusses the basic characteristics of pancreatic SFTs, based on all the cases reported so far.

Peer-review

The authors report a case of a rare pancreatic tumor and compare it to cases in the existing bibliography.

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Gastrointestinal bleeding and obstructive jaundice: Think of hepatic artery aneurysm

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Abstract

Hemobilia is an uncommon and potential life-threatening condition mainly due to hepato-biliary tree traumatic or iatrogenic injuries. Spontaneously ruptured aneurysm of the hepatic artery is seldom described. We report the case of an 89-year-old woman presenting with abdominal pain, jaundice and gastrointestinal bleeding, whose ultrasound and computed tomography revealed a non-traumatic, spontaneous aneurysm of the right hepatic artery. The oeso-gastro-duodenoscopy and colonoscopy did not reveal any bleeding at the ampulla of Vater, nor anywhere else. Selective angiography confirmed the diagnosis of hepatic artery aneurysm and revealed a full hepatic artery originating from the superior mesenteric artery. The patient was successfully treated by selective embolization of microcoils. We discuss the etiologies of hemobilia and its treatment with selective embolization, which remains favored over surgical treatment. Although aneurysm of the hepatic artery is rare, especially without trauma, a high index of suspicion is needed in order to ensure appropriate treatment.

Key words: Hemobilia; Hepatic artery aneurysm; Obstructive jaundice; Supra-selective micro-embolization; Gastrointestinal hemorrhage

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Core tip: Non-traumatic aneurysm of the hepatic artery leading to hemobilia as the source of gastrointestinal bleeding may be subtle to recognize, not only because

of its low incidence but also because of its inconsistent clinical signs. These aneurysms are more commonly seen after a traumatic event on the biliary tree, however in rare cases, it occurs spontaneously, mainly in the settings of vascular degeneration and chronic gallbladder inflammatory disease. Moreover, the hepatic artery is known for multiple anatomical variants, some of which are rare. Our patient presented with both uncommon conditions and was successfully treated with micro-coils embolization.

Vultaggio F, Morère PH, Constantin C, Christodoulou M, Roulin D. Gastrointestinal bleeding and obstructive jaundice: Think of hepatic artery aneurysm. *World J Gastrointest Surg* 2016; 8(6): 467-471 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/467.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.467>

INTRODUCTION

Bleeding into the biliary tree was first described by Glisson^[1] in 1654 and later named hemobilia by Sandblom^[2] in 1948. Its classical triad - Quincke's triad - includes colicky right upper quadrant abdominal pain, jaundice and gastrointestinal hemorrhage, and is seen in 20% of hemobilia^[3]. Only about 10% of cases of hemobilia are secondary to a ruptured aneurysm of the hepatic artery^[4], which is located in intrahepatic branches in 20%^[5,6]. The occurrence of hemobilia consecutive to a spontaneously ruptured aneurysm of the hepatic artery remains uncommon and its treatment modalities are not evidence-based, although supra-selective embolization seems to overcome surgery in the management^[7]. This case represents not only a rare case of spontaneous aneurysm of the hepatic artery but also illustrates an anatomical variant of its origin. Our patient was successfully treated with supra-selective microcoils embolization.

CASE REPORT

An 89-year-old woman presented to the emergency department with increased epigastric and hyponchondrium colic since one month, associated with inappetence, nausea, vomiting and several episodes of hematemesis and hematochezia for the last 24 h. She did not have temperature during that period of time. She is known for an aorto-coronary bypass and four stents in 2001, as well as hypertension. Her current medication includes acetylsalicylic acid, amlodipine, atorvastatin, nicorandil and molsidomine. There is no history of trauma, and she is not known for hepatobiliary or gastrointestinal tract disorders.

At admission, she was hemodynamically stable and afebrile. She presented with mild scleral icterus. There was no abdominal tenderness. On rectal examination, no traces of blood were found. The laboratory tests



Figure 1 Right hepatic artery branch aneurysm. Transversal view on contrast enhanced abdominal computed tomography exhibiting a 10 mm × 6 mm aneurysm originating from a branch of the right hepatic artery irrigating segment VIII. The darker halo surrounding the aneurysm reflects secondary hepatic parenchyma lower perfusion due to mass effect. The lithiasic gallbladder is not seen on this image.

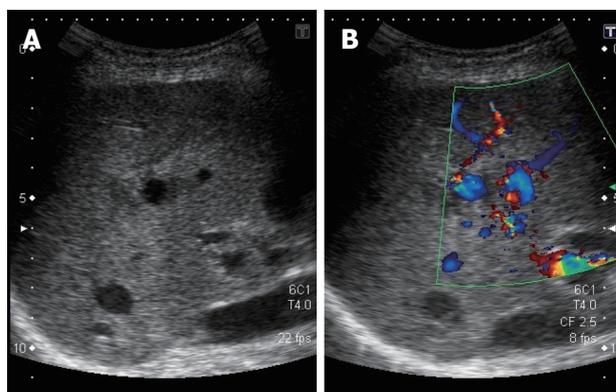


Figure 2 Aneurysm on hepatic Doppler-ultrasound. Sagittal view of the liver representing the aneurysm at the center of the echographic field (A) and Doppler signals confirming the blood flow inside the aneurysm (B). The branch from the hepatic artery the aneurysm is originating from is not seen on the image.

showed mild anemia with a hemoglobin count of 98 g/L (normal 117-157 g/L), a white blood cell count (WBC) of 11 g/L (normal 4-10 g/L), cytotoxicity and cholestasis with aspartate aminotransferase (ASAT) 111 U/L (normal < 35 U/L), alanine aminotransferase (ALAT) 103 U/L (normal < 35 U/L), gamma-GT 247 U/L (normal < 40 U/L), alkaline phosphatase 473 U/L (normal < 130 U/L), total and direct bilirubin 20 and 14 μmol/L respectively (normal < 17 and < 5 μmol/L respectively).

The abdominal computed tomography (CT) scan revealed a 10 mm × 6 mm aneurysm of a branch of the right hepatic artery irrigating segment VIII, and a lithiasic gallbladder with thickened wall (Figure 1), without signs of cholecystitis. The ultrasound (US) revealed a thrombosed aneurysm of the hepatic artery with ectasia of the upward biliary tree (Figure 2).

The upper endoscopy did not show evidence of blood at the ampulla of Vater, but revealed signs of uncomplicated gastritis. Colonoscopy showed sigmoidal diverticulosis, without any source of active bleeding.

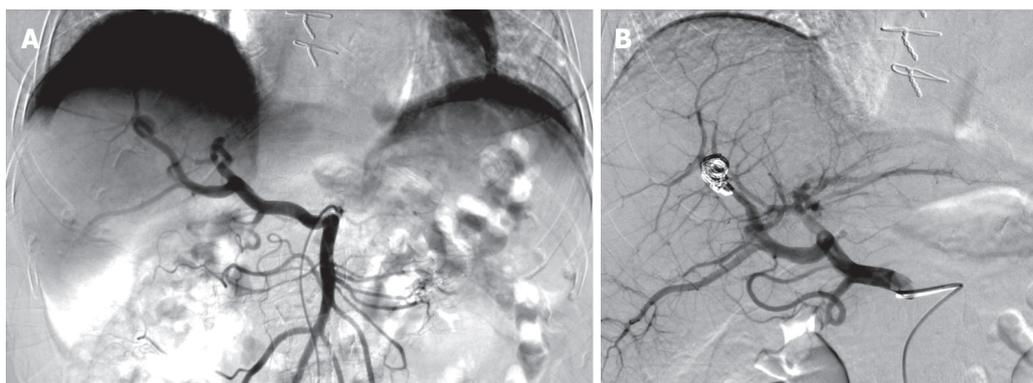


Figure 3 Supra-selective angiography of the hepatic artery branch aneurysm. A: The left image is before embolization; it shows the hepatic artery splitting and the aneurysm taking source from one of the right branches; B: The right image is after supra-selective embolization of the aneurysm with microcoils. The catheter is still visible. Note that the hepatic artery originates from the superior mesenteric artery. This exhibits a full hepatic artery variant, type IX in Michels' classification.

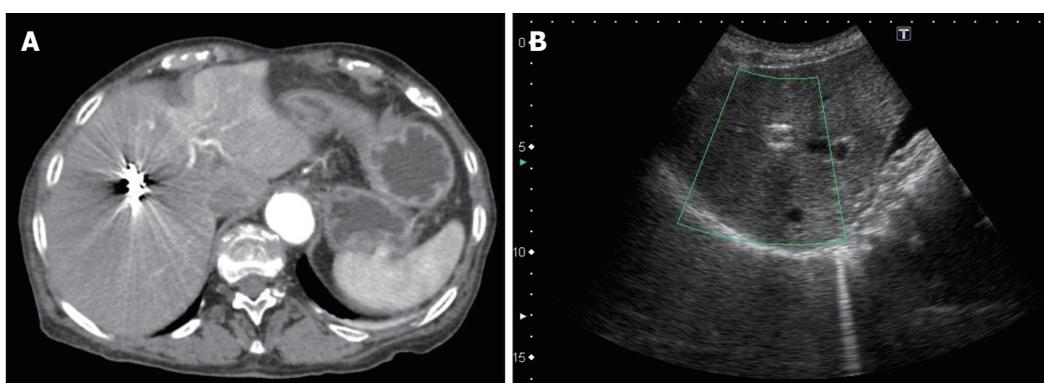


Figure 4 Post embolization imaging. A: Transversal view on the contrast enhanced abdominal computed tomography performed two days after embolization showing that the coils are in place and the absence of blood extravasation; B: Thirty-days control liver ultrasound showing coils in place in the sagittal plane.

Her hemoglobin continued to drop to 83 g/L, necessitating the transfusions of two units of blood. Since our only source of potential bleeding was this aneurysm, we practiced an angiography by catheterization of the right femoral artery with a 5-French catheter. We performed a supra-selective catheterization of the right hepatic artery with a 3-French microcatheter and embolization of the aneurysm with four 4 mm × 37 mm and two 8 mm × 140 mm microcoils. During the procedure, we realized that the hepatic artery was originating directly from the superior mesenteric artery. Thus, the aneurysm was located on the right branch of this particular hepatic artery (Figure 3).

The patient was dismissed two days later without any complications. There were no recurrences at the follow-up CT and US, at day two and thirty respectively (Figure 4).

Two months later, the patient returned to the emergency department with paroxysmal right upper quadrant colicky abdominal pain and jaundice. No blood loss was observed. She was hemodynamically stable and her physical exam did not reveal any abdominal pain upon palpation, nor fever at 36.8 °C. Her laboratory tests exhibited anemia with a hemoglobin at 96 g/L, an inflammatory syndrome with a WBC of 40 g/L and

a C-reactive protein of 117 mg/L, as well as cholestasis and cytolysis (ASAT 167 U/L, ALAT 92 U/L, gamma-GT 330 U/L, alkaline phosphatase 912 U/L, total and direct bilirubin 84 and 75 μmol/L). She benefited from an antibiotic therapy with intravenous ceftriaxone and metronidazole for 72 h, with a shift to ciprofloxacin and metronidazole *per os* for 2 wk. The cholangiography-MRI showed no traces of choledocolithiasis, but a dilated principal and intrahepatic bile ducts, a thick gallbladder wall with sludge and cholelithiasis. There were no signs of recurrent bleeding at the site of micro-embolization, nor any abscess (Figure 4). During hospitalization, she evolved without any complications. Both pain and jaundice resolved and her laboratory tests returned towards normal values before she was dismissed at day seven.

DISCUSSION

The most common causes of hemobilia are due to iatrogenic complications after diagnostic or therapeutic hepatobiliary procedures, and accounts for more than half to two thirds of the cases^[3,8], while non-traumatic causes include aneurysmal disease, which accounts for 10%, and is mainly seen in the setting of atherosclerosis,

gallbladder inflammatory diseases, hepatobiliary tract infections or neoplasia, and autoimmune systemic diseases such as juvenile polyarteritis nodosa, Behçet's disease or rheumatoid arthritis^[3,9]. Our patient was known and treated for arterial disease, which might have played a predominant role in the physiopathology of her disease.

Although upper gastrointestinal tract endoscopy is a crucial step in order to establish both diagnosis and treatment of an ongoing gastrointestinal bleeding, its ability in detecting active bleeding at the ampulla of Vater is only in about half of the patients with hemobilia^[10,11]. Nevertheless, this procedure remains mandatory to rule out and treat other more frequent causes of upper gastrointestinal bleeding.

Angiography is now favored over surgery as the best procedure for diagnosing and treating hemobilia, although there is currently no gold standard established in the literature^[12]. Angiography reveals more than 90% of sources of active bleeding^[3,12], while its success rate in managing the bleeding is more than 80% with a good tolerance and minimal risks compared to surgery^[3,12].

Although our patient presented a cholangitis, cholangiography-MRI at two months showed that the coils were in place and no recurrences had occurred. Since no signs of intraductal obstacle, extrinsic compression, or microlithiasis were found, we hypothesize that a blood clot migrated into the biliary tree, leading to cholangitis. The evolution with antibiotics was uneventful.

Our patient exhibited a relatively rare variant of full hepatic artery originating from the superior mesenteric artery (Figure 3), variant IX in Michels' classification, which is seen in about 4.5% of the population^[13]. Knowing that the hepatic artery is present in its classical anatomy in only 55%, it is crucial that the operator takes these specificities into account when performing the angiography and subsequent embolization.

In conclusion, ruptured aneurysm of the hepatic artery without trauma leading to hemobilia is a rare and life-threatening condition. Clinicians need a high index of suspicion in order to diagnose and treat it adequately. The first line treatment is now angiography and supra-selective embolization, as it has superseded surgical intervention.

COMMENTS

Case characteristics

An 89-year-old female with history of abdominal pain, inappetence, vomiting and several episodes of hematemesis and hematochezia.

Clinical diagnosis

The patient was jaundiced.

Differential diagnosis

Bleeding gastro-duodenal ulcer; biliary tumor; Mallory-Weiss syndrome.

Laboratory diagnosis

White blood cell 11 g/L, aspartate aminotransferase 111 U/L, alanine aminotransferase 103 U/L, gamma-GT 247 U/L, alkaline phosphatase 473 U/L, total

bilirubin 20 µmol/L, direct bilirubin 14 µmol/L.

Imaging diagnosis

Ruptured aneurysm of the branch of the right branch of a full hepatic artery originating from the superior mesenteric artery.

Treatment

Fluid challenge, blood transfusion, selective arteriography with selective microcoils embolization, antibiotherapy.

Term explanation

Hemobilia is a rare case of upper gastrointestinal bleeding due to arterio-biliary fistula.

Experiences and lessons

Focusing on the clinical recognition of hemobilia in this particular setting of gastrointestinal bleeding and a positive experience with selective angiography and embolization for diagnosis and treatment. It requires a high index of suspicion particularly in the absence of an established traumatic or iatrogenic event.

Peer-review

The authors demonstrated a rare case of spontaneous aneurysm of the right hepatic artery, and that the patient has been successfully treated by selective embolization of micro coils.

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Enteric duplication cyst as a leading point for ileoileal intussusception in an adult: A rare cause of complete small intestinal obstruction

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Informed consent statement: Informed written consent has been obtained from the patient before commencement of the reporting this case.

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Abstract

Duplication of alimentary tract (DAT) presenting as an ileoileal intussusception is a very rare clinical entity. Herein, a case of an ileoileal intussusception due to DAT is presented. A 32-year-old woman was hospitalized due to diffuse, intermittent abdominal pain, vomiting and constipation for 3 d associated with abdominal distention. Plain abdominal X-ray revealed dilated small bowel. Abdominal computed tomography showed grossly dilated small bowel with "sausage" and "doughnut" signs of small bowel intussusception. She underwent laparotomy, with findings of ileoileal intussusception due to a cystic lesion adjacent to the mesenteric side. Resection of the cystic lesion along with the affected segment of intestine, with an end to end anastomosis was performed. The histopathology was consistent with enteric duplication cyst. This case highlights the DAT, although, an uncommon cause of adult ileoileal intussusception should be considered in the differential diagnosis of intussusception in adults, particularly when the leading point is a cystic lesion.

Key words: Enteric cyst; Ileoileal intussusception; Duplication of alimentary tract; Small intestinal obstruction; Doughnut sign

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Core tip: I have reported this case of ileoileal intussusception in an adult due to duplication of alimentary tract (DAT) being the cause of intussusception. Although intussusception is a well-known surgical condition, the presence of DAT as a leading point is extremely

rare. Only few cases have been reported in the English literature. Computed tomography, although identified the intussusception, the exploratory laparotomy established the DAT as a leading point for the ileoileal intussusception. Resection of the enteric cyst along with the affected intestine, and end to end anastomosis was performed. The histopathology was consistent with enteric duplication cyst.

Al-Qahtani HH. Enteric duplication cyst as a leading point for ileoileal intussusception in an adult: A rare cause of complete small bowel obstruction. *World J Gastrointest Surg* 2016; 8(6): 472-475 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i6/472.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i6.472>

INTRODUCTION

Duplication of the gastrointestinal tract is a rare congenital malformation which has been termed by Fiorani *et al*^[1] as duplication of alimentary tract (DAT). Midgut is the most common site of DAT, with the majority of cases reported in the distal small bowel^[2]. The presenting symptoms and signs of DAT include nausea, vomiting, bright red blood per rectum, abdominal distention and palpable abdominal mass. The clinical presentation of DAT with intestinal obstruction is either due to adjacent pressure on the bowel wall, volvulus, or rarely due to intussusception^[3]. A rare case of DAT causing ileoileal intussusception, in which the treatment was segmental resection of the affected ileum with an end to end anastomosis is herein presented. The objective in presenting this case is to raise the awareness among clinicians of this rare cause of small bowel obstruction. The case is discussed in the context of other reported cases in the literature.

CASE REPORT

A 32-year-old woman presented to the emergency department (ED) with diffuse intermittent abdominal pain, vomiting, and constipation for 3 d associated with progressive abdominal distention. On examination, she was dehydrated, with a blood pressure of 100/55 mmHg, pulse rate of 110 beat/min, temperature of 37.6 °C. The abdomen was diffusely distended with mild diffuse discomfort and exaggerated bowel sounds. Digital and proctoscopic examinations were normal with empty rectum. Immediate resuscitation in the ED was started with intravenous infusion of crystalloid fluids through large bore intravenous cannulae. A nasogastric tube was inserted which drained large amount of greenish fluids. A Foley catheter was inserted, with drainage of concentrated, minimal amounts of urine. Laboratory values revealed a white blood cell count of 14.6 × 10⁹/L [normal range (NR) = 4.3-10.8], hemoglobin 14.4 g/dL (NR = 14-18), urea

8.5 mmol/L (NR = 3.6-7.1), creatinine 129 mmol/L (NR < 133 mmol/L), and normal coagulation profile. Plain abdominal X-ray revealed dilated small bowel loops (Figure 1). Abdominal computed tomography (CT) showed grossly dilated small bowel loops with "sausage" and "doughnut" signs of small bowel intussusception. She underwent exploratory laparotomy with a provisional diagnosis of small bowel obstruction due to intussusception. Abdominal exploration revealed massively dilated small bowel proximal to ileoileal intussusception. After manual reduction of the intussusception, segmental ileal resection with an end to end anastomosis was performed. Exploration of the resected segment showed the leading point of intussusception was a cystic lesion measuring 4 cm in diameter which was located adjacent to the mesenteric side of the ileum (Figure 2). The histopathology showed an ileal duplication cyst lined by enteric mucosa with distinct muscular layer in the cyst wall. The patient was discharged from the hospital on 7th day postoperatively with an uneventful postoperative course.

DISCUSSION

DAT has been defined by Ladd *et al*^[4] as a tubular or spherical shaped anomaly that is adherent or attached to and shared the identical phenotypic characteristics with the normal gastrointestinal tract (GIT). It is a rare congenital malformation which can occur anywhere in the GIT from the mouth to the anus, with few cases reported in extraintestinal spaces such as oropharynx, retroperitoneum and spines^[5]. It is a separate entity from GIT with their own lumen, which can occur either on the mesenteric or the contralateral side^[6]. As the mucosa of the DAT is functional and separate from the intestine, they can expand as their mucosa secret fluids and become symptomatic^[6].

The most widely accepted theory for the DAT formation is that the duplication of GIT occurs during embryological development due to a pinching off of diverticulum^[5]. The majority of cases have been reported in infants and childhood, however, rarely it has been reported in adults as well^[7]. The most commonly reported clinical manifestation of DAT in adult is small bowel obstruction but rarely it may serve as a lead point for intussusception of small bowel, GIT bleeding or iron deficiency anemia due to chronic blood loss^[3,5,6]. The etiology of GIT bleeding is varied from abrasion, irritation, or ulceration of mucosal layer within the duplication cyst, or it may arise due to either a disruption of the common blood supply or malignancy which may result in gradual or brisk blood loss^[5].

The adult patient reported here presented with a classical symptoms and signs of small bowel obstruction. Intussusception in adults is account for about 5% of all intussusceptions and the underlying cause of only 1% of bowel obstruction^[8]. However, a definite underlying cause is present in about 90% of intussusception in adults^[9]. A wide variety of ileal lesions may be responsible for ileoileal

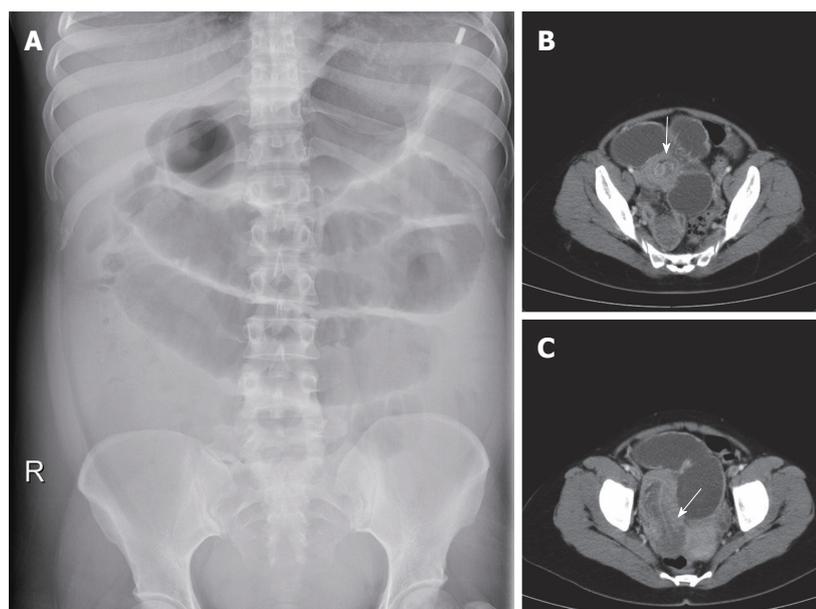


Figure 1 Plain abdominal X-ray revealed dilated small bowel loops. A: Plain abdominal radiograph showing dilated small bowel; B: Abdominal computed tomography showing grossly dilated small bowel loops with “doughnut”; and C: “sausage” signs of small bowel intussusception.

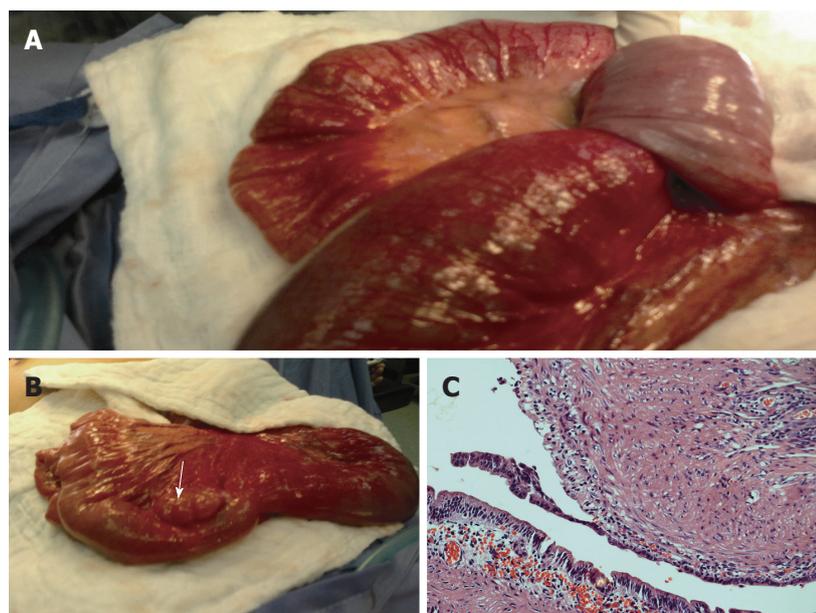


Figure 2 The leading point of intussusception was a cystic lesion measuring 4 cm in diameter which was located adjacent to the mesenteric side of the ileum. Intraoperative photography revealing the (A) ileoileal intussusception (B) enteric cyst in the mesenteric side of the ileal loop which was the lead point of the intussusception and (C) Histopathology of enteric duplication cyst lined by columnar intestinal mucosa with underlying muscular layer. The outer layer of the cyst wall was fused with normal intestine (H/E stain × 200).

intussusception. Benign tumors including inflammatory fibroid polyp, hamartomatous polyp, lipoma, as well as malignant tumors such as ileal cancer and lymphoma and Meckel's diverticulum have all been described as lead points for ileoileal intussusception^[3]. In our patient, the lead point was DAT in the mesenteric side of the mid-part of the ileum. Both DAT and intussusception are unusual pathological entities in adult patients, and it is very rare to have the combination of both events in one patient^[3]. Although it has been reported in infants and childhood^[10,11], to the best of our knowledge, this

is the second adult case of DAT identified as a lead point for ileoileal intussusception. Ultrasonography in intussusception may show a “doughnut” configuration on transverse view, while on longitudinal view it may show “pseudokidney” configuration. The detection of excess fluid should raise the suspicion of a lead point lesion^[7].

Abdominal CT scan is the most sensitive diagnostic tool for the imaging of intussusceptions. It reveals a pathognomonic appearance of soft tissue mass consisting of the central intussusceptum and the outer

intussusciens. It appears as "sausage-shaped", when the CT scan beam is parallel to the intussusception, and it appears as a "target" when the beam is perpendicular to its axis^[12]. Clinical and radiological signs of DAT may mimic those of intussusception. Hence, the diagnosis can generally be established only by surgical evaluation^[13]. In the present case, CT scan revealed grossly distended proximal small bowel, and both sausage-shape and target signs with diagnosis of small bowel obstruction due to intussusception. However, the DAT was not clear in CT scan as a lead point for intussusception. The differential diagnosis of DAT in association with ileoileal intussusception primarily includes lymphangioma, omental cyst, mesenteric lymphoma, fluid encapsulated in the mesentery during intussusception, Meckel's diverticulum and intramural neoplasm^[3]. A correct and timely diagnosis is necessary not only to resect the underlying lesion that serve as the lead point for intussusception but also to avoid the serious complications of bowel infarction and perforation secondary to obstruction. Resection of the affected bowel and the DAT is recommended to relief the bowel obstruction and to avoid the patient further complications^[7]. This patient underwent exploratory laparotomy with presumed diagnosis of complete small bowel obstruction due to intussusception. Abdominal exploration revealed intussusception in the ileum due to cystic lesion located in the mesenteric side of the bowel. The affected bowel was resected with the cystic lesion and end to end bowel anastomosis was established.

In conclusion, a rare case of ileoileal intussusception due to DAT in a young adult woman is reported herein. This case highlights the DAT as an uncommon cause of adult ileoileal intussusception. DAT should be considered in the differential diagnosis of intussusception in adults particularly when the leading point is a cystic lesion. Treatment of choice is resection of the lead point with the affected small intestine and end to end anastomoses.

COMMENTS

Case characteristics

A 32-year-old woman presented to the emergency department with diffuse intermittent abdominal pain, vomiting, and constipation for 3 d associated with progressive abdominal distention.

Clinical diagnosis

The abdomen was diffusely distended with mild diffuse discomfort and exaggerated bowel sounds.

Differential diagnosis

The clinical condition could be small bowel obstruction or large bowel obstruction.

Laboratory diagnosis

Leukocytic count was high.

Imaging diagnosis

Abdominal computed tomography showed grossly dilated small bowel loops with "sausage" and "doughnut" signs of small bowel intussusception.

Treatment

Exploratory laparotomy, resection of ileoileal intussusception and the leading point was cystic lesion measuring 4 cm in diameter which was located adjacent to the mesenteric side of the ileum.

Pathological diagnosis

Enteric duplication cyst as a leading point of intussusception.

Experiences and lessons

Enteric duplication cyst should be considered in the differential diagnosis of intussusception in adults particularly when the leading point is a cystic lesion.

Peer-review

The author describes a rare case of ileoileal intussusception due to enteric duplication cyst in adult patient.

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Umbilical hernia in patients with liver cirrhosis: A surgical challenge

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Abstract

Umbilical hernia occurs in 20% of the patients with liver cirrhosis complicated with ascites. Due to the enormous intraabdominal pressure secondary to the ascites, umbilical hernia in these patients has a tendency to enlarge rapidly and to complicate. The treatment of umbilical hernia in these patients is a surgical challenge. Ascites control is the mainstay to reduce hernia recurrence and postoperative complications, such as wound infection, evisceration, ascites drainage, and peritonitis. Intermittent paracentesis, temporary peritoneal dialysis catheter or transjugular intrahepatic portosystemic shunt may be necessary to control ascites. Hernia repair is indicated in patients in whom medical treatment is effective in controlling ascites. Patients who have a good perspective to be transplanted within 3-6 mo, herniorrhaphy should be performed during transplantation. Hernia repair with mesh is associated with lower recurrence rate, but with higher surgical site infection when compared to hernia correction with conventional fascial suture. There is no consensus on the best abdominal wall layer in which the mesh should be placed: Onlay, sublay, or underlay. Many studies have demonstrated several advantages of the laparoscopic umbilical herniorrhaphy in cirrhotic patients compared with open surgical treatment.

Key words: Umbilical hernia; Liver transplantation; Liver cirrhosis; Ascites; Hernia repair; Surgical site infection; Mesh; Ascites drainage

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Core tip: Umbilical hernia management in cirrhotics is controversial. Indication, timing, and surgical options of herniorrhaphy such as mesh use and laparoscopic

access in these patients remain controversial. This comprehensive review shows that umbilical hernia prevalence is very high in cirrhotic patients with ascites. The etiopathogenesis of umbilical hernia in these patients is discussed in detail. Umbilical hernia management changed markedly in the last decades due to better medical care of cirrhotic patients. Ascites control is the mainstay to avoid surgical complications and recurrence.

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INTRODUCTION

Umbilical hernia is a common condition, with a prevalence of 2% in the general adult population^[1]. Hernia incidence in cirrhotics with ascites is 20%^[2,3]. Umbilical hernia in these patients has a tendency to enlarge quickly and become symptomatic^[4]. Unlike the general population, in which female sex and obesity are risk factors for umbilical hernia, cirrhotic patients who form umbilical hernias are more likely to be men with ascites^[2-4].

The treatment of cirrhotic patients with umbilical hernia is controversial^[5-8]. In the past, these patients were usually treated expectantly due to the elevated rate of complication and hernia recurrence^[5,6]. Nonetheless, expectant management may lead to severe complications, such as hernia incarceration and necrosis and perforation of the overlying skin followed by evisceration, ascites drainage, and peritonitis^[7,8]. Many recent studies showed that the results of surgical repair depend on the presence of ascites and liver function grade^[9-12]. Elective umbilical herniorrhaphy is safe and effective in most cirrhotic patients in which ascites is adequately controlled^[12]. However, it should be avoided in patients in which ascites is not controlled.

At present, there is no high-quality prospective randomized study on management of cirrhotic patients with umbilical hernia to guide decision-making^[4]. Indication, timing, and technical aspects of herniorrhaphy in these patients remain controversial^[6-10]. Use of mesh and laparoscopic access is also subject to debate^[13-15]. Our objective in the present article is to review the management of cirrhotic patients with umbilical hernia, including the indications and results of the surgical treatment. Use of mesh and the laparoscopic access employed in the surgical repair is also reviewed.

PREVALENCE AND ETIOPATHOGENESIS

Umbilical hernia is the third most common abdominal hernia in the general population, after inguinal hernia and incisional hernia^[1]. In cirrhotic patients, the preva-

lence of umbilical hernia is higher^[16]. Nearly 20% of cirrhotic patients with ascites have umbilical hernia^[2,3]. Prevalence of inguinal hernias is relatively unaffected by ascites^[6].

Umbilical hernia etiology in cirrhotics is multifactorial^[3-5]. Elevated abdominal pressure secondary to ascites may initiate protrusion of abdominal content through a potential defect at umbilicus^[15]. Ascites is possibly the major etiologic factor^[6-10]. In cirrhotics, umbilical hernias occur almost exclusively in patients with persistent ascites^[11-14]. In addition to increase intra-abdominal pressure, ascites correlates with liver dysfunction. Other important contributory factor is abdominal wall muscle weakness due to hypoalbuminemia and recanalization, dilation and varices formation of the umbilical vein at the umbilicus as a result of portal hypertension^[16,17].

In the general population with no co-morbidities, acquired umbilical hernia increases in size very slowly^[1]. On the contrary, in individuals with intraabdominal pressure elevated, such as in cirrhotic patients with ascites, umbilical hernia size increases rapidly^[6,16]. In addition, ascites is also important in the development of complications in these patients. Ascites may precipitate hernia incarceration of intestine or omentum into the dense fibrous ring at the neck of the hernia^[17-20]. Enormous increase of intraabdominal pressure secondary to tense ascites may also cause pressure necrosis and perforation of the overlying skin followed by evisceration, ascites drainage, and peritonitis^[19,21].

INDICATIONS AND TIMING OF HERNIA REPAIR

Elective umbilical herniorrhaphy in the general population is the standard treatment^[1]. Hernia repair in individuals with no co-morbidities is an operation associated with low complication rate^[9]. On the contrary, umbilical herniorrhaphy in cirrhotic patients may cause expressive morbidity, such as wound infection and dehiscence, ascitic drainage through the incision, peritonitis, liver failure, and hernia recurrence^[9,10]. Furthermore, presence of umbilical hernia reduces the quality of life^[22].

Historically, cirrhotic patients who were subjected to umbilical herniorrhaphy had elevated morbidity and mortality rates that correlated with the severity of liver dysfunction^[9,10,16]. The potential complications include decompensation of liver disease, hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, infection, and high hernia recurrence rate^[7,8]. Therefore, in the past, surgeons avoided to perform elective umbilical herniorrhaphy in cirrhotic patients despite the operation simplicity^[9,23-26].

Umbilical herniorrhaphy in cirrhotics was performed only in patients with hernia complications. Conservative management was the initial option. Nonetheless, expectant management is associated with elevated rate of complications, such as hernia incarceration,

evisceration, ascites drainage, and peritonitis^[2,18,21]. Morbidity and mortality are high when umbilical hernia repair is performed on these patients^[2,18,27,28].

With improvement in the medical care of cirrhotic patients in the last decades, some studies have showed a significant reduction of umbilical herniorrhaphy complications in these patients^[4,6,23]. Marsman *et al*^[7] have compared elective surgical repair ($n = 17$) with expectant treatment ($n = 13$) in cirrhotic patients with umbilical hernia and ascites. The authors reported that expectant treatment was associated with elevated morbidity and mortality^[7]. Hospital admission for hernia incarceration was observed in 10 of 13 patients (77%), of which 6 needed emergency herniorrhaphy^[7]. Two patients (15%) who were subjected to expectant treatment died from hernia complications. Conversely, no complications or hernia recurrence was recorded in 12 of 17 patients (71%) who underwent elective herniorrhaphy.

Other studies have also describe superior results and have suggested elective umbilical herniorrhaphy in cirrhotic patients in order to avoid complications associated with conservative management^[5,8,9].

Indications and the optimal timing to repair an umbilical hernia in cirrhotic patients remain controversial. Several studies have demonstrated that umbilical hernia repair outcomes in cirrhotics depend on the presence of ascites and liver function grade^[6,8]. Child's classification and MELD score have been employed to determine the surgical risk^[29-31]. Some other adverse predictors include esophageal varices, age older than 65 years, and albumin level lower than 3.0 g/dL^[10].

Most studies have demonstrated that effective treatment of ascites is the essential for umbilical herniorrhaphy in cirrhotic patients^[5,7]. In addition, effective ascites control also reduces complications, such as wound infection, evisceration, ascites drainage from the wound, and peritonitis^[6].

Medical treatment of ascites with sodium restriction, diuretics, and paracentesis should be the first step in the management. In patients with no significant comorbidities in whom medical treatment is effective in controlling the ascites, umbilical hernia repair is indicated^[6].

If medical treatment fails, ascites drainage or shunting is indicated either before or at hernia correction^[7-9]. Presently, intermittent paracentesis, temporary peritoneal dialysis catheter or transjugular intrahepatic portosystemic shunt (TIPS) may be employed. These procedures significantly reduce the incidence of hernia recurrence and wound dehiscence^[23,32].

Slakey *et al*^[32] suggested that the insertion of temporary peritoneal dialysis catheter at the end of umbilical herniorrhaphy in cirrhotic patients was effective in controlling ascites and reducing the complication rate. This approach has some advantages, such as outpatient care during the postoperative period and easy removal of the catheter^[32]. However, peritoneal catheters are

associated with a high risk of bacterial infections, which significantly increase mortality and should be discouraged^[33].

In a survey performed recently with members of the Canadian Hepato-Pancreato-Biliary Society, the preferred choice to ascites treatment in these patients was the use of temporary peritoneal dialysis catheter until wound healing was completed^[23]. However, others reported that preoperative TIPS was preferable^[27].

Rapid preoperative ascites drainage, either by paracentesis or peritoneal dialysis catheter ascites, is not a risk free procedure, and may cause strangulation of the hernia^[10,23,27]. Therefore, it is recommended that ascites drainage should be gradual. Other shuntings, such as portocaval shunt and peritoneovenous shunt, are rarely employed at present. In patients in whom the shunt is effective, surgical treatment of umbilical hernia can be safely performed in most cases^[4,34].

In patients in whom ascites control is ineffective, the best alternative is to repair the hernia during the transplant operation, if the patient is on the waiting list for liver transplant^[16,35]. Otherwise, surgical repair should not be recommended. Based on literature data, an algorithm for the management of cirrhotic patients with umbilical and ascites is shown in Figure 1.

HERNIA REPAIR IN CANDIDATES TO LIVER TRANSPLANTATION

Liver transplant candidates may underwent umbilical herniorrhaphy during the transplant operation. Patients who have a good perspective to be transplanted within 3-6 mo, herniorrhaphy should be done during transplantation^[7]. Postponement of hernia correction is not advisable due to the risk of post-transplant intestinal strangulation of an uncorrected umbilical hernia^[6,7,16]. Pressure bandage should be applied carefully on the hernia until transplantation to avoid complications^[16].

Some patients with patent large umbilical vein who underwent umbilical hernia repair may need emergency liver transplantation due to acute liver failure^[16]. Ligation of a large patent umbilical vein during hernia repair may cause acute liver failure as a result of acute portal vein thrombosis or embolization^[16,25].

The umbilical hernia may be repaired at the end of liver transplantation either from inside the abdomen through the same incision employed for the transplantation or through an additional para-umbilical incision^[16]. In a retrospective study, de Goede *et al*^[16] reported the only study of the literature comparing the two incisions. The recurrence hernia rate was higher in the same incision group than in the separate incision group (40% vs 6%)^[16]. The number of patients was small in this retrospective study to allow recommendations. At present, the decision of which incision should be used for umbilical hernia repair during liver transplantation is based on the surgeon's experience^[7,16].

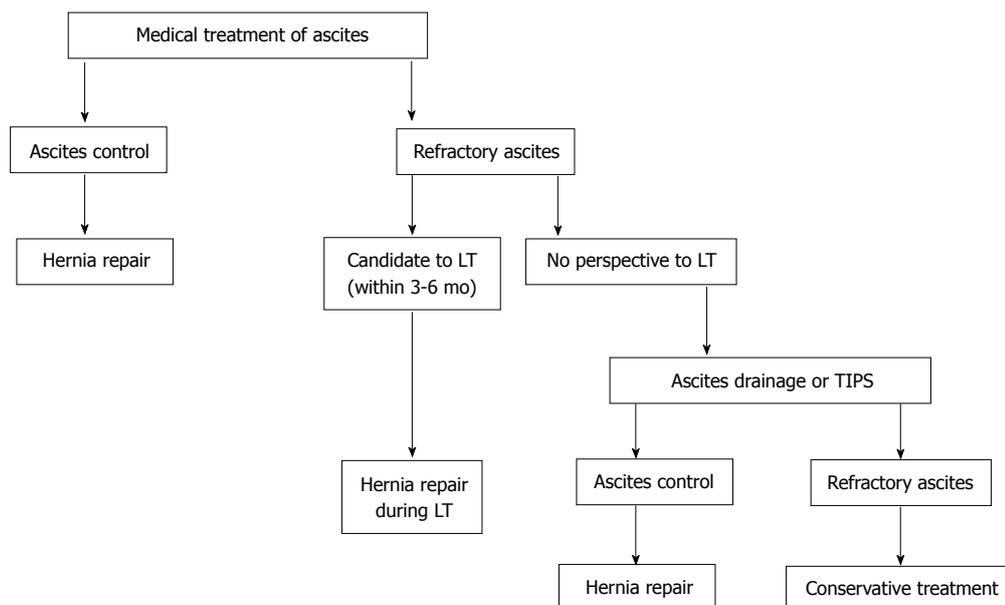


Figure 1 Management of umbilical hernia in patients with liver cirrhosis and ascites. LT: Liver transplantation; TIPS: Transjugular intrahepatic portosystemic shunt.

TREATMENT OF COMPLICATED HERNIA

The rate of complications is high in cirrhotic patients with umbilical hernia and ascites, mainly due to the enormous intraabdominal pressure that enlarges the hernia rapidly^[7]. These complications include infection, incarceration, strangulation, and rupture. Non-operative management of these complications is associated with elevated morbidity and mortality^[2,7,18,23]. The mortality rate ranges from 60% to 80% following conservative management of ruptured umbilical hernia and 6% to 20% after urgent herniorrhaphy^[2,23]. Therefore, complicated umbilical hernia in cirrhotics with ascites should be corrected urgently^[2,23].

Initially, the patient should be subjected to appropriate resuscitation with intravenous fluids and antibiotics to prevent or treat ascitic fluid infection^[2]. Sterile dressing is indicated in patients with ascitic fluid drainage or cutaneous infection. After patient stabilization, umbilical herniorrhaphy should be done with sutures^[2,18]. Mesh should be avoided to decrease the risk of infection^[2,18]. Ascites control is important to reduce complications and hernia recurrence^[7-9].

HERNIA REPAIR WITH OR WITHOUT MESH

As a result of elevated recurrence rate following the correction of abdominal hernias, including umbilical hernia, in cirrhotic patients, prosthetic mesh repair has been introduced and revolutionized hernia surgery^[13,36]. Hernia repair with mesh compared with suture repair reduces hernia recurrence rate, but increases the risk of some complications, including infection, seroma, mesh erosion, and intestinal adhesion, obstruction, and fistula^[36-38].

Several studies have demonstrated that elective mesh umbilical herniorrhaphy in cirrhotic patients with ascites is simple, safe, effective, and reduce hernia recurrence markedly^[4,7,12]. However, many surgeons are still reluctant to employ mesh for hernia correction in these patients because of the risk of wound complications^[12,23]. A significant complication in this group of patients is ascites leakage through the wound, which elevates the possibility of wound and mesh infection, followed by need of mesh removal^[36].

In a recent randomized study, 80 cirrhotic patients subjected to umbilical hernia repair were divided into two groups, with a follow-up of 6 to 28 mo^[4]. Hernia recurrence rate was lower in the group in which polypropylene mesh was used compared to the group without mesh in which the hernia correction was performed by conventional fascial suture (14.2% vs 2.7%)^[4]. In this study, surgical site infection was more likely to occur in the mesh group than in the group without mesh, even though no patient needed mesh removal^[2]. No mesh exposure or fistulas were observed in this series.

Techniques of mesh placement include onlay, inlay, sublay, and underlay^[36,38]. In the onlay repair, the mesh is sutured on external oblique fascia, after dissection of the subcutaneous tissue and closing of the fascia^[36]. In the inlay technique, the mesh is placed in the hernia defect and sutured circumferentially to the edges of the fascia^[36]. In the sublay procedure, the mesh is inserted in the preperitoneal space or retro-rectus^[36]. In the underlay procedure, the mesh is placed intraperitoneally and fixed to the abdominal wall, usually with tackers^[36].

The risks of complications are related to the space in which the mesh is placed^[36]. In the onlay technique, wound complications are more frequent, such as seroma, hematoma, ascites drainage, and infection of the surgical incision and mesh. This is due to the

Table 1 Advantages of laparoscopic umbilical hernia repair in patients with liver cirrhosis^[15,36,37]

Minimally invasive
Tension free repair
Minimal ascites leakage through the wound
Less damage to the large collateral veins
Restricts electrolyte and protein loss due to non-exposure of viscera
Reduced blood loss
Decreased pain
Better aesthetics
Early recovery
Reduced hernia recurrence

extensive detachment of subcutaneous tissue from the fascia, which typically creates a dead space between the mesh fixed on the fascia and the subcutaneous tissue. At present, inlay repair is used only occasionally due to high wound infection and recurrence rates^[36].

Wound complications are less common in the sublay and underlay mesh repair techniques because the mesh lies quite deep in the preperitoneal space and intraperitoneally respectively and therefore distant from the subcutaneous tissue and skin^[13,36-38]. In the underlay technique, the mesh is in contact with abdominal contents and therefore is subjected to complications, such as intestine adhesion, obstruction, erosion, and fistula^[12,13,36,39]. For open surgery, the best abdominal wall layer to place the mesh is still controversial^[3,12,14,36]. For laparoscopic umbilical herniorrhaphy, the mesh is routinely inserted intraperitoneally and fixed to the abdominal wall^[13,37,38].

At present, countless types and brands of mesh for hernia repair are available. They may be absorbable and permanent synthetic meshes, allograft material, and xenograft material. There is no consensus on the best mesh^[12-14,36,37]. The selection is based on several aspects, including type of hernia, presence of infection, location or space of mesh placement, cost and surgeons's preference. The most common mesh used in onlay, inlay, and sublay techniques is the polypropylene mesh^[13,37,38]. For intraperitoneal mesh placement (underlay technique), synthetic meshes with different coatings or composite meshes are preferred in order to avoid intestine adhesion, occlusion, and fistula^[12,14,38].

OPEN OR LAPAROSCOPIC HERNIA REPAIR

The first laparoscopic umbilical herniorrhaphy was described by Sarit *et al*^[3] in 2003 in a patient with liver cirrhosis complicated with strangulated hernia. Several studies have documented the advantages of the less invasive laparoscopic access compared with the open surgical approach to treat umbilical hernia in cirrhotic patients^[13,15,37]. The laparoscopic umbilical herniorrhaphy is a minimally invasive and tension-free procedure in which a mesh is placed and fixed into the abdominal wall to close the inlet of the hernia^[21,40].

By minimizing the access incision, the laparoscopic approach reduces postoperative pain, recovery time, and morbidity^[15]. Advantages of laparoscopic umbilical herniorrhaphy in cirrhotics with ascites compared to open surgical treatment are shown in Table 1.

One possible disadvantage of laparoscopic herniorrhaphy is the higher cost, mainly of the equipment and material^[23,37,38,41,42]. As mentioned earlier, expansive synthetic meshes with different coatings or composite meshes are needed for laparoscopic hernia repair in order to avoid intestine adherence, occlusion, and fistula. Although, several studies have demonstrated higher costs of laparoscopic abdominal hernia repair, there is no specific study on cost associated with laparoscopic umbilical herniorrhaphy in cirrhotic patients^[3,39,41,42]. Considering the postoperative advantages of laparoscopic approach, additional studies are essential to establish the cost-effectiveness of umbilical herniorrhaphy in cirrhotics^[23,40].

The laparoscopic approach has been also used for complicated umbilical hernia in cirrhotics. Sarit *et al*^[3] performed laparoscopic repair for a strangulated umbilical hernia with refractory ascites successfully by releasing the incarcerated bowel loops and fixing a mesh.

Some technical details are important to be observed at laparoscopic umbilical herniorrhaphy in cirrhotic patients with ascites in order to avoid complications. Oblique insertion of trocars into abdominal wall may avoid postoperative ascitic fistula^[3]. Angulation of trocar insertion allows the layers of the abdominal wall to overlap and obstruct potential ascitic drainage. Veres's needle and trocar must be inserted carefully in the left subcostal region to avoid lesion of an enlarged spleen secondary to portal hypertension. In order to decrease the risk of hemorrhage, reduction of incarcerated umbilical hernia contents should be performed meticulously due to the proximity and adherence of umbilical varices^[17].

HERNIA RECURRENCE

Umbilical hernia recurrence rate in cirrhotics with ascites ranges from 0% to 40%^[3,4,6,7]. Effective ascites management is essential to achieve umbilical hernia repair success as well as to reduce recurrence rate. In a recent literature review, McKay *et al*^[23] identified only 3 retrospective studies comparing the hernia recurrence in cirrhotic patients with ascites control and without control. When the data of these studies were grouped in a meta-analysis evaluation, the recurrence rate was 45% (22 of 49 patients) in the ascites uncontrolled group and 4% (2 of 47 patients) in the controlled group. The authors concluded that uncontrolled ascites strongly correlates with umbilical hernia recurrence in cirrhotic patients^[7,23].

Several studies have reported lower umbilical hernia recurrence following hernia repair with mesh than repair without mesh in cirrhotic patients with ascites^[3,4]. In a randomized study with 80 cirrhotic patients who were

subjected to umbilical hernia repair, Ammar^[4] reported recurrence rate of 2.7% after hernia repair with polypropylene mesh compared with 14.2% following hernia repair without mesh. However, the rate of wound complications, such as seroma, hematoma, and wound and mesh infection, is higher following umbilical hernia repair with mesh.

In summary, most studies have demonstrated that cirrhotic patients with ascites should have umbilical herniorrhaphy electively after ascites control^[12]. When hernia complications occur, such as infection, incarceration, strangulation, and rupture, umbilical herniorrhaphy should be performed urgently. Ascites control is critical to reduce hernia recurrence and postoperative complications. For patients scheduled for liver transplantation, umbilical herniorrhaphy should be done during transplantation.

CONCLUSION

Expectant treatment of cirrhotic patients with umbilical hernia and ascites is associated with elevated rate of complications, such as incarceration, evisceration, ascites drainage and peritonitis. These complications require emergency surgical treatment, which carries expressive morbidity and mortality. Conversely, elective hernia correction may be performed with much less complications and it is therefore advocated. Ascites control is essential to reduce perioperative complications and recurrence. In candidates to liver transplantation, umbilical herniorrhaphy should be performed during transplantation, unless the patient presents with significant symptoms or hernia complication or if the perspective to be transplanted exceeds 3-6 mo. This review has major limitations due to lack of high-quality randomized studies. Most publications on umbilical hernia management in cirrhotic patients are case series or retrospective cohort studies with small number of patients. Definitive answers await large-scale prospective randomized controlled studies.

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Chronic haemorrhagic radiation proctitis: A review

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Abstract

Chronic haemorrhagic radiation proctitis (CHRP) is a difficult problem faced by the patients following radiation for pelvic malignancy. There is no standard

treatment for this condition, but many methods of treatment are available. The aim of this study was to review the literature to see whether there is an improvement in the available evidence in comparison with previously published systematic reviews in treating patients with CHRP. The PubMed/Medline database and Google Scholar search was selectively searched. Studies, which treated patients with rectal bleeding due to chronic radiation proctitis or CHRP, were included. Seventy studies were finally selected out of which 14 were randomized controlled clinical trials. Though these studies could not be compared, it could be seen that there was an improvement in the methodology of the studies. There was an objective assessment of symptoms, signs and an objective assessment of outcomes. But, still, there were only a few studies that looked into the quality of life following treatment of CHRP. To increase recruitment to trials, a national registry of cases with established late radiation toxicity would facilitate the further improvement of such studies. Some of the conclusions that could be reached based on the available evidence are 4% formalin should be the first line treatment for patients with CHRP. Formalin and argon plasma coagulation (APC) are equally effective, but formalin is better for severe disease. Refractory patients, not responding to formalin or APC, need to be referred for hyperbaric oxygen therapy or surgery. Radio-frequency ablation is a promising modality that needs to be studied further in randomized trials.

Key words: Radiotherapy; Complications; Systematic review; Proctitis; Formalin

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Core tip: The aim of this study was to review the literature to see whether there is an improvement in the available evidence in comparison with the previously published systematic reviews in treating patients with chronic haemorrhagic radiation proctitis (CHRP). The PubMed/Medline database and Google Scholar search was selectively searched. Seventy studies were finally

selected out of which 14 were randomized controlled clinical trials. It could be seen that there was an improvement of the methodology of the studies though they were not comparable. Based on the available evidence, 4% formalin should be the first line treatment for patients with CHRP.

Nelamangala Ramakrishnaiah VP, Krishnamachari S. Chronic haemorrhagic radiation proctitis: A review. *World J Gastrointest Surg* 2016; 8(7): 483-491 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/483.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.483>

INTRODUCTION

One to five percent of patients who receive radiotherapy as adjuvant or neoadjuvant therapy for pelvic malignancy will develop chronic haemorrhagic radiation proctitis (CHRP). In one of the recently published series, it was noted that 1319 patients received radiation for carcinoma of cervix over a period of 22 mo and 124 similar patients during the same period needed treatment for CHRP in the same centre^[1]. The meaning of the above sentence shows the magnitude of the problem of CHRP. Newer methods of radiotherapy like three-dimensional conformal radiation therapy and intensity-modulated radiation therapy can use higher doses of radiation to the target tissues with less exposure to adjacent normal tissues. Protons and neutrons, so-called particle radiation, are also being tested but the long-term outcomes of these modalities are not known, and these are expensive. The use of brachytherapy is also found to be associated with fewer complications. Thus, the incidence of CHRP is related to the dose of radiation, the area of exposure, methods of delivery, the use of cytoprotective agents and other factors^[2].

Because the rectum has a fixed position in the pelvis, it becomes more susceptible to radiation injury. Acute radiation injury of rectum occurs within three months of starting radiotherapy. It is an inflammatory process of rectal mucosa with a loss of microvilli, oedema, and ulceration. It is self-limiting and manifests as abdominal pain, tenesmus, diarrhoea, incontinence and urgency and resolves within three months^[3]. Unlike acute radiation proctitis, chronic radiation proctitis takes a period of 3 mo after pelvic radiation, but usual median time is 8-12 mo. It can also continue from acute phase^[3]. It is due to obliterative endarteritis, submucosal fibrosis, and neo-vascularization (Figure 1). Chronic radiation proctitis can present with rectal bleeding, tenesmus, mucus discharge, diarrhoea, incontinence, and urgency. It may be asymptomatic also. The diagnosis of radiation proctitis should be suspected if a patient presents with the above mentioned symptoms and gives a history of pelvic radiation. The diagnosis is confirmed by sigmoidoscopy or colonoscopy that shows

pale, friable mucosa with telangiectasia. Rectovaginal, recto-urethral, recto-vesicular fistulizing disease is a late-presenting sign. There is no role of biopsy to confirm the diagnosis since it may produce complications.

There is no standard treatment for CHRP. However many treatments are available like amino salicylates, butyric acid enema, steroid enemas, formalin, argon plasma coagulation (APC), hyperbaric oxygen, radiofrequency ablation and even surgical therapy. The outcome of any of these medical and surgical treatment can be disappointing^[1]. There are not many good-quality placebo-controlled trials.

In this study, our aim was to review the literature to see whether there is an improvement in the available evidence in comparison with previously published systematic reviews in treating patients with CHRP. The PubMed/Medline literature database was selectively searched for articles with the keywords "Proctitis/drug therapy"(Mesh) or "Proctitis/radiotherapy"(Mesh) or "Proctitis/surgery"(Mesh) and "radiotherapy", "Management of CHRP" "Related Review articles". In addition Google search and Google Scholar search was also made using key words "Radiation proctitis" "Formalin" "Endoscopic therapy" "APC" "Radiofrequency ablation" "cryotherapy" "Hyperbaric oxygen therapy" and "surgery". The literature search was mostly limited to articles in English and human patients. No limitations for the year of publication were applied. All the studies that treated patients with rectal bleeding due to chronic radiation proctitis or CHRP were included in the review. Studies of patients treating acute radiation proctitis were excluded.

We could find 142 articles in total. After removing the duplicates and studies on acute radiation proctitis, there were about 86 articles. Out of these 86, 16 were further excluded because of various reasons such as anecdotal studies. Various studies that were found to be relevant are summarized below. Importance was given to randomized controlled clinical trials.

STUDIES USING ANTI-INFLAMMATORY DRUGS, STEROIDS, SUCRALFATE AND PENTOSAN POLYPSULPHATE

Sulfasalazine or 5-aminosalicylates, steroids are the drugs used initially for treating CHRP. Their mechanism of action is by inhibition of prostaglandin synthesis. It may also be due to inhibition of folate-dependent enzymes^[4]. Sucralfate stimulates epithelial healing and forms a protective barrier^[5]. Sucralfate is shown to be better than anti-inflammatory agents^[6]. Pentosan polysulphate is similar to sucralfate. There are more than seven to eight publications using these drugs.

In a prospective double-blind, randomized controlled trial involving 37 consecutive patients with radiation-induced proctosigmoiditis^[6], there were 36 females treated for cervical cancer and one male treated for prostate cancer. The mean duration after completion

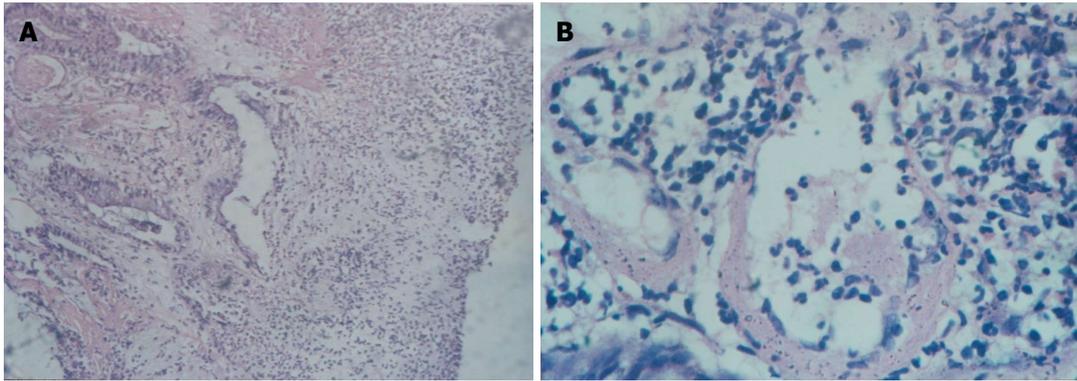


Figure 1 Chronic radiation proctitis. A: Chronic radiation proctitis (low power view). This picture shows the mucosa with severe oedema, non-specific inflammation, lymphocytosis, hyalinization in the stroma and fibrin thrombi in the postcapillary venules (Hematoxylin and Eosin stain, 10 ×); B: Chronic radiation proctitis (High power view). This picture shows two veins in the lamina propria, one with patchy occlusive fibrin thrombus. The wall shows thickening and hyalinization. A dense non-specific inflammation including few eosinophils also seen (Hematoxylin and Eosin stain, 40 ×).

of the radiotherapy was 8.3 mo. These patients were randomized to receive either 3 g oral sulfasalazine plus 20 mg twice daily of rectal prednisolone enemas (group I, $n = 18$) or 2 g of rectal sucralfate enema plus oral placebo (group II, $n = 19$) for four weeks. These two groups were comparable with respect to demography, clinical symptoms and endoscopic staging of the disease. Patients in Sucralfate enema showed a better clinical response although endoscopically the response was not statistically significant. Follow-up was limited to 4 wk.

Rougier *et al*^[7,8], in their randomized trial, compared betamethasone enema (5 mg bd) with hydrocortisone mousse (90 mg bd) and concluded that hydrocortisone group had a better outcome. There were 32 patients with CHRP in this study. The outcomes used were bowel activity, tenesmus, rectal bleeding and endoscopic grading. Follow-up was limited to 4 wk.

In another randomized study by Cavčić *et al*^[9], compared combination of oral metronidazole (400 mg tds), mesalamine (1 g tds) and rectal betamethasone to oral mesalamine and rectal betamethasone and found that the rectal bleeding and ulcers were significantly lower in the metronidazole group. In this study, there were sixty patients randomized into either group. The efficacy of metronidazole was assessed on the basis of rectal bleeding, diarrhoea and proctosigmoidoscopy in all patients. The follow-up was up to 12 mo. Grigsby *et al*^[10] prospectively showed the benefit of oral pentosan polysulphate given for a period of 1 year in 13 patients.

STUDIES USING SHORT-CHAIN FATTY ACID ENEMAS

Short-chain fatty acids (SCFA) stimulate the growth of colonic mucosa. The vasodilatation effect may improve the blood flow of colonic mucosa^[11]. Butyric acid is the main SCFA. There are more than six studies using SCFA. Many of them are case series.

Two randomized studies showed non-significant

improvement of symptoms and signs but both the studies were underpowered^[12,13]. Talley *et al*^[12] in their randomized double-blind placebo-controlled cross over trial of 15 patients treated one group with the butyric acid enema and another group with normal saline placebo. Symptoms score, endoscopic scores and even histology were compared.

Similarly, Pinto *et al*^[13] in their randomized prospective double blind controlled trial of 19 patients treated one group with SCFA enema and another group with placebo. In this study apart from symptoms and endoscopic features, biopsies for mucosal DNA and protein content were also measured. Patients were followed up to 6 mo.

Though we were treating patients with CHRP in our institute since 1985, study on chronic haemorrhagic proctitis were started in 1999. The first study on CHRP in our institute, done by Senthil Kumar *et al*^[14] in 2001, compared sucralfate-steroid enema (25 mg of prednisolone and 1 g of sucralfate twice daily for 14 d) with butyric acid retention enema (60 mL containing 40 mmol of butyric acid twice daily for 14 d) in a double-blind randomized controlled trial. There were thirty patients randomly allocated. They were followed up to 4 wk. Outcomes were measured by the improvement in the colonoscopic grading of severity and clinical symptoms. Histopathological improvements were also compared by taking the biopsy before and after treatment. The conclusion was that both the methods of treatment were equally effective since there was relief of symptoms of radiation proctitis in both the methods of treatment without improvements in endoscopic scores or histology. However, the sucralfate-steroid enema was easier to prepare^[14]. No toxicities were reported in any of these studies.

STUDIES USING FORMALIN THERAPY

Formalin scleroses and seals fragile neovasculature in tissues damaged due to radiation and prevents further bleeding. In 1986, Rubinstein was the first

to use formalin for a CHRP patient to get a good response^[15]. Following this, there are several reports in the literature^[16-30]. But the majority are retrospective in nature, a few are prospective studies. The technique and the concentration of formalin used in these studies also differ. The two main methods of using it are 4% solution as irrigation or as soaks. There are reports of using 10% solution of formalin also^[31]. There are four randomized trials using formalin for CHRP.

Ours is one of the first published randomized trial comparing the efficacy of the 4% formalin dab with Sucralfate-steroid retention enema (100 mg of prednisolone and 1 g sucralfate in 100 mL of normal saline twice daily for 14 d)^[1]. In this study, 102 patients were randomly allocated to either of the treatment arms. This study objectively assessed the symptoms scores using the radiation proctopathy system assessment scale (RPSAS) and also the sigmoidoscopic grade (Modified Chi grading) before and after treatment and found that Formalin dab is superior to sucralfate-steroid enema in treating CHRP involving only the rectum. It was also observed that a single session of formalin dab can effectively treat CHRP in 90% of the patients, and multiple sessions could effectively treat 99% of the patients whereas sucralfate-steroid enema was effective only in 75% of patients. These patients were followed up to 9 mo. There was no complications or toxicity.

Following this Yeoh *et al.*^[32] showed in their randomized study that APC and topical formalin had comparable efficacy in the durable control of rectal bleeding associated with chronic radiation proctitis but had no beneficial effect on anorectal dysfunction. In this study thirty patients were randomized into each group. Anorectal symptoms, (modified LENT-SOMA questionnaire) anorectal manometry and anorectal morphology by endorectal ultrasound were assessed before and after treatment.

Guo *et al.*^[33] in their randomized trial showed that 10% formalin is associated with complications and 4% formalin should be the choice for treating CHRP. In this study 122 patients were randomized into 4% or 10% formalin application. Outcomes were compared with symptoms score and rectoscopy scores. Follow-up was up to 1 year. Wong *et al.*^[34] from their prospective database, after a decade of experience of treating patients with radiation proctitis, have shown that formalin is more effective than APC in treating patients with CHRP. APC has the potential to complement topical formalin application and can be used to treat the proximal and distal rectum concurrently.

The contrary report has been published by Alfadhil *et al.*^[35] in their retrospective comparative study of 22 patients who received formalin application or APC. Improvement in Hb% was used to assess the outcome. The severity of the proctitis was not assessed before the treatment. The lag time between radiation and endoscopic treatment was not known. The study was underpowered, and the groups were not comparable.

The details of the adverse events not mentioned. They concluded that APC is more effective than formalin and has less adverse effects.

Sahakitrungruang *et al.*^[36] in their randomized controlled trial comparing colonic irrigation with oral antibiotics administration vs 4% formalin application for treatment of CHRP have shown that the former method is better than 4% formalin application. Fifty patients were randomly allocated to each arm. Daily self-administered colonic irrigation of 1 L tap water and a 1-wk period of oral antibiotics-ciprofloxacin and metronidazole were given in one arm. Four percent formalin application for 3 min was done in another arm. Patient's satisfaction was surveyed. The limitation was that the study was a 2-armed design without a crossover trial. Hence, it could not illustrate whether the antibiotics and irrigation were equally important. Some of the adverse events noted in the literature regarding the use of formalin for CHRP are the rectal stricture, worsening of incontinence, anococcygeal pain, and formalin colitis^[24,30].

STUDIES USING THERMAL COAGULATION THERAPY

Endoscopic coagulation with a variety of devices has been reported to be effective for CHRP^[7]. The technique involves coagulation of a bleeding point rather than the entire friable mucosa. Several treatment sessions are often required^[7]. The modalities include heater probe, bipolar Electrocoagulation, neodymium:yttrium-aluminium-garnet (Nd:YAG) laser, potassium titanyl phosphate (KTP) laser, argon laser and APC. Simple heater probe and APC are preferred for their better safety profile^[37].

Both the heater probe and bipolar cautery are contact probes. The heater probe has a Teflon-coated heating element at its tip that delivers standardized energy over set times. Bipolar electrocautery probe has a pair of electrodes at its tip through which current is passed using the tissue for conduction^[38]. Jensen *et al.*^[39] in his randomized study showed that 21 patients treated either with a heater probe, or bipolar cautery showed benefits without much difference between the two modalities^[39]. A mean of four sessions was needed in each arm during treatment in this study. Patients were followed up to one year. The increase in haematocrit, endoscopic resolution, and patient satisfaction were compared. No complications were noted.

Nd:YAG laser is the first endoscopic laser used for treating CHRP. Some of the complications reported with this are transmural necrosis, fibrosis, necrosis, stricture formation and recto-vaginal fistula. Nd:YAG laser use for CHRP has declined due to several reasons, firstly its cost; second, the need to aim directly at telangiectasias and the possibility of severe endoscopic damage if the laser strikes the endoscope in retroflexion^[40]. Taylor *et al.*^[41] used KTP laser for treating 26 patients

with bleeding secondary to CHRP using 4-10 W and a median of two sessions. They reported a symptomatic improvement in 65% patients while there was no change in 7 (30%), and symptom like hematochezia increased in 1 (5%). Similarly, there are only case series using argon laser for treating CHRP.

There are more than 15 published reports of APC for CHRP. Many are retrospective studies, and some of them are prospective case series. Many of the series report unsuccessful medical treatment before going for APC. In APC bipolar diathermy current is applied using inert argon gas as a conducting medium. It can be applied tangentially and radially.

Karamanolis *et al*^[42] showed in their prospective study treating more than 56 patients, that APC was successful in all patients with mild and in almost all patients with moderate CHRP. In contrast, APC failed in 50% of patients, wherever the presence of severe mucosal damage was present. The grading of severity was based on endoscopic criteria taking into consideration telangiectasia distribution and surface area involved. For APC application, a 2.3 mm diameter front firing APC probe inserted through the working channel of the flexible sigmoidoscope was used. The argon flow rate and the electrical power were set at 2 L/min and 40 W, respectively. Patients were followed up for a mean of 17 mo. Patients required 1-2 sessions of APC for mild proctitis while patients with moderately to the severe form required a statistically significantly higher number of APC sessions. In cases of severe and diffuse involvement of the rectum, multiple treatments sessions are required, and success is less certain as shown by other reports also^[43-51]. In many of these series, the response is objectively scored using bleeding severity score, haematological parameters, and endoscopic scores.

Chrusciewska-Kiliszek *et al*^[52] in their randomized, double-blind trial comparing oral sucralfate or placebo following APC for CHRP have shown that additional sucralfate treatment after APC did not influence the clinical or endoscopic outcomes. One hundred and seventeen patients completed the treatment protocol, 57 in the sucralfate group and 60 in the placebo group. Patients were graded clinically and endoscopically according to the Chutkan and Gilinski scales before and at 8 and 16 wk after initial APC treatment (1.5-2 L/min, 25-40 W) and after 52 wk (clinical only)^[52]. Complications (1%-15%) following APC, such as pain, ulceration, perforation, explosion, extensive necrosis and rectal stricture have been cited in the literature^[42].

STUDIES USING RADIO-FREQUENCY ABLATION

There are more than five reports of case series and retrospective studies using radio-frequency ablation (RFA) for CHRP. Many case series have shown, using BARRx Halo90 electrode catheter that was fit on the

distal end of the flexible sigmoidoscope, an energy density of 12 J/cm² at a power density of 40 W/cm², hemostasis could be obtained after 1 to 2 sessions^[53-56].

Several benefits RFA have been claimed, these include squamous re-epithelialization, lack of stricturing and ulceration. Using RFA much broader area of tissue can be treated simultaneously compared to the point by point approach by other methods^[37]. The radio-frequency unit is mobile and can be used in different rooms of an endoscopy unit. Zhou *et al*^[54] have used real-time endoscopic optical coherence tomography (EOCT) to visualize epithelialization and subsurface tissue microvasculature pre- and post-treatment RFA in their case series and have shown the potential of EOCT for follow-up assessment of endoscopic therapies.

STUDIES USING CRYOABLATION

Cryoablation is similar to APC and involves the non-contact application of liquid nitrogen or carbon-dioxide to tissues for superficial ablation. It is possible to treat a larger surface area like in RFA. Its effect is due to ischemic necrosis which can be immediate or delayed.

There are only case series of 20 patients. During cryoablation, a decompressive rectal tube has to be inserted because of the risk of over insufflation and perforation. Cryotherapy units are less mobile. Unlike in Radiofrequency ablation, the depth of tissue penetration may be more here. This may lead to strictures. However, colonic lavage is not necessary since there is no risk of explosion. The number of required sessions range from one to four^[57-59].

STUDIES USING HYPERBARIC OXYGEN THERAPY

There are more than 12 published studies using hyperbaric oxygen therapy (HBOT) for CHRP. New reports have started appearing in the literature regarding the efficacy of HBOT.

Clark *et al*^[60] in their randomized controlled double-blind crossover trial (150 patients) with a long-term follow-up, up to 5 years, showed that in patients with refractory CHRP, HBOT had a significant healing response. Primary outcome measures involved were the late effect in normal tissue-subjective, objective, management, analytic (SOMA-LENT) score and standardized clinical assessment. The secondary outcome was the change in the quality of life^[60].

In one of the largest Australasian study using HBOT for chronic radiation injuries, Tahir *et al*^[61] showed a clinical response rate for CHRP of 95%, where around half of the cases had a durable major response, with some patients experiencing symptom relief lasting as long as seven years.

At pressure greater than atmospheric pressure and using 100% oxygen, HBOT has an angiogenic effect and has been shown to cause an eight to nine-fold increase

in the vascular density of soft tissues over air-breathing controls^[7]. HBO acts to stimulate collagen formation and re-epithelialization. There is no uniformity in the methods of treatment using HBOT^[42,61-65]. Although it can be perceived from the studies that HBOT is useful in refractory radiation proctitis, there is marked variation between the studies. There are no major adverse effects. Minor adverse event recorded is transient aural barotrauma. The reported number of HBOT sessions for a successful treatment range from 12 to 90. The cost of HBOT is high, and hence, it is not widely applicable.

Other interventions

Oxidative stress is thought to be one of the mechanisms in the development of chronic radiation proctitis and antioxidants have been used to treat CHRP. Use of vitamin C and E have been reported. Kennedy *et al*^[66] treated twenty consecutive patients with CHRP. They used a combination of vitamin E at a dose of 400 IU tid and vitamin C at a dose of 500 mg tid. They assessed the response by symptom index and lifestyle questionnaire. A good number of study patients in the study seem to benefit. This pilot study was not studied further.

Retinol palmitate (vitamin A) has been shown to increase wound healing because of increased collagen cross-linking. This has been used in a randomized study to show improvement of symptoms of chronic radiation proctopathy by Ehrenpreis *et al*^[67]. They randomized 19 patients, 10 patients to retinol palmitate group and nine to the placebo group. Five placebo nonresponders were crossed over to the retinol palmitate. The RPSAS scores before and every 30 d for 90 d were measured. The definition of response was a reduction in two or more symptoms or by at least two RPSAS^[67]. There was a significant improvement in symptoms in the treatment group compared with the control and also when the controls were crossed over to treatment. But the study was underpowered.

Surgical interventions

Surgery is the last resort in patients with CHRP. Around 10%-25% of patients with CHRP finally need surgery^[68]. Intractable bleeding, perforation, stricture, and fistula are some of the indication for surgery in patients with chronic radiation proctitis. There are case reports of non-surgical dilatation for strictures for this condition^[69]. Significant improvement of bleeding by diversion has been shown by one of the retrospective study^[70]. Fistula with the adjacent structures may need resection or resection with reconstruction with a diverting stoma. Whenever surgical treatment became a necessity, studies report poor outcomes with high complications (15%-80%) and mortality (3%-9%)^[70-73]. Since nonoperative interventions are commonly used nowadays in managing patients with CHRP, There are no recently published series on surgical interventions on this issue.

Discussion

Evidence-based medicine requires the systematic and critical evaluation of published and unpublished trials^[74]. In 2002, when Denton *et al*^[7] first published their systemic review of the non-surgical intervention of late radiation proctitis, they could identify only six randomized controlled trials. The majority of the evidence available was either one individual's or one center's experience with a specific intervention without comparison to a control or another agent. This is probably due to the low incidence of chronic radiation proctitis in the majority of centers and the difficulties that co-exist in compiling a series large enough to be randomized between therapies^[34].

Thirteen years later we could identify a total of 14 randomized controlled trials treating 804 patients with CHRP. In many of these studies, we could get the details of the reason for radiation therapy and the dosage. The diagnosis was based on the history and the endoscopic findings. At present, there is no validated score for CHRP, which can be used universally for grading the severity. There can be the inter-observer difference of the same findings. Tissue biopsy may not be conclusive. Patients may not tell their exact symptoms unless directed questions are asked. The severity of the radiation proctitis was graded in many of the studies objectively using symptoms score like RPSAS^[1,67] or LENT-SOMA scale^[32,60] and intraluminal findings by the sigmoidoscopic or colonoscopic grade (modified Chi grading^[1] or Chutkan and Gilinski scales^[52]). But different studies used different severity scores and hence the inter-institutional comparison of data is still difficult. The same is true with the outcome measures. Yeoh *et al*^[32] have tried to see the rectal functions as well as morphology by using anorectal manometry and endorectal ultrasound. Zhou *et al*^[54] have shown the most efficient objective assessment of the response to treatment by using EOCT. There were only a few studies that surveyed the quality of life following treatment^[36,60]. However, unlike the previous studies, follow-up of recent studies is fairly long and is usually more than 9 to 12 mo^[1,33,36,52,60]. With these randomized trials it is possible to say that there is evidence to make the following judgments: (1) Sucralfate enema appears to have a better effect than anti-inflammatory agents; (2) Anti-inflammatory drugs appear to have a better effect if used with oral metronidazole; (3) Rectal hydrocortisone appears to have a better effect than rectal betamethasone; (4) Sucralfate-steroid retention enema and short chain fatty acid enema are both equally but moderately effective in treating CHRP, but sucralfate-steroid enema is easy to prepare; (5) Four percent formalin is more effective than sucralfate-steroid retention enema and can be effective in 99% of the patients of CHRP; (6) Four percent formalin should be preferred over 10% formalin in treating patients with CHRP since 10% formalin is likely to cause adverse events; (7) Heater probe and bipolar

cautery are equally effective in treating patients with CHRP; (8) Both APC and formalin don't improve the rectal dysfunction but only stop the bleeding; (9) Both APC and formalin are equally effective, but formalin may be better in severe disease; (10) Additional oral treatment after APC will not improve the outcomes; (11) Radiofrequency ablation is a promising upcoming modality of treating CHRP but more robust data in the form of randomized trials needed; (12) HBOT is the only treatment modality, currently, which addresses the underlying problem and effective in treating CHRP patients but is costly and available in a few centers; (13) Vitamin A and other modalities have to be kept in mind while treating these patients since some report shows its efficacy. Further trials and robust data needed to show its efficacy; and (14) Surgical intervention is to be kept as a last resort in patients not responding to any of the methods described above.

Looking at the available evidence, it is clear that there is some improvement in the methodology of these studies. There is an objective assessment of symptoms and signs and also the objective assessment of the outcomes in some of these studies. The major drawback is that the objective assessment is not uniform, different studies using different scores. Also, not much importance is given to the quality of life assessment following treatment. It has been felt by the previous reviewers that one study, even if well conducted, will not be able to modify the changes in practice^[7]. It has been felt by Denton *et al*^[7] that in order to increase recruitment to trials a national registry of CHRP cases would facilitate multicenter trials with uniform entry criteria, uniform baseline and uniform therapeutic assessments providing standardized outcome data^[75].

Limitations of this review: The search was limited to PubMed/Medline, Google and Google Scholar and was not complete and was limited to English language journals only. Individual authors were not contacted.

CONCLUSION

Based on this evidence, it can be concluded that the first line treatment of a patient with CHRP, the most effective way of treating CHRP, should be 4% formalin application. Since it is cheap, easily available, can be applied easily and effective in 99% of the patients. If the radiation proctitis extends beyond rectum, then APC will be a better alternative. Alternatively, both formalin and APC can be used as complementary methods. Those patients who are refractory to formalin or APC may be referred for treatment with HBOT. In centers where radiofrequency ablation is available, further randomized studies should be done to see the efficacy of it in treating patients with CHRP. Those patients with CHRP who do not respond to any of the modality may need surgery in the form of diversion colostomy. Those patients with CHRP presenting with complications like stricture, fistula or other complications like obstructions may need surgery at presentation.

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Retrospective Cohort Study

Early surgery in Crohn's disease a benefit in selected cases

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Abstract

AIM: To compare the outcomes of a cohort of Crohn's disease (CD) patients undergoing early surgery (ES) to those undergoing initial medical therapy (IMT).

METHODS: We performed a review of a prospective database CD patients managed at a single tertiary institution. Inclusion criteria were all patients with ileal or ileocolonic CD between 1995-2014. Patients with incomplete data, isolated colonic or perianal CD were excluded. Primary endpoints included the need for, and time to subsequent surgery. Secondary endpoints included the number and duration of hospital admissions, and medical therapy.

RESULTS: Forty-two patients underwent ES and 115 underwent IMT. The operative intervention rate at 5 years in the ES group was 14.2% *vs* IMT 31.3% (HR = 0.41, 95%CI: 0.23-0.72, $P = 0.041$). The ES group had fewer hospital admissions per patient [median 1 *vs* 3 ($P = 0.012$)] and fewer patients required anti-TNF therapy than IMT (33.3% *vs* 57%, $P = 0.003$). A subgroup analysis of 62 IMT patients who had undergone surgery were compared to ES patients, and showed similar 5 year (from index surgery) re-operation rates 16.1% *vs* 14.3%. In this subset, a significant difference was still found in median number of hospital admissions favouring ES, 1 *vs* 2 ($P = 0.002$).

CONCLUSION: Our data supports other recent studies suggesting that patients with ileocolonic CD may have a more benign disease course if undergoing early surgical intervention, with fewer admissions to hospital and a

trend to reduced overall operation rates.

Key words: Crohn's disease; Surgery; Inflammatory bowel disease; Terminal ileitis; Operation

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Core tip: This study supports the growing body of evidence that asserts that selected patients with ileocolonic Crohn's have reduced requirement for medical therapy and a trend to fewer surgical interventions. Expanding on the evidence, this study also demonstrated fewer admissions to hospital for Crohn's disease related illness.

An V, Cohen L, Lawrence M, Thomas M, Andrews J, Moore J. Early surgery in Crohn's disease a benefit in selected cases. *World J Gastrointest Surg* 2016; 8(7): 492-500 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/492.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.492>

INTRODUCTION

Surgery is often an integral part of the management algorithm for patients with Crohn's disease (CD), with up to 20%-40% requiring surgery within in their first year^[1-4] and up to 80% at some time during their disease^[5]. As a chronic condition with a relapsing remitting course, surgery does not provide cure, but is an adjunct for the management of acute complications of penetrating and stricturing disease and also after maximal medical therapy fails to control disease or presents unacceptable side effects. Advances in medical therapy have seen a reduction in long-term steroid use and longer disease remission. Despite these advances older studies suggest no reduction in the proportion of patients requiring surgery. In a retrospective series, Cosnes *et al*^[6], reported that 35% patients required surgery at 5 years, which was the same as historical cohorts.

However, the advent of biologic agents has significantly influenced the clinical course of patients of CD and also surgical decision-making. ACCENT 1 reported higher clinical remission (OR = 2.7) in patients receiving maintenance infliximab compared with placebo^[7]. Similar findings have been reported for Adalimumab with higher rates of clinical remission compared with placebo (36% vs 12%)^[8]. Additionally in a report from the Nationwide Inpatient Sample in the United States, rates of surgical intervention have fallen from 17.3% in 1997 to 12.4% in 2007^[9].

Contention exists in the literature regarding the optimal timing of surgery in the management algorithm of CD, particularly in patients with short segment disease where resection of all macroscopic disease is feasible. Some evidence suggests that early surgery (ES) in CD may lead to a longer time to clinical recurrence^[10]

and lower long-term reoperation rate (14% at 5 years) compared with later surgery (30% at 5 years)^[11]. Additionally, ES cohorts are reported to have reduced requirements for steroids and immunosuppression^[3,11]. This study aims to determine whether patients who have ES for ileal or ileocolonic CD run a more benign clinical course, as determined by the need for fewer operations, hospital admissions and the ongoing medical therapy required for disease control than those managed with conventional medical therapy.

MATERIALS AND METHODS

This study is a cohort comparison study between patients who underwent ES compared with those that underwent initial medical therapy (IMT). We examined a consecutive series of patients with ileal and ileocolonic CD managed at a major metropolitan teaching hospital from 1995 to 2014. Data were extracted from a clinical IBD database within the IBD service at the Royal Adelaide Hospital. This database was prospectively maintained from 2007, and prior to this, data were sourced from case notes review. Additional data were collected from review of medical records and pathology records.

ES was defined as patients who have undergone upfront surgery for CD due to an acute complication and those who underwent surgery within 6 mo of their diagnosis of CD. This arbitrary time frame was chosen as within this time period there is limited scope to have established of medical therapy. Acute complications included abdominal pain with peritonism, obstruction, perforation or fistulisation. The IMT cohort included patients with a histological or clinical diagnosis of CD made after 1995 referred to our health service who have undergone at least 6 mo of medical therapy. Patients diagnosed prior to this date were excluded. Patients in this cohort who went on to require bowel resection for their disease were also identified for a subgroup analysis and considered to have deferred surgery (DS).

Data collected included patient demographics, disease phenotype according to the Montreal classification^[12], medical and surgical therapy. The primary endpoint for each patient was need for subsequent surgical resection. Secondary endpoints were the number of hospitalizations and days in hospital over the duration of their disease. All inpatient care data (number of admissions and total length of stay) were captured by a statewide computer database, which records admissions to all public hospitals within the state in this period.

Inclusion criteria were patients with ileal or ileocolonic CD, with or without perianal involvement. Patients with isolated colonic or isolated perianal CD or those with incomplete records were excluded.

Data regarding patients' medical therapy for CD were collected, but due to the retrospective nature of

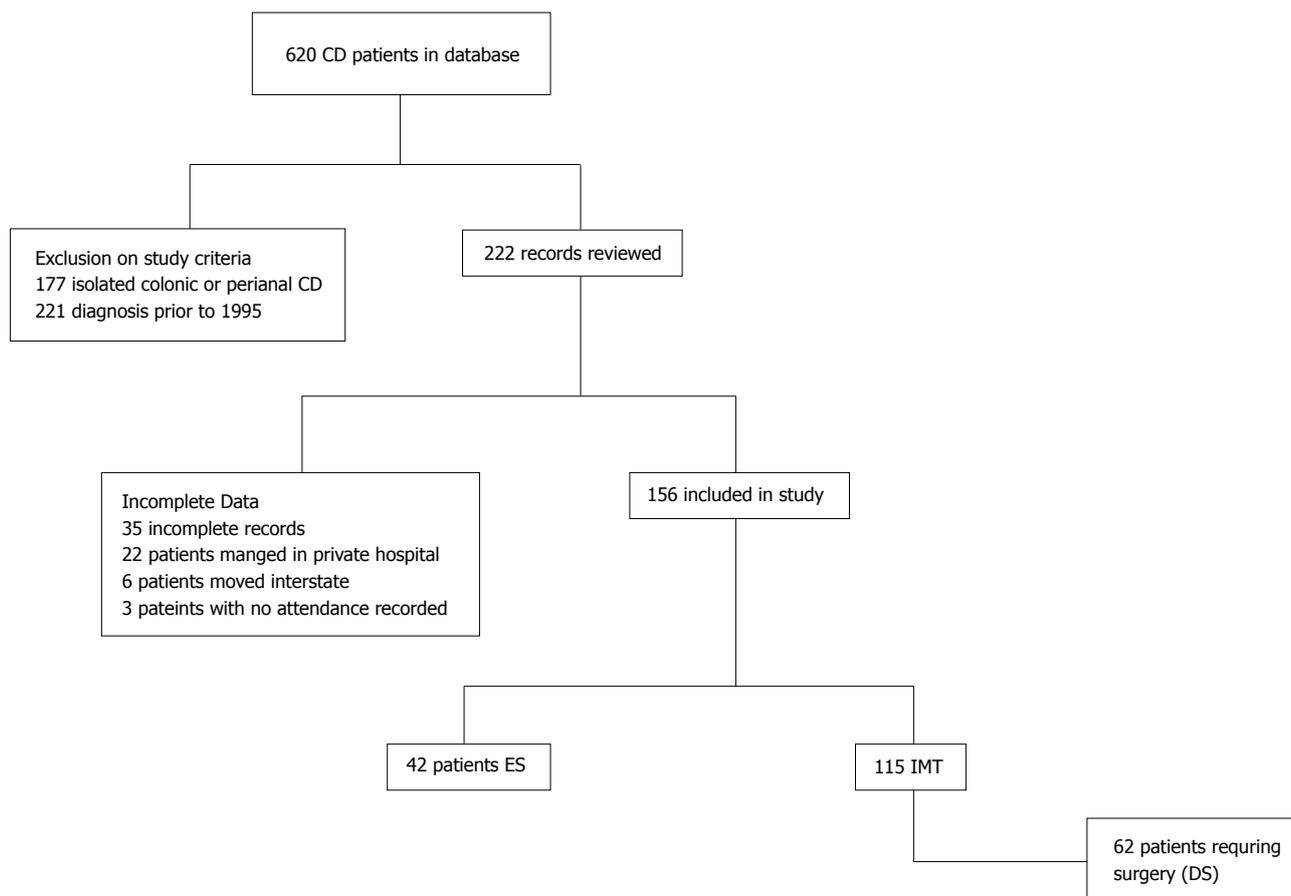


Figure 1 Consort diagram. ES: Early surgery; IMT: Initial medical therapy; DS: Deferred surgery; CD: Crohn's disease.

the database prior to 2007, the accuracy of fine details such as time course, dose and duration of therapy could not be assured. Consequently, medical therapies received by each patient are reported as a categorical outcome, described by type of treatment (none, steroid, immunosuppressive or biologic therapy).

This project was reviewed and approved by the Royal Adelaide Hospital Human Research Ethics committee. As this was a clinical audit, individual patient consent was not necessary and not sought. Data were tabulated in a Microsoft Excel™ spreadsheet. Statistical analyses were performed utilizing SPSS™ ver. 22. Differences between groups were compared using the χ^2 test for categorical data, and ordinal data were compared using the Student's *t*-test or Mann-Whitney-*U* test for non-parametric distributions. To determine a difference in time to further surgery between groups, Kaplan-Meier analyses were performed and differences tested using the Mantel-Cox log rank test.

RESULTS

A total of 620 patients with CD were identified on the database. Exclusions are shown on a consort diagram (Figure 1). A total of 157 patients met inclusion criteria and were included in the study. There were 42 patients in the ES cohort, who either presented with

an acute complication requiring emergency surgery or underwent an operation within 6 m of diagnosis due to a progression or complication of CD. The remaining 115 patients were treated with IMT, 62 (53.9%) of whom underwent surgery by the end of the study period (DS).

Demographics of the cohorts are shown in Table 1. Patients in the ES group were significantly older with a median age at diagnosis of 34.5 years (24-45) compared to 24 (19-33) in the IMT group ($P = 0.0001$) and a shorter duration of disease (ES 5.6 years, IMT 8.9, $P = 0.014$). Not surprisingly, ES patients were more likely to have a stricturing or penetrating phenotype than IMT patients. The DS cohort, who were medically treated patients who went on to have a resection, had the same proportion of patients with penetrating and stricturing disease (B2 and B3), 38.7% and 54.8% respectively as the ES patients (40.5% and 52.4% respectively $P = 0.968$). There was also a significant difference in disease location, with a higher proportion of L3 disease compared to L1 disease and subsequently in the proportion of patients with perianal disease in the IMT cohort.

Table 2 outlines the mode of presentation of patients requiring ES. Over half the ES cohort presented with either acute obstruction or perforation necessitating emergency surgery and data was unavailable for 5 patients in this cohort. In contrast, of the patients in

Table 1 Demographic and clinical data *n* (%)

Clinical details	Early surgery (<i>n</i> = 42)	Initial medical therapy (<i>n</i> = 115)			
		IMT (<i>n</i> = 115)	<i>P</i> value	DS (<i>n</i> = 62) ¹	<i>P</i> value
Gender M:F	22:20	50:65	0.531	24:38:00	0.227
Age at diagnosis (yr), median (IQR)	34.5 (24-46)	24 (19-33)	0.0001	23.5 (18.25-31.75)	0.006
Smoking	15 (35.7)	43 (37.4)	0.852	25 (40.3)	0.685
Phenotype					
B1 (non-stricturing)	3 (7.1)	38 (36.2)	0.001	4 (6.5)	0.968
B2 (stricturing)	17 (40.5)	26 (24.8)		24 (38.7)	
B3 (penetrating)	22 (52.4)	41 (39.0)		34 (54.8)	
Location					
L1 (ileal)	28 (66.7)	25 (24.5)	0.0001	17 (26.3)	0.0001
Perianal disease	0	6 (5.2)		3 (4.8)	
L3 (ileocolonic)					
Perianal disease	14 (33.3)	74 (69.4)		45 (70.2)	
	5 (11.9)	40 (34.8)		16 (25.8)	

¹Patients in the DS group are a subset of IMT patients. IMT: Initial medical therapy; DS: Deferred surgery; IQR: Interquartile range; M: Male; F: Female.

Table 2 Indications for early surgery *n* (%)

Clinical details	Early surgery (<i>n</i> = 42)	Deferred surgery (<i>n</i> = 62)
Indication for surgery		
Acute obstruction - emergency resection	9 (21.4)	4 (23.0)
Subacute obstruction - elective resection	-	20 (32.3)
Perforation	15 (35.7)	7 (11.3)
Fistula/phlegmon	5 (11.9)	15 (24.2)
Abdominal pain	5 (11.9)	2 (3.2)
Haemorrhage	3 (7.1)	-
Not specified	5 (11.9)	14 (23.0)

the DS cohort, 11 patients presented with an acute complication necessitating emergency surgery despite upfront medical therapy, 4 with acute obstruction and 7 with perforation. Thirty-five (56.5%) of the DS cohort required surgery due to progression in obstructive symptoms (6.5%) or fistula formation (24.2%).

The number of patients in each cohort requiring surgical resection, hospital admission and medical therapy is shown in Table 3. The proportion of patients requiring subsequent resection at 5 years was significantly lower in the ES group compared with the IMT group (14.2% vs 31.3%, $P = 0.041$). Of note though, 57.3% of IMT patients required no surgery. Endpoints for the DS subgroup of patients were determined from the time of their index operation, allowing a fairer comparison to the ES group, as the two cohorts have all undergone one operation. The rate of subsequent surgery in the subgroup of 62 DS patients was 16.1%, which was not significantly different to the ES cohort. The median duration of between diagnosis and index operation in the DS cohort was 46.4 mo (IQR 23-97). The extent of resection and need for stoma were similar in each group and shown in Table 4.

The ES group had a higher estimated proportion of patients not having a subsequent resection at 10 years than those having IMT (Figure 2) (83.7% vs 52.7%; $P_{\text{Log-rank}} = 0.0001$). The comparison of ES to DS groups is

shown in Figure 3 with an estimated probability of no subsequent surgery at 10 years of 83.7% and 43.7% ($P_{\text{Log-rank}} = 0.032$) respectively.

The median number of hospital admissions differed between the two groups, with the ES group having fewer admissions than each of the IMT and DS patients (ES 1 vs IMT 3, $P = 0.012$) and vs (DS subset 2, $P = 0.002$). The median number of days in hospital over the duration of each patients' disease did not differ significantly between the groups. However, this includes the index admission for surgery in the ES cohort.

Rates of immunomodulator and steroid use were similar when comparing the ES group to both IMT and DS cohorts. The proportion of patients receiving biologic therapy was significantly lower in the ES cohort than those having IMT (ES 33.3% vs IMT 60.0%, $P = 0.004$) and also the DS subgroup (ES 33.3% vs DS 67.7%, $P = 0.001$). The proportion of patients requiring no treatment for their disease differed between the groups (ES 23.8% vs IMT 4.3% vs DS 0%, $P < 0.0001$).

DISCUSSION

CD remains a challenging chronic condition where there has been a progressive evolution in the positioning and roles of medical and surgical therapy. Our study has found that 31.3% of patients initially managed with medical therapy will come to surgery within 5 years, in line with other studies^[2,4,6,13]. This is significantly higher than the 5 year subsequent resection rate of those patients undergoing ES (14.2%).

An alternative interpretation of our data is that 68.7% of patients undergoing medical therapy avoided the need for surgery altogether within a 5 year period. However, the IMT cohort likely represented a less aggressive phenotype of CD as demonstrated by lower rates of stricturing and penetrating disease in this group compared with the ES group. The IMT patients who have had subsequent surgery (DS), had a similar phenotype to the ES group and comparison between

Table 3 Comparison of early vs initial medical therapy in Crohn's disease n (%)

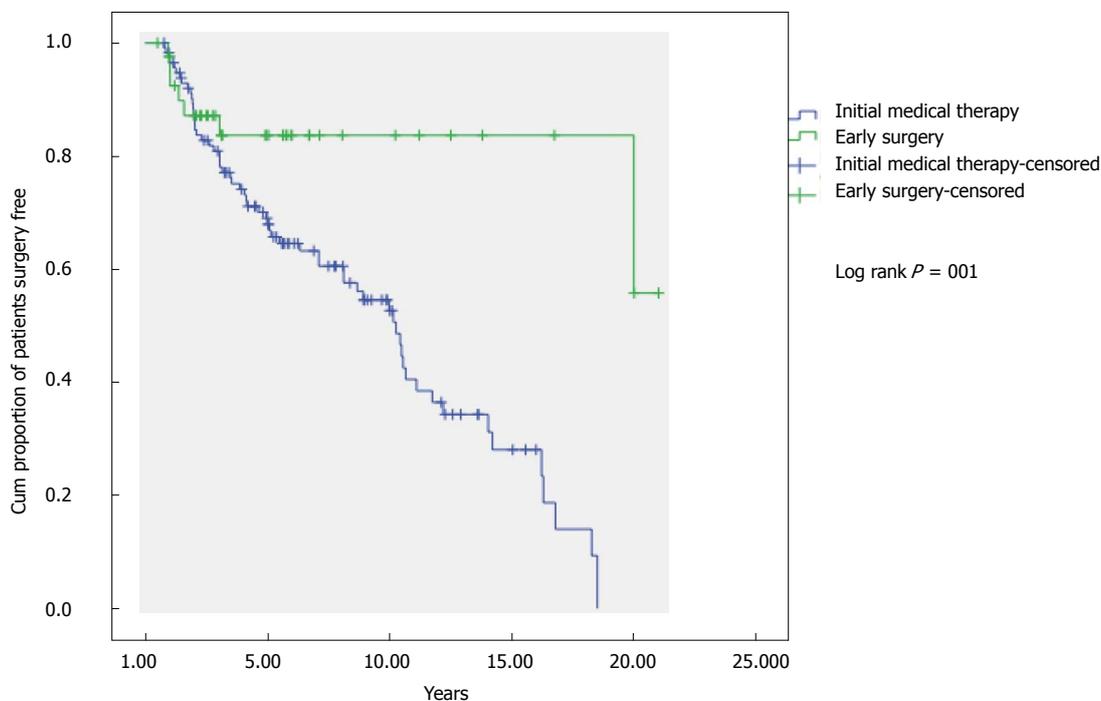
Clinical details	Early surgery (n = 42)	Initial medical therapy (n = 115)		P value	Deferred surgery (n = 62) ¹	P value
		Initial medical therapy (n = 115)	Deferred surgery (n = 62)			
Number requiring surgery						
3 yr	5 (11.9)	24 (20.7)	0.250	5 (8.1)	0.521	
5 yr	6 (14.2)	36 (31.3)	0.041	10 (16.1)	NS	
Completion of study period	7 (16.7)	62 (53.9)	< 0.0001	20 (32.3)	0.110	
Number of admission to hospital per patient, median (IQR)	1 (1-2)	3 (1-5)	0.012	2 (1-4.5)	0.002	
Days in hospital (d), median (IQR)	12.5 (9-22.5)	11 (3-28)	0.230	17 (8-28)	0.347	
Medical therapy						
Immune modulator	32 (76.2)	101 (87.8)	0.083	54 (87.1)	0.189	
Steroids	12 (28.6)	34 (29.6)	NS	23 (37.1)	0.404	
Anti-TNF	14 (33.3)	69 (60.0)	0.004	42 (67.7)	0.001	
No requirement for medical therapy	10 (23.8)	5 (4.3)	0.008	0 (0)	< 0.0001	
Follow-up months (mo), median (IQR)	67 (31-114)	97 (58-150)		64 (19-121)		

¹Data for this subset regarding length of stay and hospital admissions was taken from the date of first operation and not from date of diagnosis. IQR: Interquartile range; TNF: Tumour necrosis factor; NS: Not significant.

Table 4 Comparison of extent of resection performed in early surgery vs deferred surgery cohorts n (%)

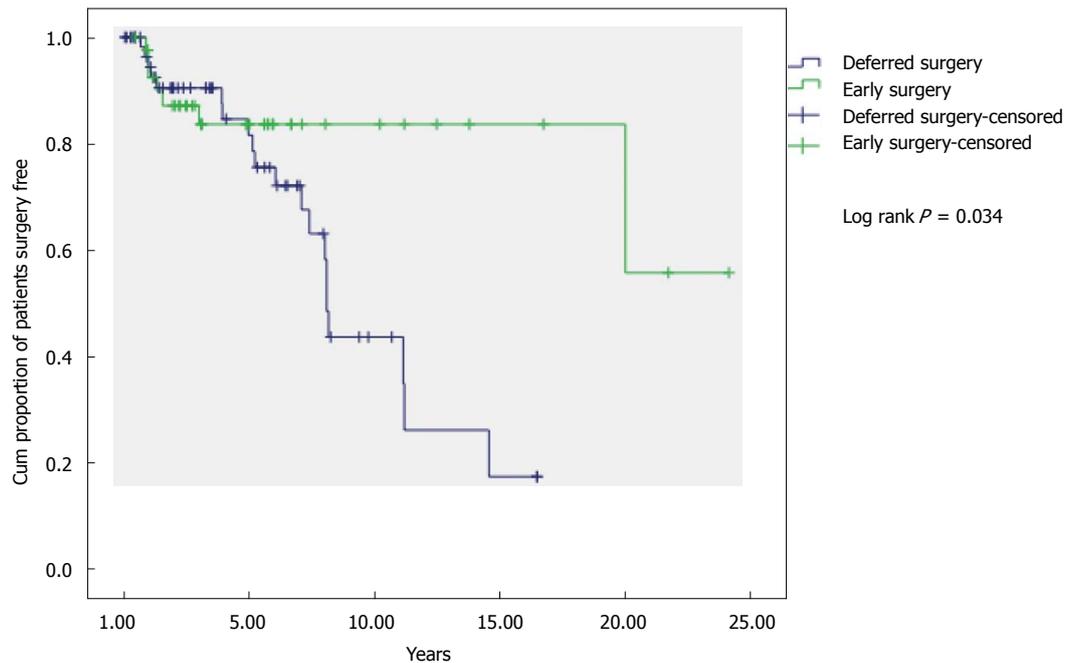
Clinical details	Early surgery (n = 42)	Deferred surgery (n = 62)	P value
Operation			
Small bowel resection	5 (11.9)	7 (11.3)	NS
Ileocolic resection	31 (73.8)	30 (48.4)	0.015
Small bowel and segmental colonic resection	3 (7.1)	9 (14.5)	0.352
Small bowel and total colectomy	2 (4.8)	9 (14.5)	0.193
Data unavailable	1 (2.9)	7 (11.3)	0.139
Stoma formation	3 (7.1)	5 (8.1)	NS

NS: Not significant.



No. At risk				
Initial medical therapy	64	28	9	0
Early surgery	20	8	4	2

Figure 2 Cumulative event curve time to subsequent surgical resection in early surgery vs initial medical therapy.



No. at risk				
Deferred surgery	27	5	2	
Early surgery	20	8	4	2

Figure 3 Cumulative event curve: Time to further surgical resection in early surgery vs deferred surgery.

these two groups may be more relevant. Indeed at 5 years, similar numbers had had further resection (ES 14.2% vs DS 16.1%), even a trend to higher rates of surgery in the DS group by the end of the study (ES 16.7% vs DS 32.3%). The estimated proportion of patients not requiring subsequent surgery at 10 years for the ES and DS groups were 83.7% and 43.7% respectively. These findings are similar to reports by Golovics *et al*^[3] and Latella *et al*^[11], which give validation to these results across different healthcare settings in different countries.

This is the only study to the authors' knowledge that additionally examined inpatient healthcare utilization (hospital admissions and length total cumulative of stay) as an endpoint in comparing ES and IMT. The ES patients had fewer hospital admissions for the duration of their disease than IMT patients and the subset of DS patients [ES 67, IMT 107, DS 50 (median, months)] suggesting disease control may be better in the ES group. However a conservative interpretation of this is necessary given the longer follow-up and higher incidence of L3 and perianal disease in the IMT group.

What is difficult to quantify in the literature is the health related quality of life (HRQOL) of medically managed patients. There is a paucity of data in the literature examining this, whilst more surgical data exist with Thirlby *et al*^[14] reporting an improvement in 7 of 8 domains in HRQOL at 12 mo after surgical resection. Casellas *et al*^[15] reported significant differences in HRQOL scores between patients with active disease and those in disease remission. Such assessments at diffe-

rent time intervals of the two cohorts would be valuable in determining the true effect of ES and whether early resection conferred an improvement in quality of life and disease control.

We did not find a difference in steroid use between the groups, unlike Aratari *et al*^[10], who reported a need for corticosteroid therapy in 39.8% of ES patients compared with 62.1% of medically treated CD at 5 years. The similar rates of immunomodulator use we observed in ES and IMT patients, 76.2% and 87.8% respectively, are in line with current evidence supporting pro-active tailored post resection therapy to reduce clinical and endoscopic recurrence^[16-18].

Immune modulators and biologic agents have added to the armamentarium of medical therapy for CD. Careful consideration should be given regarding the timing of surgery in patients with ileal CD, especially where there is a stricturing or penetrating phenotype, and this should be balanced against the aggressive pursuit of medically induced clinical remission. This balance of medical therapy and surgery may best be achieved in a multidisciplinary environment involving gastroenterologists, surgeons and radiologists. Patients with CD are now often coming to surgery on at least an immunomodulator, and in our cohort 67.7% on a biologic agent. Recent systematic reviews reported an increase in the post-operative, infective and anastomotic complications in patients on anti-TNF α agents^[19,20] which lends further weight for considering earlier surgery.

It is clear that biologic agents improve rates of clinical remission and HRQOL scores in the short

term^[21-23]. Long term it is unclear whether they alter disease course. Disease recurrence rates at 5 years were reported at 36.6% with infliximab therapy^[24] suggesting that for some the response is short lived for some patients. Resection rates in the literature are contradictory, with some studies reporting a decline in surgical resection^[24,25], whilst others have reported no change despite increasing use of biologic agents^[6,26-28], which may reflect the use of biologic agents at a later stage in the disease process where fibrosis and scarring predominate over inflammation, reducing their efficacy.

It is worth noting that the European evidence based consensus from the European Crohn's and Colitis Organization recommends resection for patients with ileocolic disease with obstructive symptoms^[29]. Silverstein *et al.*^[30] reported on the high costs associated with surgical intervention, accounting for 44% of the total lifetime health costs (USD17562) in a patient with CD, but also that it offered the longest remissions. However, this study pre-dates the widespread use of biologic agents and the high costs associated with them. A Canadian study estimated a direct health care cost of USD21416 per patient for the first year of Infliximab treatment^[31]. No formal cost analysis was performed, however, given the lower proportion of patients requiring medical therapy in the ES cohort, the cost effectiveness of ES vs IMT should be explored as, notably 23.8% of the ES cohort avoided the need for ongoing medical therapy altogether.

There are naturally limitations to any retrospective analysis, which prevent strong conclusions being drawn. However, a study prospectively randomizing to early and DS would be difficult to conduct, require long follow up and may not be ethically acceptable. We therefore need to examine real world data such as these whilst taking account of possible sources of bias. Data was not available regarding short term complication rates of surgery and medical therapy so not included in this study. We have used the emergency operation for an acute complication as a surrogate for ES. The phenotypes of the two cohorts are different, however, we feel that the ES group had generally a more aggressive phenotype given then higher proportion of penetrating and stricturing disease presenting with an acute complication requiring resection at index presentation. The younger patients higher proportion of L3 disease in the IMT group reflects a real world cohort with potentially multifocal disease in whom the treating team have adopted medical therapy upfront. However we still believe the groups are comparable as, despite this, the type of surgery and extent of bowel resection are similar between the ES and medically treated cohorts. Our definition of ES is arbitrary, but in six months medical therapy is unlikely to be established. Being a tertiary centre, there is a potential for a referral bias, with less complex disease managed at regional centres.

Our study lends weight to the argument that in

selected patients with stricturing or penetrating ileocolonic CD, those undergoing ES may have a more benign disease course, possibly with less need for further surgical intervention and fewer hospital admissions for CD related illness. This is perhaps even more meaningful, given that a significant number of these patients present with aggressive phenotypes requiring ES. Surgery should not be considered as treatment of last resort after all medical therapy has failed. Rather a more considered approach to the timing of resection for symptomatic patients is needed, possibly to achieve longer periods of disease remission with reduced drug exposure and costs to health care.

COMMENTS

Background

Despite the advances in medical therapy for patients Crohn's disease (CD), from the introduction in immunomodulatory agents and biologic agents targeting TNF- α , there has been minimal decline in the rate of surgical resection in these patients. There is evidence in support of an aggressive "top-down" strategy, utilizing more effective agents earlier in the disease course such as the immunomodulators and biologic agents to control the inflammatory process and prevent progression. It must be considered whether a more aggressive approach still, with early surgery (ES) in selected patients may further improve outcomes in these patients.

Research frontiers

The authors in selecting patients with symptomatic ileo-colonic CD, undertaking early surgical resection prior to starting medical therapy for their CD may confer a benefit in the long term, regarding the need for further surgery reduced requirement for medical therapy in maintaining control of their disease.

Innovations and breakthrough

This study supports evidence in the literature that ES may confer a benefit in selected patients with CD, as patients required fewer admissions to hospital, spent fewer total days in hospital by the end of this study period in spite of the inclusion of their index admission for their acute presentation and operation. In addition, the authors found a longer time duration between their index operation and their subsequent operation when compared to those undergoing initial medical therapy.

Applications

Decision making in the management of patients with CD is complex and best undertaken in a multidisciplinary setting. Traditionally surgery has been reserved as an act of last resort. This study suggests a bolder approach may be of benefit in symptomatic patients with ileal or ileocolonic disease.

Peer-review

It is a study about an interesting topic in CD: The effectiveness of ES in avoiding CD recurrence.

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Retrospective Cohort Study

Aspirin use for primary prophylaxis: Adverse outcomes in non-variceal upper gastrointestinal bleeding

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Abstract**AIM:** To compare outcomes of patients with non-variceal upper gastrointestinal bleeding (NVUGIB) taking aspirin for primary prophylaxis to those not taking it.**METHODS:** Patients not known to have any vascular disease (coronary artery or cerebrovascular disease) who were admitted to the American University of Beirut Medical Center between 1993 and 2010 with NVUGIB were included. The frequencies of in-hospital mortality, re-bleeding, severe bleeding, need for surgery or embolization, and of a composite outcome defined as the occurrence of any of the 4 bleeding related adverse outcomes were compared between patients receiving aspirin and those on no antithrombotics. We also compared frequency of in hospital complications and length of hospital stay between the two groups.**RESULTS:** Of 357 eligible patients, 94 were on aspirin and 263 patients were on no antithrombotics (control

group). Patients in the aspirin group were older, the mean age was 58 years in controls and 67 years in the aspirin group ($P < 0.001$). Patients in the aspirin group had significantly more co-morbidities, including diabetes mellitus and hypertension [25 (27%) *vs* 31 (112%) and 44 (47%) *vs* 74 (28%) respectively, ($P = 0.001$)], as well as dyslipidemia [21 (22%) *vs* 16 (6%), $P < 0.0001$]. Smoking was more frequent in the aspirin group [34 (41%) *vs* 60 (27%), $P = 0.02$]. The frequencies of endoscopic therapy and surgery were similar in both groups. Patients who were on aspirin had lower in-hospital mortality rates (2.1% *vs* 13.7%, $P = 0.002$), shorter hospital stay (4.9 d *vs* 7 d, $P = 0.01$), and fewer composite outcomes (10.6% *vs* 24%, $P = 0.01$). The frequencies of in-hospital complications and re-bleeding were similar in the two groups.

CONCLUSION: Patients who present with NVUGIB while receiving aspirin for primary prophylaxis had fewer adverse outcomes. Thus aspirin may have a protective effect beyond its cardiovascular benefits.

Key words: Aspirin; Morbidity; Mortality; Non-variceal upper gastrointestinal bleeding; Outcomes

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Core tip: Aspirin is known to increase the risk of upper gastrointestinal bleeding (UGIB), and it is customary to stop aspirin in patients presenting with gastrointestinal bleeding. Some studies have shown that being on aspirin is associated with better outcome in those patients. Our study compared clinical outcomes in patients who presented with non-variceal UGIB while taking aspirin for primary prophylaxis only to those of patients not taking aspirin. We found that patients taking aspirin had lower mortality and shorter hospital stay than patients not taking aspirin.

Souk KM, Tamim HM, Abu Daya HA, Rockey DC, Barada KA. Aspirin use for primary prophylaxis: Adverse outcomes in non-variceal upper gastrointestinal bleeding. *World J Gastrointest Surg* 2016; 8(7): 501-507 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/501.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.501>

INTRODUCTION

Aspirin is being used widely in primary and secondary prevention of cardiovascular diseases, and it is taken by more than 25%-33% of people older than 65 years^[1]. In addition, both individual studies and meta-analysis of trials of anti-platelet therapy indicate that aspirin and other anti-platelet drugs reduce the risk of serious vascular events by approximately 25%^[2].

Despite its cardiovascular protection, aspirin is associated with a 2 fold increase in risk of upper gastr-

ointestinal bleeding (UGIB)^[3]. However, most studies suggest that aspirin decreases mortality and hospital stay in patients with non-variceal upper gastrointestinal bleeding (NVUGIB)^[4,5], while some report no significant effect^[6].

We recently reported that being on aspirin on presentation confers protection against mortality and morbidity in peptic disease related-UGIB^[7], and in patients with NVUGIB overall^[8]. We also reported that in-hospital mortality from cardiovascular causes in patients taking aspirin was similar to controls. Hence, it is not clear if the protective effect of aspirin is due to its known cardiovascular benefits. This study aims to determine if the protective effect of aspirin in NVUGIB persists in patients with no known cardiovascular or cerebrovascular disease. This is done by comparing clinical outcomes in patients presenting with NVUGIB while receiving aspirin as primary prophylaxis to those who are not taking it.

MATERIALS AND METHODS

This was a retrospective cohort study of patients admitted to American University of Beirut Medical Center (AUBMC) with NVUGIB between 1993 and 2010. AUBMC is a tertiary referral medical center that provides health care for around 1.5 million people in Lebanon.

The study was approved by the Institutional Review Board of AUBMC (IM.KB.09).

Inclusion and exclusion criteria

In this study we included all patients who were admitted with hematemesis, coffee ground vomiting, and/or melena in the presence of an identified source of UGIB site on upper gastrointestinal endoscopy^[7]. We also considered patients with hematochezia to have UGIB if upper endoscopy showed a source of bleeding and colonoscopy was negative. For patients who didn't have endoscopy, we classified patients as having UGIB if they had coffee ground emesis, hematemesis or melena.

We excluded all patients who presented with melena and/or hematochezia who had a colonic source of bleeding. Patients who met the criteria of UGIB from esophageal/gastric varices and those who had occult gastrointestinal or small bowel bleeding were excluded.

We also excluded all patients with documented history of coronary artery disease, cerebrovascular accident/transient ischemic attack (TIA), peripheral vascular disease, and those on any non-aspirin anti-platelets or anticoagulants.

Data collection

Medical records of patients with signs and symptoms of UGIB were reviewed, using the ICD-9/ICD-10 coding system (codes for the following symptoms: UGIB, melena, hematochezia, hematemesis, coffee ground emesis). The data was collected from charts using a standardized data collection form. During chart review,

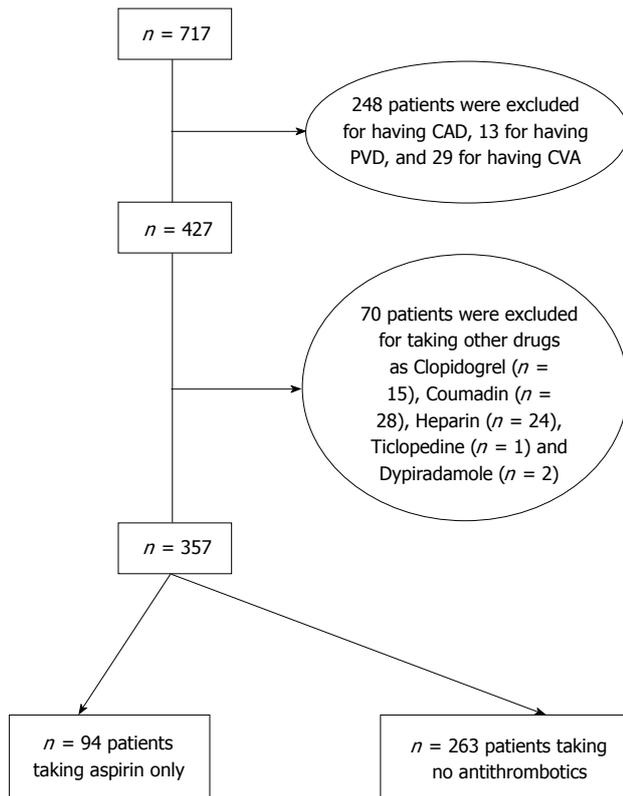


Figure 1 The flow and inclusion/exclusion criteria of patients with non-variceal upper gastrointestinal bleeding in the study. CAD: Coronary artery disease; PVD: Peripheral vascular disease; CVA: Cerebrovascular accident.

we extracted the following information: Patient's age, sex, comorbid conditions (hypertension, diabetes mellitus, renal insufficiency, dyslipidemia, active systemic or gastrointestinal cancer, congestive heart failure, valvular heart disease, atrial fibrillation and deep vein thrombosis); mode of clinical presentation; duration of bleeding; vital signs and initial blood studies obtained upon arrival to the emergency room including complete blood count, international normalized ratio (INR), and prothrombin time; management in the emergency room and the hospital including blood transfusion. We also recorded findings on diagnostic upper gastrointestinal endoscopy and the source of bleeding; type of therapeutic endoscopic procedure undertaken whenever applicable; angiography and embolization, surgical treatment and in hospital mortality. The frequency of the following outcomes were determined: In-hospital mortality, need for surgery, severe bleeding (hypotension with a systolic blood pressure < 90 mmHg on admission, tachycardia with heart rate > 119 beat/min, or transfusion of more than 3 units of packed red blood cells), re-bleeding (re-bleeding after 24 h from the initial endoscopic evaluation) and therapy (recurrence of bleeding within 1 mo from discharge was also considered rebleeding), in-hospital complications including myocardial infarction, angina, deep vein thrombosis, pulmonary embolism, stroke, TIA, pneumonia, urinary tract infection, skin infections, sepsis, acute respiratory distress syndrome,

renal failure, need for mechanical ventilation, and disseminated intravascular coagulopathy; duration of hospitalization, need for blood transfusion, and number of blood units transfused were also recorded. The primary outcome was in-hospital mortality. The secondary outcomes included re-bleeding, severe bleeding, need for surgery or embolization, and the occurrence of any bleeding related composite outcome defined as the occurrence of any of the following: In hospital mortality, re-bleeding, severe bleeding, need for surgery or embolization^[7]. We also compared in hospital complications and length of hospital stay. We divided the patients into two main groups: Those who were on aspirin upon presentation, and those who were not. We compared all the characteristics and outcomes listed above between the two groups.

Statistical analysis

Data management and analysis were carried out using the Statistical Analysis Software (SAS, version 9.1). Descriptive analyses were carried out by calculating the numbers and percent for categorical variables, and the mean and standard deviation SD for the continuous ones. Bivariate analyses were performed using the χ^2 test or the independent student *t*-test, as appropriate.

To control for the effect of potentially confounding variables, multivariable analyses were carried out while controlling for different risk factors. For categorical outcomes multivariate logistic regression analyses were carried out where the OR, 95%CI, and *P*-value were reported. On the other hand, for continuous variables multivariate linear regression was carried out where the β -coefficient, 95%CI, and *P*-value were reported. Variables included in the regression model were those of either statistical or clinical significance. A *P* value < 0.05 indicates statistical significance.

RESULTS

Subjects

A total of 1175 patients were admitted with acute gastrointestinal bleeding between 1993 and 2010. Out of the 1175 patients, 717 patients had NVUGIB, of which 357 were included in this study. A total of 94 patients were on aspirin only and 263 patients were on no antithrombotics (control group, Figure 1).

Demographics and clinical characteristics

The mean age was 58 years in controls and 67 years in the aspirin group ($P < 0.001$). Most patients were males. Patients on aspirin were more likely to have diabetes mellitus and hypertension [25 (27%) vs 31 (112%) and 44 (47%) vs 74 (28%) respectively, ($P = 0.001$)], as well as dyslipidemia [21 (22%) vs 16 (6%), $P < 0.0001$]. Smoking was more frequent in the aspirin group [34 (41%) vs 60 (27%), $P = 0.02$] (Table 1).

Controls had a higher prevalence of cancer (20.9% vs 6.4%, $P < 0.001$) and were more likely to have a history of peptic ulcer disease. The use of PPI was

Table 1 Clinical characteristics of patients with non-variceal upper gastrointestinal bleeding in both groups *n* (%)

Group	No anti-thrombotics <i>n</i> = 263	Aspirin <i>n</i> = 94	<i>P</i> value
Age mean (SD)	58.4 (19.1)	66.8 (13.1)	< 0.001
Male gender	169 (64.3)	71 (75.5)	0.05
Smoking	60 (27.0)	34 (41.0)	0.02
Diabetes mellitus	31 (11.8)	25 (26.6)	0.001
Hypertension	74 (28.1)	44 (46.8)	0.001
Dyslipidemia	16 (6.1)	21 (22.3)	< 0.0001
Cancer	55 (20.9)	6 (6.4)	0.001
NSAIDS	47 (17.9)	16 (17.0)	0.85
PPI	29 (11.0)	4 (4.3)	0.05
History of peptic ulcer disease	69 (26.2)	13 (13.8)	0.01

P < 0.05 is considered significant. NVUGIB: Non-variceal upper gastrointestinal bleeding; Aspirin: Aspirin only; No anti-thrombotics: Including clopidogrel, coumadin, heparin, ticlopedine and dipyridamole; SD: Standard deviation; NSAIDS: Non steroidal anti-inflammatory drug; PPI: Proton pump inhibitor.

higher in controls [29 (11%) vs 4 (4%), *P* = 0.05] (Table 1). Controls also had a higher INR than patients on aspirin (Table 2).

Presentation and endoscopic findings

Upon presentation, patients in the aspirin group had more syncope and melena, but less hematemesis than controls [21.3% vs 12.5%, *P* = 0.04, 51 (54.3%) vs 109 (41.4%), *P* = 0.03 and 18.1% vs 28.9%, *P* = 0.04, respectively]. Upper gastrointestinal endoscopy was done on 83% of patients in the aspirin group and 71.5% of patients in the control group. The prevalence of peptic lesions found at endoscopy was higher in the aspirin group, including gastric ulcers (28.7% vs 15.2%, *P* = 0.004), erosive duodenitis (16% vs 5.3%, *P* = 0.001), and erosive gastritis (40.4% vs 12.9%, *P* < 0.0001) (Table 2).

In hospital medical and endoscopic management

The percentage of patients transfused with blood was similar in both groups, 70.2% in aspirin vs 61.2% in control (*P* = 0.12); and the average was 4 units of packed red blood cells per transfused patient. In both groups, the frequencies of endoscopic therapy and surgery were similar (Table 2).

Outcomes

After adjusting for age and comorbidities (congestive heart failure, systemic cancer, diabetes mellitus, chronic renal failure), patients on aspirin were less likely to die in-hospital (OR = 0.15, 95%CI: 0.03-0.64, *P* = 0.002), less likely to experience the composite outcome (OR = 0.42, 95%CI: 0.20-0.89, *P* = 0.01), and tended to have a shorter hospital stay (4.9 d vs 7 d, *P* = 0.01) compared to controls. However, they had similar rates of in-hospital complications, re-bleeding and severe bleeding (Table 3).

Table 2 Association between aspirin use and presentation/management *n* (%)

Group	No anti-thrombotics <i>n</i> = 263	Aspirin <i>n</i> = 94	<i>P</i> value
Melena	109 (41.4)	51 (54.3)	0.03
Hematemesis	76 (28.9)	17 (18.1)	0.04
Hematemesis + Melena	46 (17.5)	16 (17.05)	0.92
Hematochezia	8 (3.0)	2 (2.1)	0.48
Syncope	33 (12.5)	20 (21.3)	0.04
Hgb, g/L, mean (SD)	9.2 (2.8)	9.1 (2.4)	0.80
Hct, (%), mean (SD)	27.4 (8.2)	27.0 (7.1)	0.70
INR, mean (SD)	1.2 (0.7)	1.0 (0.2)	0.003
Gastric ulcers	40 (15.2)	27 (28.7)	0.004
Duodenal ulcers	65 (24.7)	31 (33.0)	0.12
Erosive esophagitis	31 (11.8)	10 (10.6)	0.76
Erosive gastritis	34 (12.9)	38 (40.4)	< 0.0001
Erosive duodenitis	14 (5.3)	15 (16.0)	0.001
Mallory Weiss	18 (6.8)	4 (4.3)	0.37
Hiatal Hernia	24 (9.1)	11 (11.7)	0.47
AVM	11 (4.2)	3 (3.2)	0.47
Cancer	6 (2.3)	0 (0.0)	0.16
Transfusion-unit Mean (SD)	4.7 (5.5)	4.0 (3.8)	0.25
Transfusion %	161 (61.2)	66 (70.2)	0.12
Thermal coagulation	25 (9.5)	14 (14.9)	0.15
Hemostatic clips	2 (0.8)	0 (0.0)	0.54
Argon-plasma coagulation	4 (1.5)	2 (2.1)	0.50
Angiography-embolization	1 (0.4)	0 (0.0)	0.74
Surgery	21 (8.0)	5 (5.3)	0.39

P < 0.05 is considered significant. NVUGIB: Non-variceal upper gastrointestinal bleeding; Aspirin: Aspirin only; No anti-thrombotics: Including clopidogrel, coumadin, heparin, ticlopedine and dipyridamole; SD: Standard deviation; Hgb: Hemoglobin; Hct: Hematocrit; INR: International normalized ratio; AVM: Arteriovenous malformation; Surgery as any type of surgical procedure performed to control gastrointestinal bleeding.

Because the prevalence of cancer was higher in the control group, we did a multivariate analysis in which cancer was considered a covariate rather than one of the comorbidities. The protective effect of aspirin against in hospital mortality remained unchanged.

As there were some patients who did not have endoscopy, a multivariate analysis was done on patients who had endoscopy. Regarding the mortality, it was significantly lower with aspirin group vs non aspirin OR: 0.68, 95%CI: 0.63-0.74; but this difference was not seen with severe bleeding OR = 1.03, 95%CI: 0.69-1.52 and rebleeding OR = 1.51, 95%CI: 0.67-3.39.

DISCUSSION

Our study suggests that patients without known vascular disease who present with NVUGIB while taking aspirin appear to have better outcomes than patients not taking any antithrombotics. Specifically, these patients had lower mortality and morbidity, and shorter hospital stay than patients not on antithrombotics.

It is known that patients who have more than one risk factor for developing vascular events are more likely to use aspirin as primary prophylaxis^[9]. In this

Table 3 Multivariate analyses of the outcomes in aspirin users *vs* non users

Group	No anti-thrombotics <i>n</i> = 263	Aspirin <i>n</i> = 94	<i>P</i> value	Crude OR (95%CI)	Adjusted OR (95%CI)
Mortality	36 (13.7)	2 (2.1)	0.002	0.14 (0.03-0.58)	0.15 (0.03-0.64)
Hospital stay (d) Mean (SD)	7.0 (10.3)	4.9 (3.5)	0.01		
Complications-Thrombo-embolic	3 (1.1)	3 (3.2)	0.19	2.86 (0.57- 14.41)	4.79 (0.77-29.96)
Complications-infection ¹	40 (15.2)	14 (14.9)	0.94	0.98 (0.50-1.89)	0.90 (0.45-1.81)
Complications-respiratory ²	15 (5.7)	3 (3.2)	0.42	0.55 (0.15-1.93)	0.58 (0.15-2.19)
Complications-myocardial infarction	3 (1.1)	1 (1.1)	1	0.93 (0.10-9.07)	0.68 (0.07-6.79)
Complications-renal failure	30 (11.4)	9 (9.6)	0.63	0.82 (0.38-1.80)	0.68 (0.30-1.55)
Complications-DIC	7 (2.7)	0 (0.0)	0.2		
All in hospital complications	79 (30.0)	26 (27.7)	0.66	0.89 (0.53-1.50)	0.76 (0.43-1.32)
Composite outcome ³	63 (24.0)	10 (10.6)	0.01	0.38 (0.19-0.77)	0.42 (0.20-0.89)
Severe hemorrhage	97 (36.9)	37 (39.4)	0.67	1.11 (0.69-1.80)	1.18 (0.70-1.99)
Re-bleeding	5 (5.3)	27 (10.3)	0.15	0.49 (0.18-1.32)	0.42 (0.15-1.19)

¹Complications-infection composite: Including pneumonia, aspiration pneumonia, sepsis, urinary tract infection, skin infection; ²Complications-respiratory composite: Including ARDS and mechanical ventilation; ³Composite outcome include mortality, severe bleeding, re-bleeding, need for surgery or embolization. Severe hemorrhage was defined as BP < 90 mmHg, HR > 120 b/min, Hb < 7 g/dL on presentation, or transfusion of > 3 units of blood during hospitalization; rebleeding was defined as recurrence of hematemesis, coffee ground emesis, or melena occurring after 24 h from initial endoscopic evaluation and/or hemostatic therapy and initial stabilization, accompanied by either a decrease in hemoglobin concentration of at least 2 g/L or change in vital signs. *P* < 0.05 is considered significant. Aspirin: Aspirin only; No anti-thrombotics: Including clopidogrel, coumadin, heparin, ticlopedine and dipyridamole; OR: Odds ratio; DIC: Disseminated intravascular coagulation.

study, patients on aspirin were older and had more comorbidity, yet they had lower mortality rates compared to controls. This occurred even though both groups had similar frequencies of therapeutic endoscopic procedures, arterial embolization and surgery making it unlikely that those contributed to the better outcome in the aspirin group. Thus, the contribution of this study is that aspirin's beneficial effect in NVUGIB appears to extend to patients not known to have vascular disease.

It has been previously reported that patients with UGIB receiving or maintained on aspirin had improved outcomes. For example, in a randomized trial of aspirin *vs* placebo in patients who presented with peptic ulcer bleeding while taking aspirin, half of the deaths in the placebo group were due to non-cardiovascular causes, further suggesting that aspirin's protective effect is not solely due to its cardiovascular benefits^[10]. In two relatively large Italian prospective database studies, use of low dose aspirin upon presentation with UGIB was an independent predictor of better outcome including lower 30-d mortality^[11,12]. This was true for both outpatient and inpatient NVUGIB. Furthermore, in a large pan-European retrospective cohort, it was reported that use of low or high dose aspirin was an independent predictor of lower 30 d mortality in NVUGIB^[13]. Finally, in a retrospective cohort of 766 patients with UGIB due to peptic ulcers, it was reported that patients using aspirin upon presentation had a markedly decreased risk of fatal outcome (OR = 0.12, 95%CI: 0.012-0.67)^[6]. Thus, the protective effect of aspirin seems to hold true for both low and high dose aspirin, and seems to cover patients with peptic ulcer related and non-peptic ulcer related NVUGIB. However, in the studies mentioned above, it was not clear whether control patients were taking other antithrombotics, and whether patients taking aspirin were using other antithrombotics con-

comitantly. Furthermore, in none of them was a cause of death analysis undertaken to determine how aspirin exerted its protective effect. In contrast, three studies reported no effect of aspirin on mortality in patients with UGIB. In a prospective observational study of 392 patients there was no effect of antiplatelet therapy (aspirin and/or clopidogrel) on re-bleeding, urgent surgery or mortality^[14]. In another study, patients using aspirin/NSAIDs had similar mortality to those not using them. Finally, it was reported that aspirin users had lower 30-d mortality than controls among 7204 patients with peptic ulcer bleeding, but this was of borderline significance^[5]. To our knowledge, there are no studies showing that aspirin increases mortality in NVUGIB.

Controls in our study had a higher prevalence of systemic cancer. In order to determine if cancer could explain, in part, the high mortality in controls, we conducted two multivariate analyses, one in which the presence of cancer was included in the composite comorbidity score, and another one in which cancer was considered a covariate. The analysis revealed that the protective effect of aspirin against in-hospital mortality remained unchanged^[8].

The mechanism for the lower rate of bleeding related hospital complications and mortality is open to speculation. Aspirin is a non-steroidal anti-inflammatory drug with inhibitory effects on cyclo-oxygenases (COX). COX inhibition has vasoconstrictive and anti-natriuretic effects, which are mediated by inhibition of prostaglandin E-2 and prostacyclin synthesis^[15]. Aspirin has been reported to inhibit nitric oxide synthesis, which in turn inhibit vasodilatation^[16]. By constricting the vessels in the gastrointestinal system, it may decrease the severity of NVUGIB. We recognize limitations in our study. Patients with risk factors for vascular disease were not excluded, and therefore some of our patients could

have occult or latent vascular disease where aspirin protects this population against in hospital complications and mortality. The study design is not prospective or a randomized controlled trial. It is a single institution study and the sample size was small, so the applicability of the findings to other populations requires further testing. We do not have long term follow up on our patients and not all patients had endoscopy. Furthermore, the Forrest classification of bleeding lesions was not documented on all patients, which is a limitation of our study. Finally, the control group had higher INR level which may increase the risk of adverse outcomes. However, our study has several strengths. First, this is the first study to examine the effect of aspirin use as primary prophylaxis on clinical outcomes in patients with NVUGIB. Second, data collection was performed using the ICD-9 codes resulting in the identification of all the potential cases of UGIB, after which each case was reviewed individually by using well developed criteria. Finally, the study was conducted in a tertiary care referral center where all diagnostic and therapeutic procedures are standardized.

In conclusion, aspirin used for primary prophylaxis has a protective effect against adverse outcomes in patients admitted with NVUGIB, and this benefit probably extends beyond its known cardio-protective effect. Further prospective and randomized controlled trials are needed to validate these findings.

COMMENTS

Background

Aspirin is being widely used as primary and secondary prophylaxis for cardiovascular disease. However, aspirin use is associated with a 2 fold increase in risk of upper gastrointestinal bleeding (UGIB).

Research frontiers

Most studies suggest that aspirin decreases mortality and hospital stay in patients with non-variceal upper gastrointestinal bleeding (NVUGIB), while some report no significant effect. However, these studies included patients using aspirin as secondary prophylaxis.

Innovations and breakthroughs

In this study the authors compared clinical outcomes in patients that presented with NVUGIB while taking aspirin for primary prophylaxis to those of patients not taking aspirin. The authors found that the use of aspirin was associated with a better outcome, less mortality and shorter in-hospital stay.

Applications

The findings may have an impact on the practice of discontinuing aspirin in patients presenting with NVUGIB, even in those taking it for primary prophylaxis.

Terminology

Aspirin use as primary prophylaxis is defined as the use of aspirin in patients with no documented cardiovascular or cerebrovascular disease.

Peer-review

This is an interesting retrospective study comparing aspirin use with none and the outcomes of NVUGIB. The better results with aspirin use are surprising despite having patients with a poorer overall status compared to the control group.

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Retrospective Study

What operation for recurrent rectal prolapse after previous Delorme's procedure? A practical reality

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Institutional review board statement: This retrospective study was using previously collected hospital and operative data and did not require Ethics Committee approval.

Informed consent statement: The study did not require a specific consent apart from informed written consent obtained from each patient at the time of procedure.

Conflict-of-interest statement: There are no conflicts of interest.

Data sharing statement: The original anonymous dataset is available from the corresponding author at dmitri.artioukh@nhs.net. No additional data are available.

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Abstract

AIM: To report our experience with perineal repair (Delorme's procedure) of rectal prolapse with particular focus on treatment of the recurrence.

METHODS: Clinical records of 40 patients who underwent Delorme's procedure between 2003 and 2014 were reviewed to obtain the following data: Gender; duration of symptoms, length of prolapse, operation time, ASA grade, length of post-operative stay, procedure-related complications, development and treatment of recurrent prolapse. Analysis of post-operative complications, rate and time of recurrence and factors influencing the choice of the procedure for recurrent disease was conducted. Continuous variables were expressed as the median with interquartile range (IQR). Statistical analysis was carried out using the Fisher exact test.

RESULTS: Median age at the time of surgery was 76 years (IQR: 71-81.5) and there were 38 females and 2 males. The median duration of symptoms was 6 mo (IQR: 3.5-12) and majority of patients presented electively whereas four patients presented in the emergency department with irreducible rectal prolapse. The median length of prolapse was 5 cm (IQR: 5-7), median operative time was 100 min (IQR: 85-120) and median post-operative stay was 4 d (IQR: 3-6). Approximately

16% of the patients suffered minor complications such as - urinary retention, delayed defaecation and infected haematoma. One patient died constituting post-operative mortality of 2.5%. Median follow-up was 6.5 mo (IQR: 2.15-16). Overall recurrence rate was 28% ($n = 12$). Recurrence rate for patients undergoing an urgent Delorme's procedure who presented as an emergency was higher (75.0%) compared to those treated electively (20.5%), P value 0.034. Median time interval from surgery to the development of recurrence was 16 mo (IQR: 5-30). There were three patients who developed an early recurrence, within two weeks of the initial procedure. The management of the recurrent prolapse was as follows: No further intervention ($n = 1$), repeat Delorme's procedure ($n = 3$), Altemeier's procedure ($n = 5$) and rectopexy with faecal diversion ($n = 3$). One patient was lost during follow up.

CONCLUSION: Delorme's procedure is a suitable treatment for rectal prolapse due to low morbidity and mortality and acceptable rate of recurrence. The management of the recurrent rectal prolapse is often restricted to the pelvic approach by the same patient-related factors that influenced the choice of the initial operation, *i.e.*, Delorme's procedure. Early recurrence developing within days or weeks often represents a technical failure and may require abdominal rectopexy with faecal diversion.

Key words: Rectal prolapse; Recurrence; Perineal repair; Delorme's procedure

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Core tip: Delorme's procedure is an attractive and often the only treatment of rectal prolapse available to elderly individuals who often have no physiological reserves to withstand abdominal rectopexy. The management of the recurrent disease is frequently restricted to the perineal approach by the same patient-related factors that limited the choice of the initial operation. Early recurrence developing within days or weeks is difficult to treat and in sufficiently fit patients may require abdominal rectopexy combined with faecal diversion.

Javed MA, Afridi FG, Artioukh DY. What operation for recurrent rectal prolapse after previous Delorme's procedure? A practical reality. *World J Gastrointest Surg* 2016; 8(7): 508-512 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/508.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.508>

INTRODUCTION

Full-thickness prolapse of the rectum is defined as a complete protrusion of the rectal wall through the anus. Although benign, the disease can be debilitating and affect patients' quality of life. The incidence of rectal

prolapse is reported as 10 per 1000 in patients aged over 65 years^[1] and the majority of affected individuals (80%-95%) are women.

More than 130 surgical operations have been described to treat the prolapse which can broadly be classified into perineal and abdominal procedures, indicating that none is entirely satisfactory^[2]. Perineal repair of rectal prolapse, as we understand it now, was named after Edmond Delorme - a French military surgeon who described a technique of mucosal stripping for treatment of procidentia in 1899^[3]. It gained popularity and today remains the most frequently used type of perineal procedure. In elderly patients with significant co-morbidities Delorme's is often a first choice procedure being the least invasive and, therefore, carrying less of surgical and anaesthetic risks. The perceived disadvantage of Delorme's procedure is high rates of prolapse recurrence making it sub-optimal operation for young and healthy patients who are able to withstand abdominal rectopexy^[4]. The choice of the procedure to deal with the recurrent rectal prolapse is often even more difficult due to the absence of established consensus among colorectal surgeons or guidelines to support decision-making process.

The primary aim of this study was to analyse our experience with the treatment of recurrent rectal prolapsed after failed perineal repair (Delorme's procedure) and, in particular, factors that influenced further management. We also report our experience with Delorme's procedure as a treatment of primary rectal prolapse.

MATERIALS AND METHODS

This was a retrospective observational study where we identified 40 consecutive cases of patients who underwent perineal repair of rectal prolapse (Delorme's procedure) by one specialist team (DYA) in Southport and Ormskirk Hospital and Renacres Hospital between 2003 and 2014. Only patients who underwent Delorme's operation as the first procedure undertaken by the team were included. Patients undergoing all other types of perineal procedures, such as excision of mucosal prolapse and perineal recto-sigmoidectomy (Altemier's procedure) were excluded. All patient records were analysed to obtain the following data: Gender; duration of symptoms, length of prolapse, operation time, ASA grade, length of post-operative stay, procedure-related complications, development and treatment of recurrent prolapse and factors influencing the choice of the procedure for recurrent disease. Post-operative complications were classified according to the Clavien-Dindo classification^[5]. The last follow-up date was considered as the date of the last documented physical examination. Treatment algorithm used for management of recurrent rectal prolapse is shown in Figure 1.

Statistical analysis

Continuous variables were expressed using non-

Table 1 Patients' demographics	
Variables	Values
Median age (yr) (IQR)	76 (71-81.5)
Median ASA score (IQR)	3 (2-3)
Male (<i>n</i>)	2
Females (<i>n</i>)	38
Median duration of symptoms (mo), (IQR)	6 (3.5-12)

IQR: Interquartile range; ASA: American society of anesthesiologists.

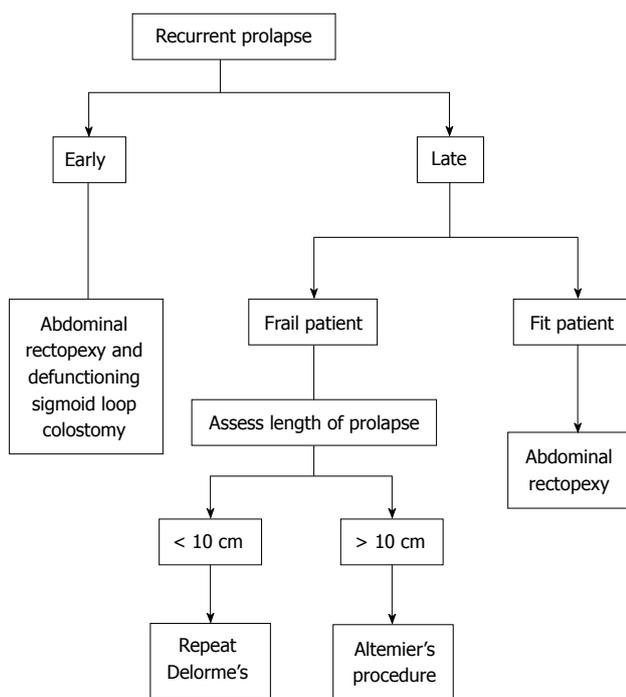


Figure 1 Treatment algorithm for management of recurrent rectal prolapse.

parametric statistics, median with interquartile range (IQR), due to small sample size. Statistical analysis was carried out using the Fischer exact test. Results were considered significant with a probability value of $P < 0.05$. All calculations were performed using Origin software (OriginPro 9). Statistical methods used in the study were independently evaluated by an expert in Biomedical Statistics.

RESULTS

There were 38 females and 2 males in our cohort with the median age of 76 years (IQR: 71-81.5) at the time of surgery (Table 1). The median duration of symptoms was 6 mo (IQR: 3.5-12). Thirty six patients presented electively whereas four patients presented in the emergency department with irreducible rectal prolapse. The median length of prolapse was 5 cm (IQR: 5-7), median operative time was 100 min (IQR: 85-120) and median post-operative stay was 4 d (IQR: 3-6). The majority of patients had no post-operative complications, seven (16%) suffered minor complications, *i.e.*, grade 1 or 2 such as - urinary

Table 2 Peri-operative data and follow up	
Variables	Values
Median length of prolapse (cm) (IQR)	5 (5-7)
Median operative time (min) (IQR)	100 (85-120)
Median post op stay (d) (IQR)	4 (3-6)
Post op complications	Clavien-Dindo
	1 - 6
	2 - 1
	3 - 0
	4a - 1
Median follow up (mo) (IQR)	6.5 (2.15-16)
Median duration of recurrence (mo), (IQR)	16 (5-30)

IQR: Interquartile range.

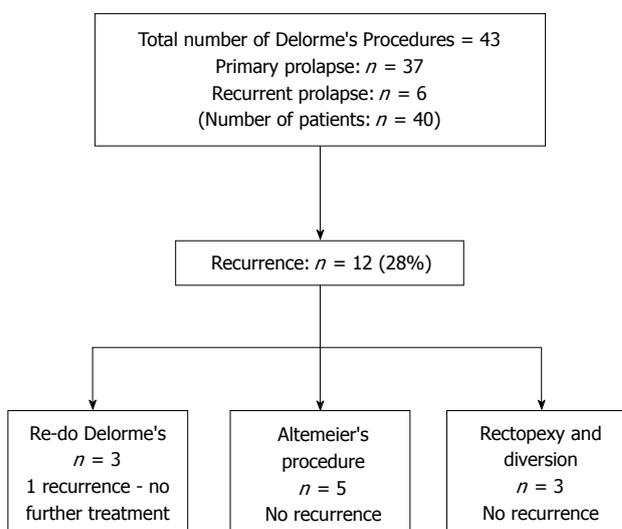


Figure 2 Summary of outcomes in patients undergoing Delorme's procedure for the treatment of full thickness rectal prolapse.

retention, delayed defaecation and infected haematoma - as defined by Clavien-Dindo classification. One patient died of pneumonia and congestive cardiac failure due to ischaemic heart disease, constituting post-operative mortality of 2.5%. Median follow-up was 6.5 mo (IQR: 2.15-16). Surgical morbidity was higher in patients undergoing surgery for recurrent rectal prolapse (2/7, 28.5%) vs primary Delorme's (4/36, 11.1%), P value 0.004, and the only mortality in the case series was that of a patient who had surgery for recurrent prolapse. Peri-operative and follow up data are shown in Table 2. Median duration of follow-up was 6.5 mo (range from 2 to 16 mo), the overall recurrence rate was 28% ($n = 12$). A summary of patients' outcome is shown in Figure 2. Recurrence rate for patients undergoing an urgent Delorme's procedure who presented as an emergency was higher (3/4, 75%) compared to those treated electively (9/39, 23%), P value 0.034. No other factors included in the analysis were identified to be statistically significant predictors of recurrence. Median duration of recurrence was 16 mo (IQR: 5-30) and there were three patients who developed an early recurrence, within two weeks of the initial procedure. The manage-

ment of the recurrent prolapse was as follows: No further intervention ($n = 1$), repeat Delorme's ($n = 3$), Altemeier's procedure ($n = 5$) and rectopexy with faecal diversion ($n = 3$). One patient was lost during follow up.

DISCUSSION

Rectal prolapse is a profoundly disabling condition which in Western populations occurs predominantly in elderly women. Surgery is the only way to address the pathology but the choice of operation can be influenced by patient, surgeon and disease-related factors. Traditionally abdominal rectopexy was advocated in young and fit patients and perineal procedures, including Delorme's, were reserved for elderly individuals who are less likely to tolerate abdominal intervention. With introduction of minimally invasive laparoscopic approach many surgeons argue that abdominal rectopexy can be safely applied in most patients with better recurrence-free outcome and minimal long-term complications such as constipation. The advantage of Delorme's procedure is that it combines minimal morbidity and shorter hospital stay with acceptable functional outcome and recurrence rate. Thus, the results of PROSPER trial, the largest randomised controlled trial comparing perineal with abdominal approaches in 293 patients, showed that there was no significant difference in recurrence rates, bowel function or quality of life between any of the treatments. Interestingly, abdominal surgery arm had the rate of recurrence much higher than previously published^[6]. Delorme's is an alternative to abdominal rectopexy not only in elderly but also in patients with a short prolapse and those wishing to avoid abdominal intervention^[7]. It is therefore not surprising that perineal procedures (Delorme's and Altemeier's) comprise 50% to 60% of all operations performed for rectal prolapse^[8]. In our series Delorme's operation was the preferred strategy for treatment unless the length of the prolapse (more than 10 cm) necessitated its resection either perineally (Altemeier's procedure) or abdominally (resection rectopexy). The overall recurrence rate in our cohort was 28% which may seem high in comparison with 20% based on the results of a meta-analysis^[9]. Sub-group analysis of electively operated patients, following exclusion of those who had urgent surgery for irreducible prolapse, reveals a recurrence rate of 18.6%. The vast majority (80%) of our patients had no post-operative complications. The only patient who died in our cohort suffered an early recurrence and had little choice but to accept abdominal rectopexy with de-functioning sigmoid loop colostomy. She developed congestive cardiac failure and pneumonia and died on the 43rd day after the second abdominal procedure, thus confirming limited physiological reserves (ASA-3) that influenced the initial choice of perineal repair.

The best management of recurrent rectal prolapse remains uncertain^[10] and there are few publications addressing this issue. A recent systematic review evaluating the results of abdominal or perineal surgery for

recurrent rectal prolapse, undertaken with the aim of developing an evidence-based treatment algorithm was unable to formulate one due to the variation in surgical techniques and heterogeneity in the quality of studies^[10]. Steele *et al.*^[11] advise that abdominal repair of recurrent rectal prolapse should be undertaken if the patient's risk profile permits. In our experience the same clinical factors, *i.e.*, lack of physiological reserves, restricted repeat surgery to perineal approach exactly as they had done at the time of the initial operation. Delorme's procedure, however, can be safely repeated. When the length of the prolapsed bowel precluded its successful plication our preferred alternative was perineal recto-sigmoidectomy (Altemeier's procedure) which was successfully performed in almost half of recurrences. Figure 1 outlines the algorithm we have adopted for the management of recurrent rectal prolapse after failed Delorme's procedure. We echo the opinion of Pikarskey *et al.*^[12] that outcome of surgery for rectal prolapse is similar in cases of primary or recurrent prolapse. Early recurrence often represents a technical failure in the background of generalised pelvic floor weakness. In three of our patients it happened on day 7, 10 and 14 after Delorme's procedure due to "cheese-wiring" of plicating sutures and the prolapsed demucosed and inflamed rectum proved particularly difficult to manage. We chose to address it by urgent laparotomy, posterior rectopexy without incorporation of synthetic mesh and formation of defunctioning loop colostomy. This was the only practical choice as the defunctioning stoma offered the benefit of faecal diversion in conditions of rectal inflammation, served as an additional point of bowel fixation anteriorly to the abdominal wall and addressed the likely faecal incontinence in the conditions of generalised pelvic floor weakness.

Our study, being retrospective observational in its design, has inevitable limitations in comparison with a randomised controlled trial. However, a randomised controlled trial aimed to answer some of the questions that have been raised in this paper such as, for example, the best treatment of early post-operative recurrence after failed Derome's procedure may prove to be difficult, if not impossible, to set up.

Delorme's procedure is a suitable treatment in the majority of patients with rectal prolapse regardless the age. It is an attractive choice due to low morbidity and mortality and has acceptable rate of recurrence, at least in the elective setting. The management of the recurrent rectal prolapse is often restricted to the pelvic approach by the same patient-related factors that influenced the choice of the initial operation, *i.e.*, Delorme's procedure. In the event of late recurrence Delorme's procedure can be easily repeated. Long recurrent prolapse requires resection and is best addressed by perineal recto-sigmoidectomy (Altemeier's procedure). Early recurrence developing within days or weeks often represents a technical failure that is difficult to treat and in sufficiently fit patients may require abdominal rectopexy combined

with faecal diversion.

COMMENTS

Background

Many surgical procedures have been described for treatment of full-thickness rectal prolapse indicating that none of them is entirely satisfactory. The choice of the procedure to deal with the recurrent prolapse is even more difficult due to the absence of established consensus among surgeons.

Research frontiers

At present there is insufficient evidence to formulate guidance on the management of the recurrent rectal prolapse as the outcome of such treatment depends on multiple patient and disease-related factors that are often beyond surgeons' control. There is also not enough knowledge to answer the question about the best treatment of early recurrence developing in the immediate post-operative period after failed Delorme's procedure. This study was aimed to assess the outcome of treatment of recurrent rectal prolapse after previous perineal repair (Delorme's procedure) and, in particular, factors that influenced decision-making process. The authors also report their experience of Delorme's procedure as a treatment of primary rectal prolapse.

Innovations and breakthroughs

This retrospective observational study challenges the view that patients with recurrent rectal prolapse after previous Delorme's procedure can be best served with abdominal rectopexy. Despite the perceived better recurrence-free outcome of abdominal interventions the practical reality is that the vast majority of such patients cannot have abdominal rectopexy for the same patient-related reasons why it could be carried out in the first instance. This study also attempts to address the management of the difficult clinical problem of recurrence developing in the early post-operative period after failed Delorme's procedure. In such a scenario the reported experience with urgent laparotomy and posterior suture rectopexy combined with defunctioning sigmoid loop colostomy is encouraging.

Applications

This study may assist surgeons in making decisions about the management of recurrent rectal prolapse. Future studies on the treatment of early post-operative recurrence will be of potential interest.

Terminology

The term rectal prolapse refers to a full-thickness (or complete) protrusion of the rectal wall through the anus.

Peer-review

The authors reported their retrospective data regarding the Delorme's procedure, which is one of the interesting topics.

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Observational Study

Three-dimensional endoanal ultrasound for diagnosis of perianal fistulas: Reliable and objective technique

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Abstract

AIM: To evaluate accuracy of three-dimensional endoanal ultrasound (3D-EAUS) as compared to 2D-EAUS and physical examination (PE) in diagnosis of perianal fistulas and correlate with intraoperative findings.

METHODS: A prospective observational consecutive study was performed with patients included over a two years period. All patients were studied and operated on by the Colorectal Unit surgeons. The inclusion criteria were patients over 18, diagnosed with a criptoglandular perianal fistula. The PE, 2D-EAUS and 3D-EAUS was performed preoperatively by the same colorectal surgeon at the outpatient clinic prior to surgery and the fistula anatomy was defined and they were classified in intersphincteric, high or low transsphincteric, supra-sphincteric and extrasphincteric. Special attention was paid to the presence of a secondary tract, the location of the internal opening (IO) and the site of external opening. The results of these different examinations were compared to the intraoperative findings. Data regarding location of the IO, primary tract, secondary tract, and the presence of abscesses or cavities was

analysed.

RESULTS: Seventy patients with a mean age of 47 years (range 21-77), 51 male were included. Low transsphincteric fistulas were the most frequent type found (33, 47.1%) followed by high transsphincteric (24, 34.3%) and intersphincteric fistulas (13, 18.6%). There are no significant differences between the number of IO diagnosed by the different techniques employed and surgery ($P > 0.05$) and, there is a good concordance between intraoperative findings and the 2D-EAUS ($k = 0.67$) and 3D-EAUS ($k = 0.75$) for the diagnosis of the primary tract. The ROC curves for the diagnosis of transsphincteric fistulas show that both ultrasound techniques are adequate for the diagnosis of low transsphincteric fistulas, 3D-EAUS is superior for the diagnosis of high transsphincteric fistulas and PE is weak for the diagnosis of both types.

CONCLUSION: 3D-EAUS shows a higher accuracy than 2D-EAUS for assessing height of primary tract in transsphincteric fistulas. Both techniques show a good concordance with intraoperative finding for diagnosis of primary tracts.

Key words: Tridimensional endoanal ultrasound; High transsphincteric fistula; Perianal fistula; Intersphincteric fistula; Dimensional endoanal ultrasound

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Core tip: The authors think that this paper provides new information regarding the diagnosis of perianal fistulas with three-dimensional endoanal ultrasound when compared with the results obtained from two-dimensional endoanal ultrasound, physical examination, and examination under anesthesia. This allows us to validate the technique.

Garcés-Albir M, García-Botello SA, Espi A, Pla-Martí V, Martín-Arevalo J, Moro-Valdezate D, Ortega J. Three-dimensional endoanal ultrasound for diagnosis of perianal fistulas: Reliable and objective technique. *World J Gastrointest Surg* 2016; 8(7): 513-520 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/513.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.513>

INTRODUCTION

Management of perianal fistulas continues to be a challenge for the surgeon. The correct classification of the fistulas and their relationship with the anal sphincters is fundamental in choosing the adequate treatment.

Magnetic Resonance Imaging (MRI) and endoanal ultrasound (EAUS) have become the most valuable tools for diagnosing anal pathology. Two dimensional EAUS (2D-EAUS) affords sufficient information to be able to make adequate decisions in the management

of these patients^[1-4]. It does not however measure volumes of the elements of the anal canal, and gives less information regarding the anatomic structures involved^[5-7]. These limitations have been overcome with the introduction of three dimensional EAUS (3D-EAUS).

For many authors, the characteristics of 3D-EAUS (easy access, cost and accuracy) have made it the first choice for the diagnosis of perianal fistulas. To date, examination under anesthesia has been considered the gold standard. There are some groups that now believe MRI is better as it can diagnose fistulas and secondary tracts which are not seen during surgery^[8], though there are no studies as yet which investigate the value of 3D-EAUS for this purpose.

The objective of this study was to evaluate the diagnostic accuracy of 3D-EAUS vs 2D-EAUS vs physical examination (PE) for the diagnosis of perianal fistulas and correlate the results with the intraoperative findings.

MATERIALS AND METHODS

A prospective observational consecutive study was performed with patients included over a two year period. All patients were studied and operated on by surgeon from the Colorectal Unit, Hospital Clínico Universitario, Valencia. The study protocol was approved by the hospital ethics committee and all patients signed an informed consent form.

The inclusion criteria were patients 18 years and over, diagnosed with a cryptoglandular perianal fistula. The exclusion criteria were patients operated in other centres, patients with chronic inflammatory bowel disease, suprasphincteric or extrasphincteric fistulas, and patients who were already receiving nonsurgical treatment which could affect the results such as plugs, biological glues or stem cell therapy, etc.

Study protocol

History and PE: A meticulous history was taken during the first consultation. PE performed in the prone jack-knife position included palpation of the perianal region and a digital rectal exam. The fistula anatomy was defined and they were classified as intersphincteric, high or low transsphincteric, suprasphincteric and extrasphincteric. Special attention was paid to the presence of a secondary tract, the location of the internal opening (IO) and the site of the external opening (EO).

EAUS: All ultrasounds were performed by the same surgeon with over 10 years' experience in EAUS using the B and K Medical Systems Pro Focus 2202® scanner and B-K 2050 probe (B-K Medical, Herlev, Denmark).

Ultrasound evaluation was carried out at a frequency of 10 MHz initially in 2D and followed by 3D using 0.2 mm slices throughout the length of the anal canal and producing 300 sequential images that were automatically reconstructed as a cube, which could be worked on later.

This automated reconstruction of the images reduces human error as the ultrasound probe does not need to be moved throughout the examination and can be subsequently saved allowing post examination analysis of the 3D-EAUS scan in coronal, sagittal or axial planes as deemed necessary.

All patients were examined in the prone jack-knife position. The ultrasound was systematically performed from the upper to the lower third of the anal canal. When examining the inferior third of the anal canal it is important to keep the buttocks separated because the subcutaneous tissue can be confused with images of the external anal sphincter (EAS) and therefore overestimate the length of the anal canal and of the EAS. When the EO was open the examination was repeated after instilling 10% hydrogen peroxide solution through a cannula.

2D-EAUS: The IO was classified with or without the instillation of hydrogen peroxide according to the criteria proposed by Cho D-Y^[9], distance from the anal margin and radial location. The primary fistulous tract was classified as: (1) Not seen; (2) Intersphincteric: Crosses the intersphincteric space without crossing the EAS; (3) Low transsphincteric: Crosses both sphincters or the EAS in the lower two thirds of the anal canal; (4) High transsphincteric: Crosses both sphincters in the upper third of the anal canal; (5) Suprasphincteric: Crosses the intersphincteric space and courses above the upper border of the puborectalis muscle; and (6) Extrasphincteric: Lies external to the sphincteric apparatus.

Other data obtained with this technique were the presence of secondary tracts (hypoechoic tracts which join the primary tract at some point) and the presence of cavities and perianal abscesses.

3D-EAUS: Sagittal, oblique, transverse and coronal images can be obtained and recorded in video format to be reviewed later if necessary. The location and distance of the IO from the anal margin are recorded together with possible secondary tracts and abscesses, confirming or improving the information obtained from the 2D-EAUS.

Once the examination is finalized, the images can be recovered and reviewed, taking meticulous measurements. There are a series of endosonography images that can lead to error in the measurements if the examination is not performed by someone experienced in the field. The separation of the EAS from the puborectalis muscle can be seen on sagittal section as a hypoechoic line, which when combined with the transverse axial image, perfectly defines the proximal limit of the EAS. The proximal limit of the internal anal sphincter (IAS) is defined as the anorectal junction and quantitative measurements are taken in mm. The following measurements were taken in all patients: Total length of the anal canal, length of the puborectalis

muscle, total length of the EAS, total length of the IAS, length of the IAS and EAS involved by the fistula and percentage of sphincter involved by the fistula with respect to the total sphincter length.

According to the measurements obtained, the fistulas were classified by 3D-EAUS as: (1) Unidentified; (2) Intersphincteric: Crosses the intersphincteric space without crossing the EAS; (3) Low transsphincteric: Involves less than 66% of the EAS; (4) High transsphincteric: Involves over 66% of the EAS; (5) Suprasphincteric: Crosses the intersphincteric space and courses above the upper border of the puborectalis muscle; and (6) Extrasphincteric: lies external to the sphincteric apparatus.

Surgery: All patients were operated in the prone jack-knife position with locoregional anesthesia. Surgery is started with a PE under anesthesia using a Hill Ferguson retractor and the EO is probed up to the IO. The presence of secondary tracts and other pathology, which could modify the surgery, is ruled out. If the IO is not seen, 10% hydrogen peroxide is instilled through the EO. At this point, data regarding the site, type, and distance from the anal marginal are taken. The type of surgery to be performed is then chosen.

Statistical analysis

Data from the PE, 2D-EAUS and 3D-EAUS are compared with data from the examination under anesthesia considered the gold standard. The concordance rate and Kappa coefficient (degree of non-random agreement between different measurements of the same variable) are calculated. The Kappa coefficient varies between -1 and 1, considering: $k = -1$, agreement due to chance; $k < 0.2$, poor agreement; $k = 0.2-0.4$, low; $k = 0.4-0.6$, moderate; $k = 0.6-0.8$, good; $k = 0.8-1$, very good. Furthermore, the sensitivity, specificity and predictive values were calculated for each test. The chi-square test was used to compare differences between percentages. The ROC curves (curves for the receiver operating characteristics) have been determined for the diagnosis of transsphincteric fistulas by PE, 2D-EAUS and 3D-EAUS. The ideal diagnostic test has sensitivity and specificity equal to 1 (upper left corner of the curve) and will be poorer the closer it is to the diagonal (area under the curve = 0.50). Therefore, the minimum requirement for a diagnostic method would be an area under the curve greater than 0.50.

In all cases a value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS version 19.0 for Windows (SPSS, Chicago, IL, United States).

RESULTS

Seventy patients with a diagnosis of perianal fistula of criptoglandular origin were eventually included (Figure 1). The most frequent type were low transsphincteric fistulas (33, 47.1%), followed by high transsphincteric

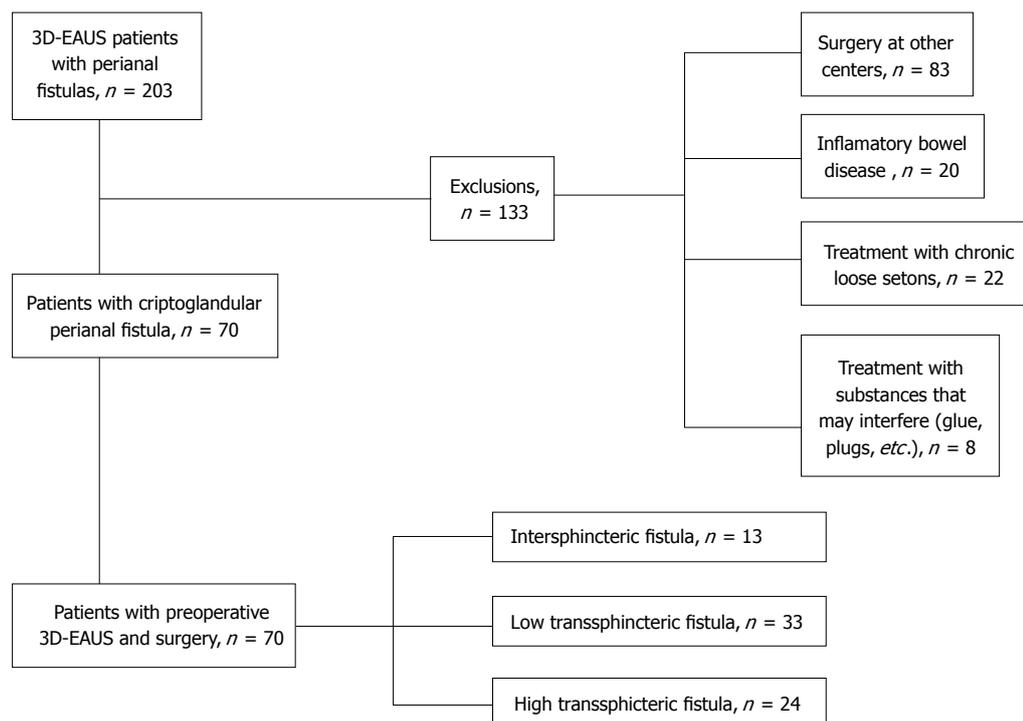


Figure 1 Patient distribution. 3D-EAUS: Three-dimensional endoanal ultrasound.

Table 1 Gynecological history and past perianal surgery

	n = 70 (n females = 19)	%
Females with vaginal deliveries	9	47.3
Episiotomy	4	21.0
Hysterectomy	2	10.5
Perianal abscesses drained	42	60.0
Seton	22	31.4
Fistulotomy	6	8.6
Fistulectomy	3	4.3
LIS	7	10.0
Hemorrhoidectomy	3	4.3
Rectal mucosal advancement flap	3	4.3

LIS: Lateral internal sphincterotomy.

Table 2 Results of fistula evaluation in 70 patients n (%)

	PE	2D-EAUS	3D-EAUS	Surgery
IO identified	3 (75.7)	67 (95.7)	67 (95.7)	67 (95.7)
Primary tract				
Intersphincteric	19 (27.1)	14 (20)	10 (14.3)	13 (18.6)
Transsphincteric				
Low	22 (31.4)	25 (35.7)	34 (48.6)	33 (47.1)
High	19 (27.1)	30 (42.9)	25 (35.7)	24 (34.3)
Unclassified	10 (14.3)	1 (1.4)	1 (1.4)	0 (0)
Secondary tract	6 (8.6)	15 (21.4)	16 (22.9)	11 (15.7)
Adjacent abscesses	12 (17.1)	17 (24.3)	19 (27.1)	8 (11.4)

2D-EAUS: Two dimensional endoanal ultrasound; 3D-EAUS: Three dimensional endoanal ultrasound; IO: Internal opening; PE: Physical examination.

fistulas (24, 34.3%) and finally intersphincteric fistulas (13, 18.6%). Gynaecological history and past perianal surgeries can be seen in Table 1. Median duration of symptoms at first consultation was 12 mo (range 1-120).

Correlation with intraoperative findings

Findings for PE, 2D-EAUS, 3D-EAUS and surgery are in Table 2.

Internal opening: Sixty-seven IOs were found in 70 patients intraoperative. The majority of IO were found by digital rectal examination (n = 53; 75.7%). Both 2D-EAUS and 3D-EAUS diagnosed 67 IO in 70 patients (95.7%). Both examinations failed to find the IO in 3 patients despite the instillation of hydrogen peroxide. Two of the patients not diagnosed by EAUS do not coincide with those not found during surgery. There are

no significant differences between the number of IO diagnosed between the different techniques employed and surgery (P > 0.05) (Table 3).

Primary fistula tract

Thirteen intersphincteric fistulas, 33 low transsphincteric and 24 high transsphincteric fistulas were diagnosed intraoperatively. PE could not classify 10 patients due to pain, or because the tract could not be palpated during the examination. Thirty-seven patients were correctly diagnosed (52.9%). 55 (78.6%) and 58 (82.8%) were diagnosed by 2D-EAUS and 3D-EAUS respectively as shown in Table 3. One patient could not be classified by 2D-EAUS or 3D-EAUS due to the difficulty in differentiating the fistulous tract from fibrosis secondary to prior anal surgeries. There is a good concordance between intraoperative and ultrasound diagnosis

Table 3 Concordance grade and k coefficient (k) between intraoperative findings and the different diagnostic techniques used

	PE		2D-EAUS		3D-EAUS	
	Concordance	k	Concordance	k	Concordance	k
IO identified	51/70 (72.8%)	¹	68/70 (97.1%)	¹	68/70 (97.1%)	¹
Primary tract	37/70 (52.9%)	0.33	55/70 (78.6%)	0.67	58/70 (82.8%)	0.75
Secondary tract	61/70 (87.1%)	0.44	64/70 (91.4%)	0.66	65/70 (92.8%)	0.60
Adjacent abscesses	58/70 (82.8%)	0.30	61/70 (87.1%)	0.57	60/70 (85.7%)	0.54

¹P > 0.05. k < 0: No agreement; k = 0: Concordance due to chance; k = 0-0.19: Insignificant; k = 0.2-0.39: Low; k = 0.4-0.59: Moderate; k = 0.6-0.79: good; k = 0.8-0.1: Very good. 2D-EAUS: Two dimensional endoanal ultrasound; 3D-EAUS: Three dimensional endoanal ultrasound; IO: Internal opening; PE: Physical examination.

Table 4 Efficacy parameters in relation to surgery for the different diagnostic techniques: Sensitivity, specificity, positive predictive value and negative predictive value

		S	SP	PPV	NPV
IO identified (%)	PE	76	33	96	6
	2D-EAUS	98	66	98	66
	3D-EAUS	98	66	98	66
Primary tract (%)	PE	69	82	47	92
	2D-EAUS	77	93	71	95
	3D-EAUS	22	98	90	93
Transsphincteric Low	PE	45	81	68	67
	2D-EAUS	67	92	88	75
	3D-EAUS	85	84	82	86
High	PE	38	87	68	78
	2D-EAUS	64	76	70	70
	3D-EAUS	88	91	84	93
Secondary tract (%)	PE	40	97	67	91
	2D-EAUS	90	90	60	98
	3D-EAUS	90	88	56	98

2D-EAUS: Two-dimensional endoanal ultrasound; 3D-EAUS: Three-dimensional endoanal ultrasound; PE: Physical examination; IO: Internal opening; S: Sensitivity; SP: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

of primary tract, the highest concordance was with 3D-EAUS (k = 0.67 and k = 0.75, respectively). There is a tendency to overestimate fistula height with 2DEAUS as can be seen by the lower specificity for high transsphincteric fistulas and lower sensitivity for low transsphincteric fistulas shown in Table 4.

Secondary fistulous tracts: One or more secondary fistula tracts were diagnosed by 2D-EAUS and 3D-EAUS in 15 and 16 patients respectively with a good concordance with surgical findings (91.4%, k = 0.66; 92.8%, k = 0.60) (Table 3).

Abscesses and adjacent cavities: 2D-EAUS diagnosed abscesses in 17 (24.3%) patients and 3D-EAUS in 19 (27.1%) patients. 12 cases (17.1%) were diagnosed by PE. 8 patients (11.4%) presented with an abscess at the time of surgery. There was a moderate concordance between EAUS and surgery (k=0.57, k = 0.54, respectively). There was a low concordance between PE and intraoperative findings (k = 0.30) (Table 3).

Table 5 Results of receiver operative characteristic curves for the diagnosis of transsphincteric fistulas

		Area under curve	95%CI	P value
Low transsphincteric fistula	PE	0.608	0.474-0.742	0.120
	2D-EAUS	0.819	0.714-0.924	0.0001
	3D-EAUS	0.829	0.724-0.934	0.0001
High transsphincteric fistula	PE	0.672	0.541-0.803	0.019
	2D-EAUS	0.842	0.745-0.939	0.0001
	3D-EAUS	0.910	0.835-0.985	0.0001

2D-EAUS: Two-dimensional endoanal ultrasound; 3D-EAUS: Three-dimensional endoanal ultrasound; PE: Physical examination.

The sensitivity and specificity (efficacy indexes) of the different examinations with respect to intraoperative findings are shown in Table 4.

ROC curves (Receiver Operating Characteristic) for the diagnosis of transsphincteric fistulas by PE and 2D/3D-EAUS are adequate for the diagnosis of low transsphincteric fistulas. 3D-EAUS is superior for the diagnosis of high transsphincteric fistulas (Figure 2). PE is clearly deficient for the classification of transsphincteric fistulas (Table 5).

DISCUSSION

3D-EAUS is a novel technique for the diagnosis of perianal fistulas and multiple studies such as ours demonstrate its' superiority with respect to 2D-EAUS. 3D-EAUS is a useful tool that gives a more reliable preoperative diagnosis of perianal fistulas with accurate diagnosis of the IO, primary tracts, secondary tracts and adjacent abscesses or cavities. Ratto *et al*^[10] published a rate of exact diagnosis with 3D-EAUS of primary and secondary tracts of 98.5% and 96.4% for the IO compared with 89.9%, 83.3% and 87.9% respectively with 2D-EAUS. Santoro *et al*^[11,12] in their study in 57 patients confirm that 3D-EAUS improves diagnosis accuracy of the IO when compared to 2D-EAUS (2D-EAUS: 66.7% vs 3D-EAUS: 89.5%; P = 0.0033). However, both techniques were similar for diagnosis of primary and secondary tracts and abscesses^[11,12]. Our study showed a 97.1% concordance for the diagnosis of the IO (for both types of EAUS), 78.6% for primary tracts, 91.4% for secondary tracts and 87.1% for cavities and abscesses with 2D-EAUS as opposed to

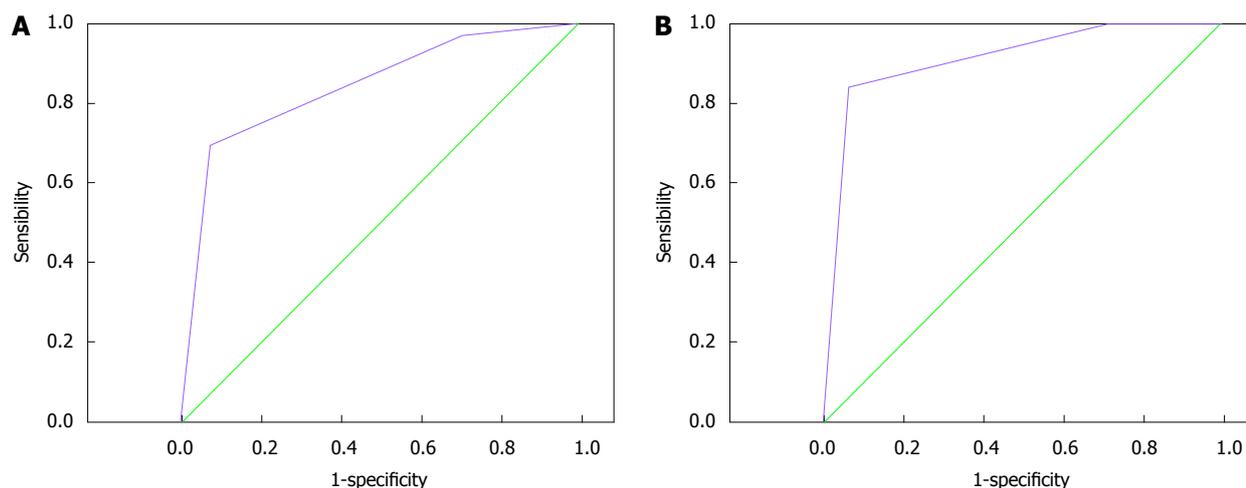


Figure 2 Receiver operating characteristic curves for the diagnosis of high transsphincteric fistulas with two-dimensional endoanal ultrasound (A) (area under curve = 0.842; 95%CI: 0.745-0.939; $P = 0.0001$) and three-dimensional endoanal ultrasound (B) (area under curve = 0.910; 95%CI: 0.835-0.985; $P = 0.0001$).

82.8%, 92.8% and 85.7% respectively when using 3D-EAUS. A preliminary study in 29 patients carried out by our group showed a concordance rate between intraoperative findings (gold standard) and 3D-EAUS of 79% for primary fistula tracts validating the latter as a useful technique in the evaluation of perianal fistulas^[13].

There are various classifications for perianal fistulas. As a practical method, various authors have modified the Parks classification^[14]. The subdivision of transsphincteric fistulas with regards to the level at which they cross the anal canal tends to be arbitrary dividing these in equal thirds. We propose a new division of transsphincteric fistulas dividing them into low (less than 66% of the total length of the EAS involved) and high (over 66% of the EAS involved). This way we can simplify the classification and guide the indication for surgery.

This study shows a good correlation between 3D-EAUS and surgical findings, with superior results to PE and 2D-EAUS, in particular with regards to high transsphincteric fistulas which are the ones raising more doubts in diagnosis and choice of treatment. According to our results, 2D-EAUS in particular for high transsphincteric fistulas tends to overestimate the amount of anal sphincter involved thus classifying them as higher than they really are, as can be seen by the lower specificity for high transsphincteric fistulas and lower sensitivity for low transsphincteric fistulas. These errors are minimized with 3D-EAUS with a notable improvement in sensitivity and specificity. According to the ROC curves, the best technique for diagnosing high transsphincteric fistulas is 3D-EAUS. Although both types of EAUS are adequate for the diagnosis of low transsphincteric fistulas, 3D-EAUS seems to be slightly superior.

The large variability between examinations have not allowed for the calculation of the IO Kappa coefficient, there were no significant differences between examination techniques and surgical findings with

regards to diagnosis of the IO. These results are similar to the study in 21 patients published by Poen *et al*^[15]. The three examinations show high sensitivity and specificity when diagnosing the location and distance from the anal margin of the IO.

Even though both types of EAUS have a good concordance 3D-EAUS has shown a higher concordance and accuracy than 2D-EAUS when compared to intraoperative findings ($k = 0.75$ vs $k = 0.67$). Various studies have shown a very good concordance between 2D and 3D-EAUS and surgery for diagnosis of the primary tract using the instillation of hydrogen peroxide^[8,13]. We did not use hydrogen peroxide in all our patients and included patients with a closed EO. This could explain the difference in results.

Similar to the results published by Poen *et al*^[15] ($k = 0.61$), 3D-EAUS shows a good concordance with surgery for the diagnosis of secondary tracts ($k = 0.60$). The concordance coefficient for 2D-EAUS is slightly higher than 3D-EAUS ($k = 0.66$ vs $k = 0.60$). In addition, EAUS diagnosed more secondary tracts than surgery. These complex or high fistulous tracts could go unnoticed during surgery. As a result of these findings we should possibly reconsider, as have done other authors, which of these examinations is truly the gold standard for the diagnosis of perianal fistulas. Surgery may not be the best diagnostic tool and we should consider MRI with an endoanal coil or 3D-EAUS^[16].

The diagnosis of adjacent abscesses and cavities shows a moderate concordance with surgery (2D-EAUS, $k = 0.57$; 3D-EAUS, $k = 0.54$) and insignificant concordance with PE. This is probably due to the fact that these cavities may not be obvious on PE but as patients had to wait sometime between examination and surgery there were probably changes (improvement or deterioration) in these parameters.

There are various studies that defend the routine use of preoperative 2D-EAUS for the diagnosis of both simple and complex perianal fistulas^[14,17]. Some

simple perianal fistulas can be diagnosed on PE and we believe a routine EAUS is unnecessary. 3D-EAUS has clearly overtaken 2D-EAUS however, and is more efficient offering more detailed information^[10,18]. Due to the common problem that these fistulas represent and the difficulty in obtaining a definitive treatment, there are various groups that as we do, use 3D-EAUS for the preoperative diagnosis of perianal fistulas^[19]. Murad-Regadas *et al*^[20] published a study in 33 patients confirming that preoperative 3D-EAUS was useful for the diagnosis of anterior transsphincteric fistulas, assisting in choosing the most appropriate treatment and reducing the incontinence rates.

Our work shows the value of 3D-EAUS in predicting the amount of sphincter involved by the fistula in an objective and quantitative manner, and allowing a more accurate classification of the fistula.

Despite the results obtained in this study there were some limitations. These include the low number of patients included even though this was similar or superior to other published studies, the exclusion of suprasphincteric and extrasphincteric fistulas, whose prevalence is very low and where the role of IRM vs 3D-EAUS is debatable^[7,16]; and that all measurements and scans in this study were performed by the same surgeon. This last point may be beneficial on the one hand as it reduces interobserver variability, but at the same time may offer some bias. We believe it would be more correct to perform the measurements by two independent examiners and then analyse the differences between them.

According to our results we can conclude that 3D-EAUS is more accurate than 2D-EAUS for estimating the height of the primary tract in transsphincteric fistulas. Both 2D and 3D-EAUS techniques show a good concordance with examination under anesthesia for the diagnosis of primary tracts with slightly superior results for 3D-EAUS. Therefore, we agree with other authors that EAUS is a fundamental tool in the evaluation of perianal fistulas allowing for a better classification. 3D-EAUS provides new advantages with respect to 2D-EAUS and is a superior technique allowing for objective and quantitative, and not only subjective, information.

COMMENTS

Background

Perianal fistulas are a common problem in the general population and affect around 10 per 100000 population per year. The relationship between fistulous tract, the sphincters and adequate management is still a challenge today. Imaging techniques play an important role in diagnosis. Various authors including us prefer endoanal ultrasound (EAUS). It is cheaper, easy to use with training, fast, non-invasive and can be used in the operating room if necessary.

Research frontiers

Controversy has been raised over the last few years over which technique [magnetic resonance imaging (MRI), ultrasound or examination under anesthesia] is the gold standard for diagnosis of perianal fistulas. The choice between EAUS and MRI mainly depends on their availability. MRI may seem to

offer better results for the diagnosis of perianal fistulas but is outweighed by its' expense and lower availability. In addition, three-dimensional (3D)-EAUS has considerably improved when compared with MRI.

Innovations and breakthroughs

This study compares the results of PE, 2D-EAUS and 3D-EAUS with examination under anesthesia for perianal fistulas providing concordance data for the different techniques. This allows the authors to determine which technique is best in each case, the need to use them as diagnostic tools and for providing optimal management of perianal fistulas.

Applications

The results of this study suggest 3D-EAUS is superior to 2D-EAUS for the diagnosis of high transsphincteric fistulas and could now be considered the gold standard for diagnosis of this pathology. EAUS is a fundamental tool for the evaluation of perianal fistulas offers an accurate classification and therefore better treatment.

Terminology

Perianal fistulas are a chronic phase of a suppurated anal disease. The currently available imaging techniques for classifying anal fistulas are: Fistulography (no longer used), MRI and EAUS. EAUS can be 2D EAUS (distance, area and volume measurements cannot be taken, with poorer imaging of spatial relations and loss of relevant information) or 3D-EAUS (offers a view of all planes and distances, angles, areas and volumes can be accurately measured).

Peer-review

The paper offers an interesting comparison of the diagnostic yield of 2D-EAUS vs 3D-EAUS for perianal fistulas. The gold standard in the present study are intraoperative findings, although other groups think that MRI can demonstrate perianal fistulas missed by the surgeon.

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Benefits of post-operative oral protein supplementation in gastrointestinal surgery patients: A systematic review of clinical trials

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Abstract

AIM: To evaluate published trials examining oral post-operative protein supplementation in patients having undergone gastrointestinal surgery and assessment of reported results.

METHODS: Database searches (MEDLINE, BIOSIS, EMBASE, Cochrane Trials, Cinahl, and CAB), searches of reference lists of relevant papers, and expert referral were used to identify prospective randomized controlled clinical trials. The following terms were used to locate articles: "oral" or "enteral" and "postoperative care" or "post-surgical" and "proteins" or "milk proteins" or "dietary proteins" or "dietary supplements" or "nutritional supplements". In databases that allowed added limitations, results were limited to clinical trials that studied humans, and publications between 1990 and 2014. Quality of collated studies was evaluated using a qualitative assessment tool and the collective results interpreted.

RESULTS: Searches identified 629 papers of which, following review, 7 were deemed eligible for qualitative evaluation. Protein supplementation does not appear to affect mortality but does reduce weight loss, and improve nutritional status. Reduction in grip strength deterioration was observed in a majority of studies, and approximately half of the studies described reduced complication rates. No changes in duration of hospital stay or plasma protein levels were reported. There is evidence to suggest that protein supplementation should be routinely provided post-operatively to this population. However, despite comprehensive searches, clinical trials that varied only the amount of protein provided *via* oral nutritional supplements (discrete from other nutritional

components) were not found. At present, there is some evidence to support routinely prescribed oral nutritional supplements that contain protein for gastrointestinal surgery patients in the immediate post-operative stage.

CONCLUSION: The optimal level of protein supplementation required to maximise recovery in gastrointestinal surgery patients is effectively unknown, and may warrant further study.

Key words: Protein supplementation; Gastrointestinal surgery; Clinical trial; Oral supplementation; Systematic review

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Core tip: Malnutrition in hospitalized patients can negatively impact recovery; protein and energy deficiencies have been documented in gastrointestinal surgery patients and trials have demonstrated benefits of peri-operative nutritional strategies, although post-operative oral nutritional supplementation have been studied to a lesser extent. The outcome of our work is that clinical trials that varied only the protein provided *via* oral supplements were not found. There is evidence to support oral protein supplements for gastrointestinal surgery patients immediately post-operatively. But the optimal level of protein supplementation required to maximise recovery in gastrointestinal surgery patients is effectively unknown, and may warrant further study.

Crickmer M, Dunne CP, O'Regan A, Coffey JC, Dunne SS. Benefits of post-operative oral protein supplementation in gastrointestinal surgery patients: A systematic review of clinical trials. *World J Gastrointest Surg* 2016; 8(7): 521-532 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/521.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.521>

INTRODUCTION

Malnutrition has been associated with increased incidence of complications such as sepsis, pneumonia, wound infections, clotting disorders, and wound dehiscence^[1,2]. Patients undergoing major gastrointestinal surgery can suffer periods of undernourishment, not only as a consequence of their presenting illness, but also due to reduced food intake and the resulting catabolic state that prevails in the post-operative period. In this population, malnutrition has been found to increase post-operative morbidity and mortality rates as well as the duration and subsequent cost of hospital stay^[3,4]. These despite multimodal nutritional regimens, include pre-operative carbohydrate loading.

In this context, nutritional supplementation has been suggested as a routine post-operative procedure for gastrointestinal surgery patients given the putative negative nitrogen balance. Indeed, intervention in

the form of post-operative protein supplementation (in the context of allowable free-fluids or light diet by mouth) has remained of interest as an effective way to improve patient recovery despite an apparent paucity of trials adequately addressing the optimum, or even appropriate, quantity of proteins or peptides. As the physiological nitrogen balance is affected by both energy and protein consumption, knowledge of the levels of each that best enable avoidance of catabolic loss after gastrointestinal surgery could benefit patient outcomes^[5].

Therefore, in this review, clinical trials of oral nutritional supplements providing increased protein levels relative to controls, administered to human patients recovering from gastrointestinal surgery, were systematically assessed with respect to clinical efficacy and cost-effectiveness.

MATERIALS AND METHODS

Search methods

The following terms were used to locate articles: "oral" or "enteral" and "postoperative care" or "post-surgical" and "proteins" or "milk proteins" or "dietary proteins" or "dietary supplements" or "nutritional supplements". In databases that allowed added limitations, results were limited to clinical trials that studied humans, and publications between 1990 and 2014. Despite these limits, multiple non-clinical trial results, non-human trials, and irrelevant studies appeared and were excluded. The search was intentionally broad as more specific searches for gastrointestinal surgery associated keywords and MeSH terms resulted in numerous missed relevant papers. Databases searched included: MEDLINE, Biosis, EMBASE, Cochrane Trials, Cinahl, and CAB. Other means of identifying records included searching reference lists of relevant papers.

Inclusion and exclusion criteria

Randomized controlled clinical trials examining protein-based oral dietary supplementation post-operatively in human gastrointestinal surgery patients were selected. Studies were excluded if: Involved immunonutrition; related to supplementation with incomplete proteins; did not specify the amount of protein supplemented; supplemented patients pre-operatively only; not strictly oral nutrition; or not published in English.

Outcomes measured

Primary outcomes included the effect of supplementation on post-operative complications, length of hospital stay, nutritional status, and weight loss. Secondary outcomes included the effect on plasma proteins, quality of life, function, and cost of care.

Data collection and analysis

Trials that met the inclusion criteria were independently assessed for eligibility by the authors (Crickmer M, O'Regan A, Dunne CP) and discrepancies were resolved

Table 1 Quality assessment tool (adapted from^[6])

Items and scores
Was the assigned treatment adequately concealed prior to allocation? 2 = method did not allow disclosure of assignment 1 = small but possible chance of disclosure of assignment or states random but no description 0 = quasi-randomized
Were the outcomes of participants who withdrew described and included in the analysis (intention to treat)? 2 = intention-to-treat analysis based on all cases randomized possible or carried out 1 = states number and reasons for withdrawal but intention-to-treat analysis not possible 0 = not mentioned or not possible
Were the outcome assessors blinded to treatment status? 2 = action taken to blind assessors, or outcomes such that bias is unlikely 1 = small or moderate chance of unblinding of assessors 0 = not mentioned
Were the treatment and control group comparable at entry? 2 = good comparability of groups 1 = confounding small 0 = large potential for confounding, or not discussed
Were care programs, other than the trial options, identical? 2 = care programs clearly identical 1 = clear but unimportant differences 0 = not mentioned or clear and important differences in care programs
Were the inclusion and exclusion criteria clearly defined? 2 = clearly defined 1 = inadequately defined 0 = not defined
Were the interventions clearly defined (including estimates of nutritional value)? 2 = clearly defined interventions are applied with a standardized protocol 1 = clearly defined interventions are applied but the application protocol is not standardized 0 = intervention and/or application protocol are poorly or not defined
Were the participants blind to assignment status following allocation? 2 = effective action taken to blind participants 1 = small or moderate chance of unblinding participants 0 = not possible, or not mentioned (unless double-blind), or possible but not done
Were the treatment providers blind to assignment status? 2 = effective action taken to blind treatment providers 1 = small or moderate chance of unblinding of treatment providers 0 = not possible, or not mentioned (unless double-blind), or possible but not done
Was the overall duration of surveillance clinically appropriate? 2 = optimal (six months or more) 1 = adequate (one up to six months) 0 = not defined, or not adequate

by discussion. Papers were read independently by the authors and themes were identified. Risk of bias was assessed by determining allocation concealment for participants, the staff and assessors. The effect of treatment was assessed relative to clinical importance and statistical significance, using *P* values of ≤ 0.05 as the cut-off point. The evaluation of the trials was guided thematically with the qualitative tool, modified from a previous Cochrane Systematic Review^[6], described in Tables 1 and 2. The characteristics of each study were tabulated and are shown in Table 3.

Where studies included both pre-and post-operative supplementation interventions, only the post-operative components are considered in this review. The numbers of trial participants per study were adjusted to reflect this.

RESULTS

Results of the search

Following PRISMA guidelines^[7], seven eligible reports

were identified (see Figure 1). Exclusions were as follows: (1) of records found *via* database searching: 358; (2) of records found by other means: 271; (3) of records screened: 629; (4) of records excluded (including removal of duplicates): 587; (5) of full text articles assessed for eligibility: 42; (6) of full text articles excluded: 35; and (7) of studies included in qualitative analysis: 7.

Assessment of studies design

All seven studies^[5,8-13] were prospective randomized controlled trials. In most cases, the patients, their carers and the assessors were not blinded. Intention to treat was not included in most studies. The control and intervention groups had similar characteristics in each trial and in all other aspects of treatment, other than the intervention. The interventions undertaken, and inclusion and exclusion criteria, were well defined in all studies. Five of the seven studies^[5,8,9,11,13] included outpatient phases that lasted between one and six months. The characteristics of the studies are outlined

Table 2 Outcomes of quality assessment, described for individual trials

	Smedley <i>et al.</i> ^[8]	Saluja <i>et al.</i> ^[10]	Beattie <i>et al.</i> ^[13]	MacFie <i>et al.</i> ^[9]	Jensen <i>et al.</i> ^[5]	Keele <i>et al.</i> ^[11]	Rana <i>et al.</i> ^[12]
Was the treatment adequately concealed prior to allocation?	2	0	2	0	0	0	2
Were candidates who withdrew included in analysis?	0	No withdrawals	0	0	0	0	1
Were the assessors blinded?	0	0	0	0	2	0	0
Were treatment and control groups comparable at entry?	2	2	0	2	1	2	2
			Specific mention of "lack of detail on patients at entry"		Specific mention of error "in the randomisation process"		
Were care programmes otherwise identical?	2	2	2	2	2	2	2
Were the inclusion and exclusion criteria clearly defined?	2	2	2	2	2	2	2
Were the interventions clearly defined?	2	2	2	1	1	2	2
Were the participants blind to assignment after allocation?	0	0	0	0	0	0	0
Were the treatment providers blinded to allocation status?	0	0	0	0	0	0	0
Was duration of surveillance appropriate?	1	1	2	2	1	1	0

in Table 3.

Sample sizes and patient population

Sample sizes ranged from 40 to 101. A total of 529 patients were involved, 262 of whom had an intervention. Participants were post-operative gastrointestinal surgery patients scheduled for acute or elective surgery. Nutritional status pre-operatively was variable, with some studies focused on malnourished patients^[10,13]. Patient age ranged from 18 to greater than 75, and all studies included both genders.

Interventions

All treatment group (TG) patients received post-operative nutritional supplementation in addition to their normal ward diet, while control groups (CGs) consumed only normal ward diet. In most cases, patients were encouraged to drink 200-400 mL of the supplement per day. Supplements comprised between 0.0078 g/mL and 0.06 g/mL of protein, with the most frequent value being 0.05 g/mL. They also provided between 0.6 kcal/mL and 1.5 kcal/mL of energy, with the most common inclusion being 1.5 kcal/mL. All studies, except Jensen^[5], began supplementation as soon as allowed by the surgical team, typically beginning one to six days post-operatively. Some studies focused on post-operative feeding only, while studies by Smedley *et al.*^[8] and MacFie *et al.*^[9] examined both pre-operative and post-operative feeding. Only the post-operative component of those studies is considered in this review and the numbers of trial participants has been adjusted to reflect this.

Themes

Assessment was according to the following eight themes:

Overall nutritional intake: Four of the studies quantified the difference in protein intake between treatment and CGs. Specifically, Saluja *et al.*^[10] found that protein intake was significantly higher ($P < 0.01$) in the group given supplementation in addition to ward diet. The TG consumed an average of 55.71 ± 11.63 g of protein per day during the study period, while the CG consumed 39.48 ± 11.14 g of protein per day ($P < 0.01$). These increases in protein consumption were accompanied by significant increases in the amount of carbohydrate consumed ($P < 0.01$). Jensen *et al.*^[5] calculated that the TG consumed 22% more protein than the CG and 16% more energy. It is noteworthy that supplementation in that trial started after discharge at about day 10, and was paired with dietetic advice, while in the previous trial by Saluja *et al.*^[10], supplementation began the first day following surgery. Keele *et al.*^[11] also found that the TG showed statistically significant increases in protein and energy consumption on study days one to four. No difference in protein intake was seen in the second phase of their trial, which examined intake for 4 mo following discharge. The inpatient results (improved overall nutritional intake) found by Rana *et al.*^[12] are similar to those found by Keele *et al.*^[11].

Weight: Four of five studies that measured this factor^[5,8,11,12] found reduced weight loss in normonourished patients receiving supplementation. Keele *et al.*^[11] found decreased loss both at day 3 of the trial and at discharge ($P < 0.001$). Rana *et al.*^[12] found that when patients started supplements as soon as they were allowed free fluids after surgery, they maintained their weight whereas by day 3, there was significant weight loss in the CG ($P < 0.05$). Statistically significant reduction in weight loss was also found by Smedley

Table 3 Summary details of eligible trials

Ref.	Method	Participants	Intervention	Outcomes	Conclusions/Notes
Smedley <i>et al</i> ^[8]	RCT	Undergoing elective moderate-major lower GI surgery <i>n</i> = 89; 39 patients were controls in the pre-op phase and in the TG in phase 2 making them the treatment group for this analysis. Fifty patients were controls throughout making them the control group	Included multiple groups with patients receiving pre and post-operative supplementation. This review focused on the group that received no supplements pre- and post-op, as well as the group that received no supplement pre-op and supplements post-operation (CG = Group 4, TG = Group 3) Supplementation began when patients allowed light diet or free fluids post-operation. Fortisip, nutricia used as supplement: 0.05 g/mL protein, 1.5 kcal/mL energy TG asked to drink as they desired in addition to meals	Complications: Fewer minor complications in TG (<i>P</i> < 0.05) Length of stay: No difference Weight loss: Significant reduction in patients given ONS before and after surgery and in patients given postoperative ONS only Quality of life: No difference (Short Form 36, EuroQol instruments were used) Cost: Reduced by GBPE300 (15%) per patient, however not statistically significant Post-surgery oral nutritional supplements were of benefit independently of nutritional status Adverse events: ONS well tolerated	The patients in this study had a baseline of good nutritional intake
Saluja <i>et al</i> ^[10]	PRCT	<i>n</i> = 60 (30/30) divided into BM, MM and SM using the NRI ^[26] Age: Between 20-60 yr Elective and emergency abdominal procedures (not just GI) Treatment started from day-1 post-operatively Assessment was done on admission, day 3 and at discharge	0.033 g/mL of protein or 16.66 g/500 mL drink and 500 kcal energy, in addition to ward diet. Ward diet only was provided to control group. Trial started once surgical team allowed fluids or light diet	Total protein intake: Increased in TG (<i>P</i> < 0.01) Voluntary protein intake higher though not significant Weight loss: TG = 2.15 kg <i>vs</i> CG = 4.6 kg (<i>P</i> < 0.01) Overall weight loss: TG = 5.6%, CG = 6.4% Severely Malnourished Patients: TG = 6.3%, CG = 10% (<i>P</i> < 0.01) No significant change in lymphocyte count Complications: No significant difference Length of stay: Statistically significant reduction in severely malnourished patients. No difference in other categories in length of stay No change in mid arm circumference No change in hand grip strength Treatment group felt better than control group (subjective assessment) No difference in voluntary intake in group consuming supplements	Severely malnourished patients have increased energy requirements and less oral intake, and will therefore lose lean body mass as a substrate for energy Albumin half-life is 20 d - early post-op period is too short to demonstrate a difference due to supplementation

Crickmer M *et al.* Post-operative oral protein supplementation: Systematic review of trials

Beattie <i>et al</i> ^[13]	PRCT	<p>Patients had a BMI < 20 or > 5% weight loss between hospital admission and trial inclusion, and other anthropometric criteria.</p> <p>Age: 18-80</p> <p><i>n</i> = 101, intervention = 52; control = 49</p>	<p>Oral nutritional supplement containing 0.06 g/mL protein, 1.5 kcal/mL energy. Patients encouraged to consume 400 mL/d postoperatively. In practice, patients had between 200 and 400 mL/d in addition to normal meals</p>	<p>Weight loss: CG lost an average maximum of 5.96 kg at 8 wk after admission, while TG lost a maximum of 3.4 kg on average in the first 4 wk and then gained weight (<i>P</i> < 0.001)</p> <p>Mean body weight loss = 9.8% in CG and 5.6% in treatment group</p> <p>Triceps skin fold and MAMC were higher in TG than CG (<i>P</i> < 0.001)</p> <p>Function: Improved grip strength at 10 wk (<i>P</i> < 0.001)</p> <p>Quality of life (UK SF-36): Statistically significant improvement in mental and physical health (<i>P</i> < 0.001)</p> <p>Complications: Reduced (<i>P</i> < 0.05)</p> <p>No difference in infection rates</p> <p>Length of stay: No difference</p>	<p>Support for nutritional intervention in patients with malnutrition:</p> <p>Post-operative oral nutritional supplementation improved nutritional status, quality of life and morbidity</p>
MacFie <i>et al</i> ^[9]	PRCT	<p>Major GI surgery patients <i>n</i> = 52; 27 had intervention of some kind.</p> <p>TG <i>n</i> = 27 (post op supplements), CG <i>n</i> = 25</p>	<p>Pre and post-operative phases. For this review, only the control group and post-operative supplementation group were looked at</p> <p>Fortisip, Nutricia given - 0.05 g/mL protein and 1.5 kcal energy/mL or an alternative Fortijuice, Nutricia containing 0.025 g/mL protein and 1.25 kcal/mL energy. Patients encouraged to consume 400 mL/d in addition to normal ward diet</p> <p>Supplementation commenced as soon as permitted fluids post-surgery, usually within 24 h</p> <p>CG was provided standard ward diet</p>	<p>Nutritional intake: Increased protein and energy seen (but no benefits could be seen)</p> <p>Morbidity: No difference</p> <p>Mortality: No difference</p> <p>Effect on voluntary food intake: No difference</p> <p>Nutritional status: No difference</p> <p>Functional status: No difference</p> <p>Hospital stay: No difference</p> <p>Weight Loss: No significant difference</p> <p>Serum albumin: No significant difference</p> <p>Psychological Status: No significant differences</p> <p>Return to normal activities at 6 mo: No difference</p> <p>No evidence that increased supplements decreased amount of ward diet eaten</p>	<p>Similar intakes of supplements as previous trials (Rana, Keele) that showed benefit</p> <p>Also concluded: No difference in benefit when looked at the 17 malnourished patients in the study</p> <p>Possible lack of difference due to small study numbers in each group, or in general, early return to eating post-surgery in practice along with dietician support normally at the hospital</p>
Jensen and Hesson ^[5]	RCT - Supplements given after discharge from colorectal surgery for 4 mo	<p>Elective and acute <i>n</i> = 87: 47 in CG and 40 in TG</p>	<p>Control group: Discharged without advice</p> <p>TG: Dietetic advice and a variety of supplements including protein only - aiming for 1.5 g protein/kg per day</p>	<p>Body mass: (50 d after discharge) lean body mass increase seen in TG of 1.3 kg (<i>P</i> = 0.009) and in overall body mass 2.0 kg (<i>P</i> = 0.005). 110 d after discharge: Total mass difference was +2.7 kg for TG relative to CG (<i>P</i> = 0.014), and lean body mass +1.4 kg for TG (<i>P</i> = 0.029)</p> <p>No significant difference in fat mass was seen at either stage</p> <p>Serum albumin: No difference was seen at any time</p>	<p>Initially patients in the intervention group gained LBM without fat mass; later there were gains in both types of mass</p> <p>Recommendation: Patients should increase protein intake to 1.5 g/kg per day for 2 mo post-surgery</p>

Keele <i>et al.</i> ^[11]	Short and long term (4 mo after discharge) benefits of intervention	<i>n</i> = 100 moderate-major elective GI surgery; <i>n</i> = 53 in CG and <i>n</i> = 47 in TG.	TG was given oral nutritional supplement post-operatively in addition to ward diet, which was given to the control group In-patient and out-patient phases (to 4 mo after discharge)	Inpatient phase Nutrient intake: Significant increase in protein and energy intake increase at days 1 and 2 (<i>P</i> < 0.001) and 3 (energy <i>P</i> < 0.01, protein <i>P</i> < 0.001), day 4 (<i>P</i> < 0.05) and day 7 - protein only (<i>P</i> < 0.05) No significant difference in intake of energy or protein from ward diet	Phase 1 assessment was at day 3 and discharge Clinically significant benefits with short term supplementation but not long term supplementation Both CG and TG had below requirement levels of protein as in-patients
	(There were four groups in this study: C/C had no supplementation before/after surgery; C/S had none before and supplementation after; S/C had supplementation before and none after; S/S had supplementation before and after surgery For the purposes of the review C/C were taken as CG and C/S were taken as TG)		Supplements - 200 mL cartons of Fortisip with 1.5 kcal and 0.05 g/mL (10 g protein/carton)	Energy intake 1 m after discharge: Significantly higher in TG Weight loss: Less in treatment group at day 3 and discharge (<i>P</i> < 0.001) Serious complications: Less in treatment group (<i>P</i> < 0.05) Handgrip: Significant reduction in CG at days 3 and 7; strength lost at day 3 in treatment group but regained by discharge Subjective fatigue: Increased fatigue in CG at day 3 and discharge (<i>P</i> < 0.001), no significant increase in fatigue in TG Complications: More in control group (<i>P</i> < 0.05) Giving food did not reduce voluntary food intake Outpatient phase Nutrient Intake: No significant difference in protein intake in the out-patient phase. Significantly higher energy intake was seen (<i>P</i> < 0.05) in groups consuming supplements post-discharge compared to controls No benefit was seen with supplementation post-discharge	By 1 mo, patients in both groups were eating well so supplements had little effect on well-being The rapidity of the effects of protein supplementation suggests that its effect is due to a direct action of key nutrients rather than repletion of tissue stores

Rana <i>et al.</i> ^[12]	Short term only: Started on day patients could receive free fluids until discharge	<i>n</i> = 40; 20 control and 20 supplemented	Ad libitum supplementation with oral nutritional sip feed in addition to control diet	Nutritional intake: significantly higher energy intake in the treatment group <i>P</i> < 0.004 (as well as the nutritional value of the supplements, more energy was consumed from ward diet by these patients) and protein intake (due solely to supplements)	In the CG there is a significant protein deficit by day 3 which persisted to day 7 (often the day of discharge)
		Major G-I surgery	7.8 g/L unhydrolysed protein. 1.5 kcal/mL energy density. 1.4 L is needed to provide all required nutrient as defined by United Kingdom health board	Significant weight loss in CG but not TG at day 3 and discharge	5-6 d on average elapsed between day of operation and day 1 of study period where diet was allowed. Study period began when surgical team allowed "free-fluids or light diet"
			Controls and given ward diet and allowed snacks	Grip strength difference at day 3 and discharge (<i>P</i> < 0.03) in favor of treatment group	Within 3 d of "free fluids/light diet" treatment patients were consuming 70 g protein/d and about 2000 kcal
				No difference in mid-arm circumference/triceps skin folds changes between groups	Observed increased number of calories (not protein) being eaten from ward diet in the treatment group
				Serious complications (pneumonia, wound infection) significantly higher in CG	- inference that supplementation helped to maintain appetite
				No difference in length of stay	
				Complications: Pneumonia and wound infection seen. <i>P</i> < 0.02 in favor of treatment group	
				Blood proteins: No difference in serum albumin, retinol binding albumin, prealbumin. Significant difference in retinol binding protein as CG declined while TG levels remained same. <i>P</i> < 0.05	
				Hospital stay length: No statistically significant difference	

TG: Treatment group; CG: Control group; RCT: Randomised controlled trial; PRCT: Prospective randomised controlled trial; ONS: Oral nutritional supplement; MAMC: Mid-arm muscle circumference; LBM: Lean body mass; BM: Borderline malnourished; MM: Moderately malnourished; SM: Severely malnourished; NRI: Nutritional risk index.

et al.^[8] (*P* < 0.05). In the trial by Jensen *et al.*^[5], supplementation was not started before discharge, typically around 10 d post-operatively, but at both 50 and 110 d after discharge, the intervention group had increased total and lean body mass. No other studies looked specifically at lean body mass. Conversely, however, MacFie *et al.*^[9] reported no significant difference in weight loss between control and intervention groups overall.

Studies by Saluja *et al.*^[10] and Beattie *et al.*^[13] noted reduced weight loss in the malnourished patient population investigated in their studies, but no difference was seen by MacFie *et al.*^[9] when he isolated the 17 malnourished patients from his study. More specifically, Beattie *et al.*^[13] found that controls lost an average of 5.96 kg in 8 wk, while intervention patients lost 3.4 kg on average in the first 4 wk and then gained weight (*P* < 0.001). Saluja *et al.*^[10] quantified the average weight loss in the TG as 2.15 kg compared to 4.6 kg in the CG (*P* < 0.01).

Postoperative complications: None of the studies found a difference in mortality between control and TGs. A wide variety of other complications were looked at including chest and wound infection, sepsis, cardiac arrest, pulmonary embolism, and wound dehiscence. Three of the 6 trials that investigated complications found a reduced number in the TG: Smedley *et al.*^[8] found reduced minor complications (*P* < 0.05) but no difference in major complications. Both Keele *et al.*^[11] and Rana *et al.*^[12] demonstrated significantly fewer serious complications in their short term studies (*P* < 0.05). No difference in post operative complications was found by Saluja *et al.*^[10] or MacFie *et al.*^[9]. Saluja *et al.*^[10] did find a reduction in infectious complications in severely malnourished patients, but numbers were too small for statistical significance. Similarly, Beattie *et al.*^[13] saw a reduction in complications that was not significant when adjusting for age and sex.

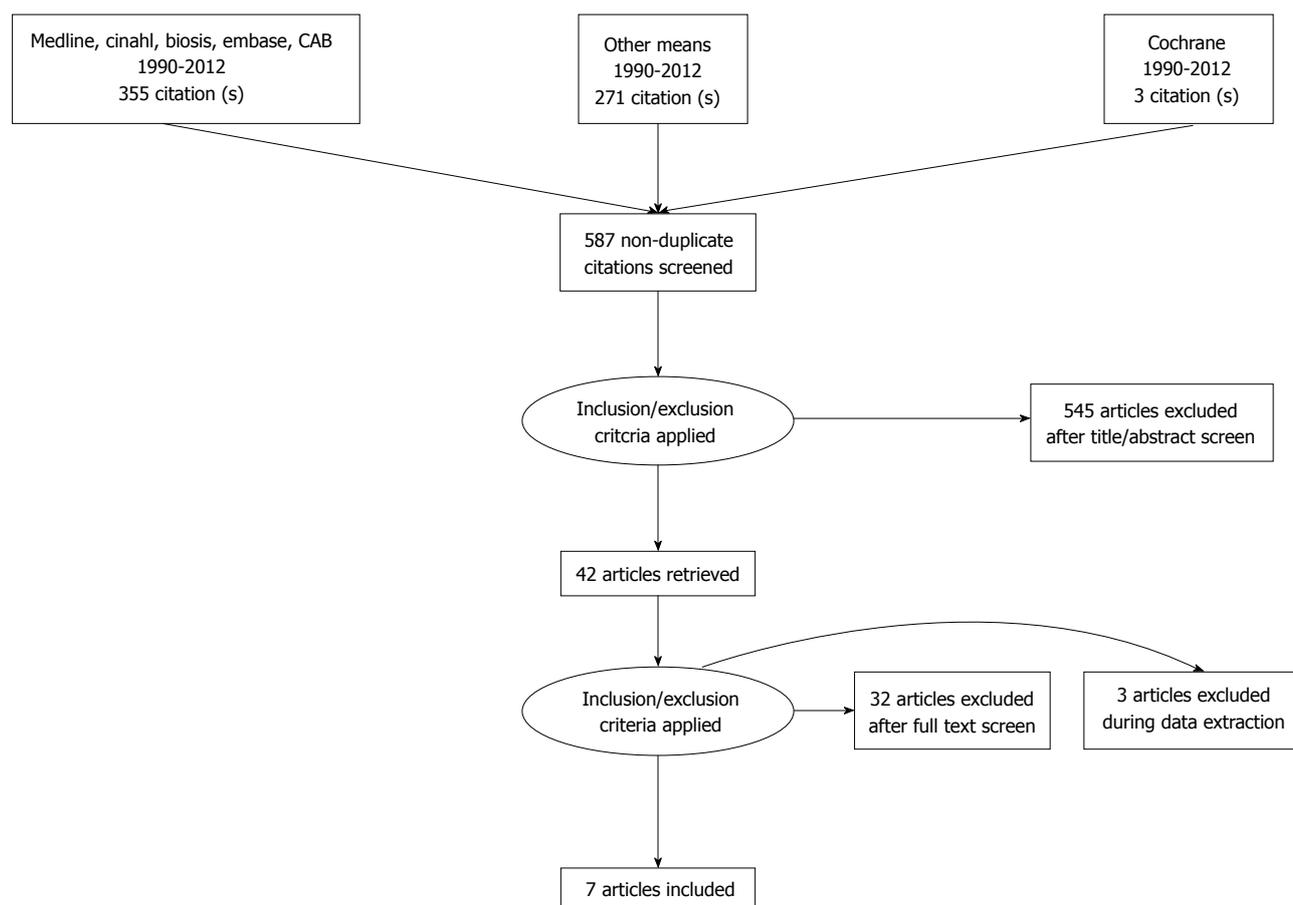


Figure 1 PRISMA guidelines.

Length of stay: The study by Saluja *et al.*^[10] determined a difference in length of stay between treatment and CGs in severely malnourished patients, but no difference in moderately or borderline malnourished patients. Beattie's study^[13], which also looked at malnourished patients, found no difference. The three studies^[8,12,13] that evaluated length of stay in normonourished patients found no difference.

Plasma proteins: Four studies investigated plasma proteins levels^[5,9,10,12], with albumin the focus of most of these studies. None of these found any significant difference in serum albumin or prealbumin. Rana *et al.*^[12] found increased retinol binding protein in the TG relative to controls at day three ($P < 0.05$).

Cost: Smedley *et al.*^[8] found that the use of oral nutritional supplementation, irrespective of when administered, decreased cost by £300 (sterling) per patient amounting to a 15% reduction compared to patients without supplementation. This was not statistically significant. No other study considered cost of care.

Grip strength: Three of five studies that investigated grip strength found reduced loss of grip strength in patients receiving oral nutritional supplements relative to controls. Keele *et al.*^[11] found that handgrip was

maintained in the intervention group and significantly reduced in controls ($P < 0.01$). Rana *et al.*^[12] found a significant difference at day three and again at discharge ($P < 0.05$). Beattie *et al.*^[13] found similar results and noted statistical significance in the differences at week 10 ($P < 0.001$). Saluja *et al.*^[10] and MacFie *et al.*^[9] detected no difference in hand grip strength after supplementation.

Quality of life and fatigue: Beattie *et al.*^[13] found increased quality of life in the TG using the short form 36 questionnaire (SF-36)^[14] in both mental and physical health ($P < 0.001$). Smedley *et al.*^[8] used SF-36 and EuroQol instruments to test quality of life and found no difference. Keele *et al.*^[11] subjectively assessed fatigue and found significant increases in control patients at study day three ($P < 0.001$), while TG increases in fatigue were not significant.

DISCUSSION

Previous reviews have concluded that oral nutritional supplements can have positive effects in terms of recovery of nutritional status post-operatively in conditions such as fractured neck of femur, colorectal surgery, and pancreaticoduodenectomy, among others^[15-17]. In these cases, the proposed benefits

could be attributed to protein supplementation (*i.e.*, the amount of orally-consumed protein that confers the greatest benefit) combined with appropriate energy intake^[18]. However, what these levels are remain unclear for patients following gastrointestinal surgery. In this review, we attempted to determine this *via* systematic review.

Our searches did not yield a single randomized controlled trial that adequately differentiated the effect of protein supplementation from carbohydrate supplementation. Therefore, analysis of the eligible reports was problematic. Limitations included the fact that protein and energy content in TG supplements were not equivalent in most of the studies. Indeed, only the study by Saluja *et al.*^[10] described using a fixed amount of supplement for daily consumption, while the remaining studies followed an "ad-libitum" approach. Arguably, the latter approach best mirrors "real-life" clinical scenarios, however it makes discerning the true effect of protein supplementation difficult. Furthermore, the characteristics of the patient cohorts were not equivalent between studies, confounding inter-study comparisons. For example, the study by Saluja *et al.*^[10] took place in Delhi and included a greater proportion of emergency surgery patients, and patients with tuberculosis, compared with the non-emergent procedures described in the Western European reports. Moreover, inadequate follow up time with control and TGs was common across studies, with some risk of bias associated with lack of blinding of participants, carers and assessors. The power of the studies was often too small, with one author conceding notably that "numbers were too small for meaningful statistical analysis"^[13] and intention to treat analysis was not used in any of the studies. Finally, the most recent of the eligible trials found in our searches was published in 2004, arguably reflecting either a shift in interest away from oral intake in favor of enteral and parenteral nutrition in this population or an emphasis placed on ordinary diet without supplement.

Despite these limitations, the authors of six of the seven studies detailed weight loss in patients receiving post-operative nutritional supplements, but to a lesser degree than the loss in control patients^[5,8,10-13]. In fact, the data suggest that this effect may be most prominent in patients malnourished initially, with statistically significant reductions in weight loss observed. While one study failed to observe this effect^[9], despite similar energy and protein intakes to other trials, the authors proposed that the lack of effect was due to a small sample size. Finally, with respect to weight gain post-operatively, it appears that weight gain commenced sooner and patients appeared to return to their preoperative weight more rapidly where supplementation was provided.

There is no evidence to suggest that nutritional supplementation post-operatively reduces mortality. While more deaths did occur in the CGs of the reported

trials, much larger samples would be needed to approach statistical significance. The topic of avoidance of both serious and minor complications is less clear. There is some precedent to suggest that post-operative supplementation decreases complications, as the effect has been documented in patients undergoing hip surgery^[15,19,20]. However, across the eligible studies here, the rate of both serious and minor complications was significantly reduced in four of the trials^[8,11-13], while no statistically significant difference was observed in two^[9,10]. This variation has been addressed somewhat by Beattie *et al.*^[13] when comparing his results to the study by MacFie *et al.*^[9] in making reference to discrepancies in defining complications. On a related topic, duration of hospitalization was reduced significantly in severely malnourished patients only^[10]. An additional study that supplemented increased amounts of protein and medium chain carbohydrates in enteral feed in gastrointestinal patients post-operatively found a 6-d reduction on average ($P < 0.05$)^[21]. However, that study had larger numbers than any of the studies considered in this review, with 229 total and 115 TG patients. It has also been suggested that length of stay is a relatively poor outcome to evaluate as it often depends on patient social circumstances and services available in addition to patient post-operative clinical condition^[12].

With respect to malnutrition, and assessment of patient incidence, low albumin has been used as a measurable indicator, but evidence suggests that it is not an effective marker of recent nutritional intake^[22]. Approximately 5% of the circulating albumin is replaced daily by the liver and, therefore, any changes in protein intake would not be evident immediately. Further, protein markers in the blood such as prealbumin, albumin and transferrin are impacted by fluid shifts and responses to injury and inflammation which complicate their use in comparisons of patients before and after major abdominal surgery, when tissue injury is present^[23]. This may explain why none of the studies in our review that monitored albumin in the early post-operative period found any disparity in albumin levels despite differences in anthropometric indicators of malnutrition (*e.g.*, triceps skin fold, mid upper arm circumference and BMI^[23]). Similarly inconsistent results were found regarding quality of life.

Evaluation of quality of life and physiological function were similarly inconsistent. For example, handgrip strength is a marker of function and results were variable across the trials. However, those variances may be explained by the use of dissimilar techniques for measurement, and confounders such as pain and fatigue post-operatively. Interestingly, the TGs in the studies conducted by MacFie *et al.*^[9] and Saluja *et al.*^[10] both described increased total body mass retention relative to CGs, but without significant increases in grip strength. Jensen *et al.*^[5] found that supplementation increased lean body mass particularly, not simply fat mass, so one could hypothesize that a functional measurement

like grip strength would also be improved, but this was not described. Previous work has documented a link between impaired muscle function and nutritionally-related complications^[24,25], but this was not consistently reflected across the eligible trials here.

The seven studies reviewed in this paper concurred that there is no difference in mortality seen with protein-inclusive nutritional supplements. There is evidence to suggest that weight reduction, nutritional intake, and nutritional status are improved, and that there may be positive cost of hospitalisation benefits, but evidence as to the effect on complications and grip strength is mixed. At present, there is some evidence to support routinely prescribed oral nutritional supplements that contain protein for gastrointestinal surgery patients in the immediate post-operative stage. However, randomized control trials using well-designed methodology to examine the optimal protein content needed to confer benefit are needed.

COMMENTS

Background

Malnutrition in hospitalized patients can negatively impact recovery; protein and energy deficiencies have been documented in gastrointestinal surgery patients and trials have demonstrated benefits of perioperative nutritional strategies, although post-operative oral nutritional supplementation have been studied to a lesser extent. The proposed benefits may be attributed to protein supplementation (*i.e.*, the amount of orally-consumed protein that confers the greatest benefit) combined with appropriate energy intake. However, what those levels may be remain unclear for gastrointestinal surgery patients.

Research frontiers

The positive impact of pre-operative nutrition has been reviewed previously and meta-analyses have demonstrated positive influence on patient outcome following gastrointestinal surgery. In the postoperative period however, the most pertinent question may be whether patients should be further supplemented. The most recent of the eligible trials found in the searches was published in 2004.

Innovations and breakthroughs

The authors' searches did not yield a single randomized controlled trial that adequately differentiated the effect of protein supplementation from carbohydrate supplementation. With only one exception, the eligible studies reviewed here involved post-operative supplements administered "ad-libitum". Although this may best mirror "real-life" clinical scenarios, it makes discerning the true effect of protein supplementation difficult. Furthermore, the characteristics of the patient cohorts were not equivalent between studies. Despite these limitations, the authors of six of the seven studies detailed weight loss in patients receiving post-operative nutritional supplements, but to a lesser degree than the loss in control patients. There is no evidence to suggest that nutritional supplementation post-operatively reduces mortality and evaluation of quality of life and physiological function were similarly inconsistent.

Applications

An intervention based on oral protein supplementation should be investigated through a double-blind randomized controlled trial.

Terminology

There are no terms used that are uncommon and that would be unfamiliar to readers.

Peer-review

The authors have made a good collation of the data to assess if there are

any benefits of post-operative protein nutritional supplementation following gastrointestinal surgery. The manuscript is well written and covers the salient points from the published studies.

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Short-term outcomes after laparoscopic colorectal surgery in patients with previous abdominal surgery: A systematic review

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Abstract

AIM: To perform a systematic review focusing on short-term outcomes after colorectal surgery in patients with previous abdominal open surgery (PAOS).

METHODS: A broad literature search was performed with the terms "colorectal", "colectomy", "PAOS", "previous surgery" and "PAOS". Studies were included if their topic was laparoscopic colorectal surgery in patients with PAOS, whether descriptive or comparative. Endpoints of interest were conversion rates, inadvertent enterotomy and morbidity. Analysis of articles was made according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS: From a total of 394 citations, 13 full-texts achieved selection criteria to be included in the study. Twelve of them compared patients with and without PAOS. All studies were retrospective and comparative and two were case-matched. The selected studies comprised a total of 5005 patients, 1865 with PAOS. Among the later, only 294 (16%) had history of a midline incision for previous gastrointestinal surgery. Conversion rates were significantly higher in 3 of 12 studies and inadvertent enterotomy during laparoscopy

was more prevalent in 3 of 5 studies that disclosed this event. Morbidity was similar in the majority of studies. A quantitative analysis (meta-analysis) could not be performed due to heterogeneity of the studies.

CONCLUSION: Conversion rates were slightly higher in PAOS groups, although not statistical significant in most studies. History of PAOS did not implicate in higher morbidity rates.

Key words: Previous abdominal surgery; Laparoscopic surgery; Colorectal surgery; Previous abdominal surgery; Laparoscopy

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Core tip: So far, there is no substantial evidence in the literature to recommend laparoscopic surgery instead of laparotomy for patients previously submitted to abdominal surgery, concerning short-term benefits, such as conversion rates and morbidity. This review, although without a meta-analysis, brings new light into this matter.

Figueiredo MN, Campos FG, D'Albuquerque LA, Nahas SC, Ceconello I, Panis Y. Short-term outcomes after laparoscopic colorectal surgery in patients with previous abdominal surgery: A systematic review. *World J Gastrointest Surg* 2016; 8(7): 533-540 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i7/533.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i7.533>

INTRODUCTION

In colorectal surgery, laparoscopy has been progressively accepted as a good alternative to open surgery since its first reports during the 90's^[1,2]. The main benefit attributed to laparoscopy is the associated better short-term outcomes observed in both benign and malignant colorectal diseases^[3-6]. Moreover, randomized clinical trials and meta-analysis have suggested that there is no prejudice of oncological outcomes as well^[3,7,8].

It is well recognized that the laparoscopic access to treat colorectal diseases is associated with an extended learning curve and has its own limitations. Many patient's, disease's and surgeon's factors may affect operative results, such as previous abdominal open surgery (PAOS), obesity, inflammatory conditions, pregnancy, surgical expertise and others. At the beginning of laparoscopic experience, some of these conditions were even considered contraindications for this approach^[9], due to the potential higher risk of intraoperative lesions, during trocar placement or because of visceral adhesions. In practice, these drawbacks were translated into a longer operative time and greater conversion rates. With growing expertise in laparoscopic techniques, surgeons gained confidence to perform more difficult cases and reports of laparoscopic procedures after PAOS

have been increasingly published^[10-12]. However, there is still a debate concerning the indication of laparoscopic colorectal surgery in patients with PAOS^[13,14]. Furthermore, there is no randomized study evaluating the possible benefit of laparoscopic colorectal surgery in the context of PAOS.

Thus, the aim of this study was to perform a systematic review concerning short-term outcomes after laparoscopic colorectal surgery in patients with or without PAOS.

MATERIALS AND METHODS

Incidence of conversion, inadvertent intraoperative intestinal lesions and overall morbidity were our main outcome measures.

Eligibility criteria

Studies were included if they reported results on laparoscopic colorectal surgery in patients with PAOS, whether previously open or laparoscopic, with a special interest if they were comparative. Abstracts only were not included in the systematic review, although they were taken into consideration for discussion.

Search strategy

All authors agreed regarding terms that should be used for online search. The literature search comprised the terms "colorectal", "colectomy", "PAOS", "previous surgery" and "PAOS" in different combinations. Articles were searched if published before August 2014 in the following databases: MEDLINE, EMBASE, Cochrane, Scopus, Scielo and LILACS. Initially the search was not limited by language, but only full texts in English were finally included. References in the selected articles were also searched for additional citations.

Study selection

Titles and abstracts were scanned to identify suitable articles; afterwards abstracts were reviewed to identify studies fulfilling inclusion criteria. Finally, full texts of the interested studies were selected. Two authors performed the study selection and one author was responsible for revision of this selection. There were no conflicts regarding suitability of studies selected or excluded.

Extraction and analysis of data

Two investigators were responsible to extract data from the studies to a previously designed datasheet, interesting outcomes of this study. Another investigator was responsible to review the information and to solve any conflicts. Information collected from the studies was: Overall conversion, inadvertent intraoperative lesions and morbidity. Definition of conversion was not always mentioned in the articles or differed between them. Mostly, conversion referred to unplanned incisions or size of incision in order to complete surgery. We have considered conversion as described in each study, as

Table 1 Definition of conversion in the 13 studies included in the review of patients submitted to laparoscopy with or without previous abdominal surgery

Ref.	Definition of conversion
Hamel <i>et al</i> ^[19]	“any incision unplanned, made sooner than planned or longer than 5 cm”
Kwok <i>et al</i> ^[26]	“abdominal incision exceeded 8 cm; or the incision was extended for any reasons other than division of the bowel and extraction of specimens”
Law <i>et al</i> ^[22]	N/A
Arteaga González <i>et al</i> ^[21]	N/A
Franko <i>et al</i> ^[23]	“change in operative strategy requiring exsufflation of capnoperitoneum and elongation of the surgical incision to allow direct visualization for continued dissection”
Vignali <i>et al</i> ^[14]	“abdominal incision longer than 7 cm or an abdominal incision made earlier or different from that planned at the start of the procedure”
Nozaki <i>et al</i> ^[17]	N/A
Offodile <i>et al</i> ^[25]	“final incision length longer than 7 cm (after skin closure)”
Barleben <i>et al</i> ^[16]	N/A
Fukunaga <i>et al</i> ^[24]	“performance of an unplanned incision”
Maggiori <i>et al</i> ^[18]	“any unplanned incision or a planned incision longer than 6 cm”
Naguib <i>et al</i> ^[20]	N/A
Yamamoto <i>et al</i> ^[13]	“any incision more than 8 cm in length needed to complete or facilitate the procedure that could not be completed” laparoscopically

N/A: Not available.

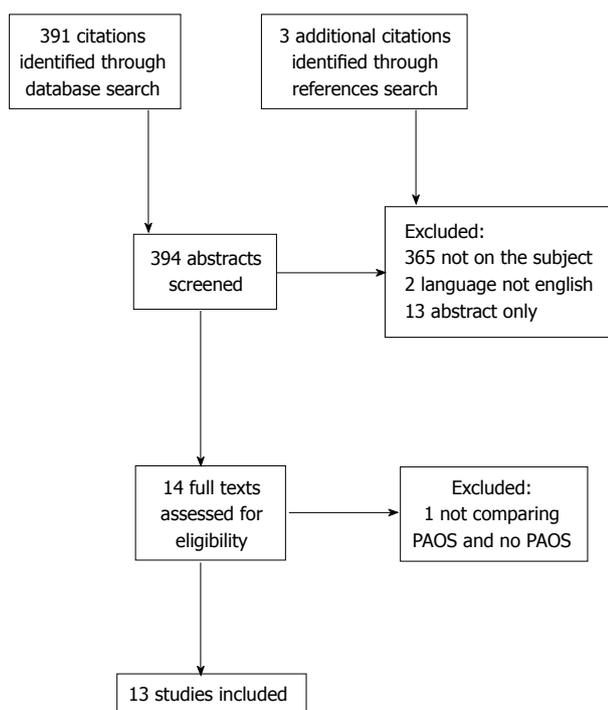


Figure 1 Flow chart: Literature search on MEDLINE, EMBASE, LILACS, Scopus, Scielo, Cochrane.

shown in Table 1.

Analysis of articles was done according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses^[15]. Forest plots were done using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

RESULTS

The literature search initially identified 391 articles. Search within references led us to include other 3

articles. Subject of citation did not meet the interest criteria of this study in 365 citations. Two studies were excluded because of language (Chinese and Italian) and 13 had only presented abstracts. Fourteen full-text articles were analysed and 13 studies were included in the present manuscript. One article was excluded because it did not describe nor compared laparoscopy with and without PAOS^[13,14,16-26] (Figure 1).

Regarding their characteristics, with one exception, all studies were retrospective and comparative, but only two were case-matched^[14,18]. One study was not comparative and only described a group of patients with PAOS^[16] (Table 2).

The selected studies comprised a total of 5005 patients, 1865 with PAOS. Four papers included not only open but also laparoscopic previous surgeries, and in most of them some kind of resection was done (*i.e.*, excluding diagnostic laparoscopy and bypasses), excluding one study that included a few patients submitted to a diverting stoma^[16]. In two studies^[17,23], colorectal surgery included totally laparoscopic and also hand-assisted techniques. Regarding the type of surgical procedures performed, two studies^[19,25] described only right colectomies, one included only anterior resections for upper rectum cancer^[26], while others included all types of colorectal resections. Three articles included only patients diagnosed with colorectal cancer^[17,24,26].

All but three studies^[14,18,21] included previous appendectomy. Most previous surgeries described in the studies were appendectomies, gynaecological procedures or cholecystectomies. Of 1865 patients, only 294 (16%) were cited as having had a midline incision for previous gastrointestinal surgeries, while 702 (38%) had a previous appendectomy. Although we cannot separate results of only previous gastrointestinal procedures from gynaecological procedures and cholecystectomies, these 294 cases are the object of our

Table 2 Intraoperative findings of 13 studies in patients submitted to laparoscopy with or without previous abdominal surgery

Ref.	Type of study	No. of patients			Conversion rate (%)			Inadvertent enterotomy (%)		
		Total	PAOS	non PAOS	PAOS	non PAOS	P-value	PAOS	non PAOS	P-value
Hamel <i>et al</i> ^[19]	Comparative	85	36	49	17	12	0.754	N/A	N/A	N/A
Kwok <i>et al</i> ^[26]	Comparative	91	26	65	15.4	7.7	0.55	N/A	N/A	N/A
Law <i>et al</i> ^[22]	Comparative	295	84	211	17	11	0.181	N/A	N/A	N/A
Arteaga González <i>et al</i> ^[21]	Comparative	86	27	59	26.1	5.1	0.02	0	1.7	NS
Franko <i>et al</i> ^[23]	Comparative	820	347	473	19	11	< 0.001	1.4	0.2	0.04
Vignali <i>et al</i> ^[14]	Case-matched	182	91	91	16.5	8.8	0.18	N/A	N/A	N/A
Nozaki <i>et al</i> ^[17]	Comparative	121	21	100	0	0	N/A	N/A	N/A	N/A
Offodile <i>et al</i> ^[25]	Comparative	414	171	243	17	15	0.42	N/A	N/A	N/A
Barleben <i>et al</i> ^[16]	Observational; not comparative	55	55	0	14.5	N/A	N/A	N/A	N/A	N/A
Fukunaga <i>et al</i> ^[24]	Comparative	607	192	415	5.2	2.6	0.108	2.6	0	0.001
Maggiore <i>et al</i> ^[18]	Case-matched	367	167	200	22	13	0.017	N/A	N/A	N/A
Naguib <i>et al</i> ^[20]	Comparative	181	68	113	13.2	10.6	0.6	2.9	0	0.14
Yamamoto <i>et al</i> ^[13]	Comparative	1701	580	1121	12.4	10.2	0.16	0.9	0.1	0.037
Total		5005	1865	3140						

NS: Not significant; N/A: Not available; PAOS: Previous abdominal surgery.

Overall conversion

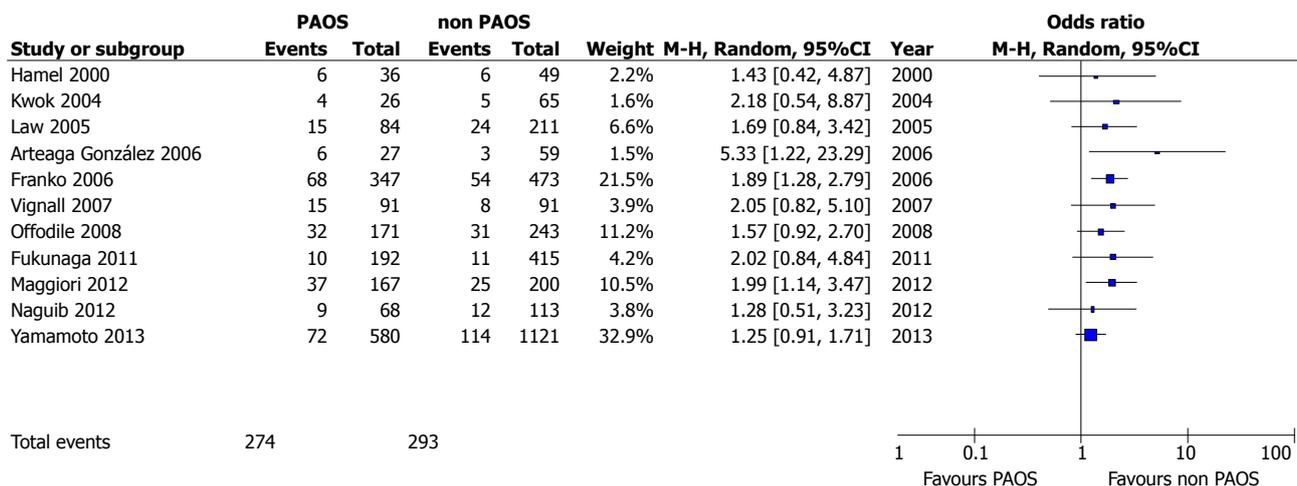


Figure 2 Forest plot showing comparison between studies regarding overall conversion.

interest in this paper.

All studies were retrospective and with great heterogeneity, so a quantitative analysis (meta-analysis) was not carried out because it would not be of value. Nonetheless, a forest plot was made in order to provide an idea of trend in the results of this review, in case data could be adequately extracted.

Conversion

Overall conversion rates were described in all 12 studies (Table 2). These rates were higher in all of the studies but only 3 of studies showed statistical significance^[18,21,23] (Figure 2). There were no conversions in one of the studies^[17].

Intraoperative inadvertent enterotomy

In 3 of 5 studies, rates of intraoperative intestinal lesions (Figure 3) were higher in the PAOS groups (not necessarily leading to conversion)^[13,23,24], while in two

studies they were similar^[20,21]. The other 8 papers did not describe such data (Table 2).

Postoperative morbidity

In the 9 studies that reported postoperative complication rates, similar rates were reported between patients with and without PAOS (Table 3). In 3 other studies the P value comparing overall morbidity rates was not available, but numbers for independent complications were summed in order to perform odds ratio analysis (Figure 4).

DISCUSSION

To date, very few studies have been devoted to evaluate the impact of PAOS on the short-term results after laparoscopic colorectal surgery. The present literature review with more than 5000 patients (including 1800 that had PAOS and 264 with previous gastrointestinal

Inadvertent enterotomy

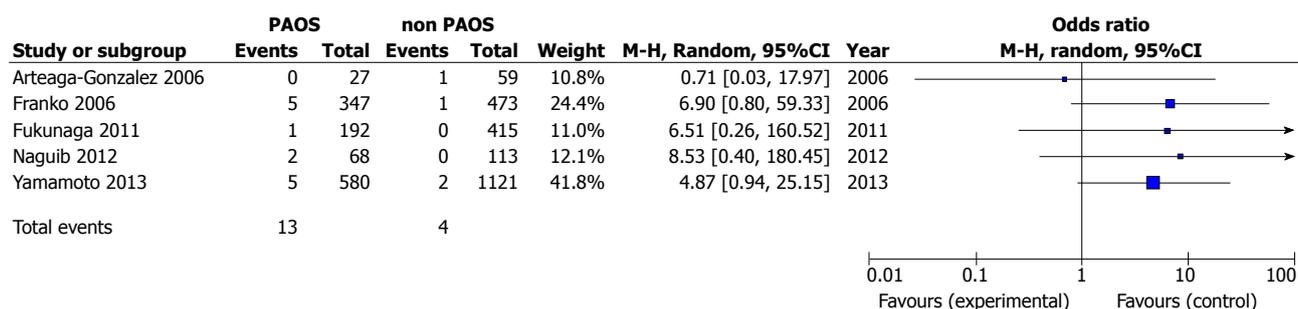


Figure 3 Forest plot showing comparison between studies regarding inadvertent enterotomy.

Morbidity

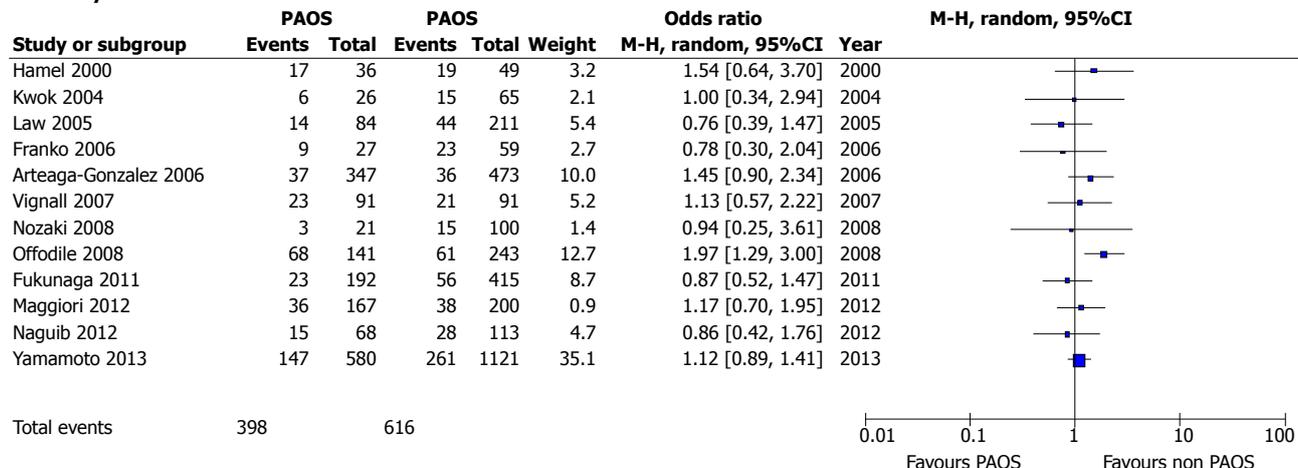


Figure 4 Forest plot showing comparison between studies regarding morbidity.

Table 3 Postoperative findings of 13 studies in patients submitted to laparoscopy with or without previous abdominal surgery

Ref.	No. of patients			Morbidity (%)		
	Total	PAOS	non PAOS	PAOS	non PAOS	P-value
Hamel <i>et al</i> ^[19]	85	36	49	47	37	0.18
Kwok <i>et al</i> ^[26]	91	26	65	23	23	0.79
Law <i>et al</i> ^[22]	295	84	211	16	20	0.516
Arteaga González <i>et al</i> ^[21]	86	27	59	39	38	NS
Franko <i>et al</i> ^[23]	820	347	473	N/A	N/A	N/A
Vignali <i>et al</i> ^[14]	182	91	91	25.3	23.1	0.86
Nozaki <i>et al</i> ^[17]	121	21	100	14	15	0.94
Offodile <i>et al</i> ^[25]	414	171	243	N/A	N/A	N/A
Barleben <i>et al</i> ^[16]	55	55	0	N/A	N/A	N/A
Fukunaga <i>et al</i> ^[24]	607	192	415	15.6	14.5	0.767
Maggiori <i>et al</i> ^[18]	367	167	200	22	19	0.543
Naguib <i>et al</i> ^[20]	181	68	113	N/A	N/A	N/A
Yamamoto <i>et al</i> ^[13]	1701	580	1121	25.3	23.3	0.345

NS: Not significant; N/A: Not available; PAOS: Previous abdominal surgery.

resection by midline incision) suggests that PAOS has probably little impact on postoperative morbidity after laparoscopic colorectal surgery.

It is important to state that previous surgery away from the site of the current surgery might not interfere in short-term outcomes, for ex. previous gynaecological surgery in a patient that is going to be submitted to a

transverse colon resection should not present a problem regarding technical aspects and subsequent results.

Although conversion rates were higher in few studies (mainly because of adhesion), and the risk of inadvertent enterotomy was also slightly increased, overall postoperative morbidity was similar with or without PAOS. According to the literature, conversion

from laparoscopic to open surgery does not seem to influence directly in post-operative morbidity^[27]. In our study, although 3 studies reported higher conversion rates in the PAOS groups, morbidity was similar in both groups.

Due to the heterogeneity of the studies, it was not possible to perform a meta-analysis with qualitative results. This heterogeneity refers not only to statistical methods or study design, but also to different types of surgery (previous and actual) and diseases, as well as experience of the surgeon, which makes it hard to compare as equal.

In a pragmatic approach, laparoscopy should not be contraindicated in patients with PAOS and this is common sense for most surgeons, though it is not well established by current medical literature so far. Although surgeon and patient must be aware of the higher risk of conversion and possible accidental enterotomy, because of all the possible benefits previously demonstrated after laparoscopic colorectal surgery, laparoscopy might be attempted in most of the patients.

Short-term benefits of laparoscopic colorectal resection are clearly demonstrated by several randomized studies, including faster recovery, lower pain, earlier feeding and shorter return of normal intestinal function and shorter hospital stay^[6,28-30]. However, it remains controversial if patients still profit from laparoscopic advantages in cases of PAOS. There is no doubt that intra-abdominal adhesions may substantially impair intra and postoperative outcomes, mainly due to difficulties when performing adhesiolysis and the risks of visceral perforations. In fact, abdominal adhesions following laparotomy have been described in up to 70% to 90% of patients^[31,32], and this may reflect in a longer operative time, mainly due to adhesiolysis, even in open surgery^[33], and may lead, also in open surgery, to a higher risk of small bowel lesion in up to 20%^[34].

Conversion rates in laparoscopic colorectal surgery range between 5% and 23%^[4,35-40]. Although some studies did not find PAOS as a risk factor for higher conversion rates^[36,39,41,42], it is believed that PAOS has the potential to increase these rates. In our opinion and practice, we believe that a systematic laparoscopic approach in colorectal surgery for patients with PAOS should be done, except for those with wound dehiscence for which repair is indicated.

Our literature review about laparoscopic surgery in patients with PAOS is in accordance with our strategy: Overall postoperative morbidity was similar whether there was PAOS or not. However, it must be noticed that conversion rates are probably slightly higher in cases of PAOS (demonstrated in only 3/12 studies) mainly because of adhesions, as suggested in 5/6 studies.

We are aware that inflammatory cases (Inflammatory Bowel Disease and diverticulitis) may sometimes present as an even bigger challenge than colorectal cancer and that a learning curve is fundamental for a surgeon to achieve advanced laparoscopic skills and overcome technical difficulties. Therefore, surgeons

without significant experience in laparoscopy should carefully select PAOS cases. However, with growing experience in laparoscopic surgery, we consider that adhesion is no more a contraindication to laparoscopic surgery. Even if several minutes might be necessary in the beginning of the procedure to perform adhesiolysis, we consider that avoiding an unnecessary laparotomy may bring several advantages. First, it avoids a traumatic aggression on a previous healed abdominal incision, with the risk of long-term hernia; second, it allows keeping all the short-term advantages of laparoscopy.

In our systematic review, risk of inadvertent enterotomy seems higher with than without PAOS, but this aspect was in fact evaluated in only 5 of 12 studies, and demonstrated in only 3 of those 5 studies.

The main limitation of our review is the heterogeneity of the studies and the absence of prospective studies. For these reasons, it does not allow us to perform quantitative analysis, pooling the results together. Among the studies excluded from our review for being abstracts only, we could also perceive a trend suggesting that conversion rates in patients with PAOS is not higher than that in non PAOS groups^[43-47]. In one abstract referring to risk factors for conversion during laparoscopy in colorectal surgery, PAOS was not identified as one^[48]. Furthermore, in the context of Crohn's disease, where redo surgery is frequent, two teams have demonstrated that performing a redosurgery by laparoscopy is feasible without increased morbidity rate^[43,49], even though short-term benefits might not be the same as in first-time laparoscopies for IBD.

In conclusion, this review suggests that laparoscopic surgery in patients with PAOS is feasible and it is not associated with higher morbidity rates. Although the potential risks of conversion (due to adhesions) and inadvertent enterotomies must not be forgotten, we consider that they are not enough to contraindicate laparoscopy in these patients.

COMMENTS

Background

Laparoscopy became the standard technique in many gastrointestinal procedures. But still there is controversy when it comes to perform colorectal surgery in patients that were operated on by a previous laparotomy, since there are no definite studies in this matter. Adhesions and consequent conversion might pose a problem as well as possible higher morbidity rates derived from those. Several articles have compared patients with and without previous abdominal open surgery, but most have a small number of patients, making it harder to make definite assumptions.

Research frontiers

If the authors could consider only patients with previous gastrointestinal resections through midline incision they might bring an even better light in this subject of laparoscopy in case of previous abdominal surgery.

Innovations and breakthroughs

A systematic review concerning a theme that has not been so far elucidated by the current literature, to try to stimulate the debate and since a controlled study with such design is not probable, they might have to take the best evidence

from uncontrolled studies.

Applications

Surgeons might use a systematic revision as an extra support to the belief that previous surgery is no longer a contraindication for laparoscopy in colorectal surgery.

Peer-review

This manuscript is a satisfactorily written systemic review on this problematic subject.

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Unexpected gallbladder cancer: Surgical strategies and prognostic factors

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Abstract

Gallbladder cancer is the most common tumor of the biliary tract and it is associated with a poor prognosis. Unexpected gallbladder cancer is a cancer incidentally discovered, as a surprise, at the histological examination after cholecystectomy for gallstones or other indications. It is a potentially curable disease, with an intermediate

or good prognosis in most cases. An adequate surgical strategy is mandatory to improve the prognosis and an adjunctive radical resection may be required depending on the depth of invasion. If the cancer discovered after cholecystectomy is a pTis or a pT1a, a second surgical procedure is not mandatory. In the other cases (pT1b, pT2 and pT3 cancer) a re-resection (4b + 5 liver segmentectomy, lymphadenectomy and port-sites excision in some cases) is required to obtain a radical excision of the tumor and an accurate disease staging. The operative specimens of re-resection should be examined by the pathologist to find any "residual" tumor. The "residual disease" is the most important prognostic factor, significantly reducing median disease-free survival and disease-specific survival. The other factors include depth of parietal invasion, metastatic nodal disease, surgical margin status, cholecystectomy for acute cholecystitis, histological differentiation, lymphatic, vascular and perineural invasion and overall TNM-stage.

Key words: Gallbladder cancer; Laparoscopic cholecystectomy; Liver resection; Lymphadenectomy; Incidental gallbladder cancer; Unexpected gallbladder cancer

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Core tip: Unexpected gallbladder cancer is diagnosed, as a surprise, after cholecystectomy for gallstones. A second surgical procedure consisting in a re-resection may be required depending on the depth of invasion. The discovery of cancer represents a challenge for the surgeon who must inform the patient many days after cholecystectomy and must evaluate the indication for a re-resection. The presence of a residual disease in the operative specimen after re-resection is the most important prognostic factor.

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INTRODUCTION

Gallbladder cancer (GBC) is the most common tumor of the biliary tract and it is recognized as one of the most aggressive cancers^[1]. It is generally associated with a poor prognosis with a reported 5-year survival rate of 5%^[2,3]. The delay in diagnosis is considered the main cause of the high mortality. GBC is a relatively rare disease in Western countries: In the United States an incidence of 1.2/100.000 is reported^[4] but, in some countries (Chile, Northern India), the incidence is ten times higher. Unexpected GBC (UGBC) can be defined as a cancer incidentally discovered, as a surprise, at the histological examination after cholecystectomy for gallstones or other indications. In recent years, the widespread diffusion of laparoscopic techniques has caused an increase in the number of laparoscopic cholecystectomies and therefore an increase of diagnoses of UGBC. Today, between 0.2% and 3% of patients undergoing cholecystectomy has a diagnosis of UGBC, depending on regional prevalence. In some tertiary centers such as Johns Hopkins University^[1] and the Memorial Sloan-Kettering Cancer Center^[4], UGBCs account for about half of all GBCs. Unlike the GBC, UGBC is a potentially curable disease with an intermediate or good prognosis in most cases. The adoption of an adequate surgical strategy is mandatory to improve the prognosis and an adjunctive radical resection may be required depending on the depth of invasion. However, UGBC represents a challenge for the surgeon who must inform the patient many days after cholecystectomy and must evaluate the indication for a re-resection.

DIAGNOSIS AND TREATMENT

After histological confirmation of the diagnosis, the first step is to obtain, as much as possible, all the information regarding the first surgical procedure. Circumstances and operative details of cholecystectomy must be accurately reviewed: Emergency or elective surgery, opening and emptying of the gallbladder, occurrence of bile spillage and method of gallbladder extraction (with or without bag). If possible, the original specimen could be re-reviewed by an experienced pathologist to more accurately define the exact site of the tumor, the depth of parietal invasion, the cystic duct involvement and the presence of metastatic lymph nodes. Unfortunately, as reported in a multicenter French survey, we are not always able to obtain all relevant information^[5].

In any case, if the cancer is a pTis or a pT1a, and the operation was rightly performed without loss of bile or stones, a second, revisional, surgical procedure is not mandatory. However, in these cases, a close

surveillance is still required. Unfortunately, in most cases pathology shows a muscular layer involvement (pT1b), a perimuscular tissue involvement (pT2) or a serosal involvement (pT3). A CT evaluation is required to detect any macroscopic residual disease or distant metastases; indeed, in these cases, a second surgical procedure is contraindicated. On the contrary, if any residual disease is absent, a second, radical surgical procedure can be planned. Re-resection for gallbladder carcinoma incidentally discovered after cholecystectomy is considered safe and effective^[6] and it is routinely advocated in the majority of cases^[7].

Although some authors consider unnecessary a second procedure in patients with T1b cancer, the majority performs a re-resection also in this indication. The aim of re-resection is to obtain a radical excision of the tumor and an accurate disease staging. Usually, this include a 4b + 5 segmentectomy, because a more extensive hepatectomy is not associated with a more favourable prognosis. Nevertheless, as the aim is to achieve a margin free resection, a right extended hepatectomy may be required in some cases^[8]. Lymphadenectomy should include the regional lymph nodes (gallbladder, hepatic pedicle, hepatic artery and periportal). Some topics of this surgical treatment are still under discussion: (1) the role of a preliminary laparoscopy before definitive treatment; (2) indications for CBD excision with hepatico-jejunostomy; and (3) port-sites excision. A preliminary laparoscopy could be useful in pT3 tumors to avoid an unnecessary laparotomy in cases with peritoneal carcinomatosis or liver metastases not detected by CT or MRI. The removal of the CBD with a hepatico-jejunostomy was emphasized in the past in order to obtain a more extensive lymphadenectomy. At present, there is no evidence to support prophylactic common bile duct excision^[9]. However, this maneuver, if routinely performed, increases the morbidity without any benefit on survival; therefore, it should be reserved for cases with cystic duct involvement^[10]. The routine port-sites excision is not associated with improved survival or disease recurrence^[11]. Today, this maneuver is not considered mandatory and could be reserved for cases in which the frozen-sections show residual disease on peritoneal surface at the level of the trocar-sites. However, it is advisable to excise the port-sites if the gallbladder was extracted without bag during cholecystectomy, or when this information is not available. Finally, the re-resection and lymphadenectomy can be performed by laparoscopy, as recently reported by Machado *et al*^[12]. Obviously, this approach can be pursued only in centers with extensive experience in hepatobiliary and advanced laparoscopic surgery.

PROGNOSTIC FACTORS

The operative specimens of re-resection should be examined by the pathologist to find any "residual" tumor. The "residual disease" can be found on the liver,

at the level of the gallbladder bed, on the lymph nodes or at the level of the trocar-sites excised. The presence of residual disease is found in about 50%-70% of cases and it can be predicted by the pT stage after cholecystectomy. Pawlik *et al*^[7] reported a risk of residual disease within the liver and to loco-regional lymph nodes of 0% and 12.5%, respectively, for cancers pT1, of 10.4% and 31.3% for pT2, of 36.4% and 45.5% for pT3. The residual disease is the most important prognostic factor, significantly reducing median disease-free survival and disease-specific survival^[13]. The other factors include depth of parietal invasion, metastatic nodal disease, surgical margin status (R0 resection), cholecystectomy for acute cholecystitis, histological differentiation, lymphatic, vascular and perineural invasion and overall TNM-stage^[14-16]. On the contrary, the time interval between cholecystectomy and re-resection is not significant for the prognosis^[13]. This fact allows, when the discovery of cancer occurs during the operation, to refer the re-resection to a later date. It also allows to refer the patient for re-resection in a tertiary center if the cholecystectomy was performed in a non-specialized hospital.

With regard to the prognosis after radical surgery, it is very favorable in patients with pT1b cancer with a 10-year survival up to 90%-100%^[6,17]. Re-resection significantly increases survival in patients with carcinoma pT2 and pT3. A 5-year survival rates ranging from 49.8% to 78.3% for pT2 cancers and from 0% to 23% for pT3 cancers was reported in the literature^[6,17,18]. In the same way, an increase in 5-year survival rate up to 62% for patients with pT2 cancer and up to 19% for patients with pT3 was reported in a multicenter French study^[16]. On the contrary, poor 5-year survival rates, ranging from 10% to 22%, were reported after simple cholecystectomy for pT2 cancers^[17,19]. In conclusion, radical re-resection, including liver resection and lymph node dissection, is the operation of choice for the treatment of pT2 and pT3 unexpected gallbladder cancers; it allows to obtain a significant survival benefit compared with simple cholecystectomy^[19,20].

CONCLUSION

A second, radical surgical procedure, when possible, improves prognosis in patients with UGBC. The possible occurrence of UGBC after cholecystectomy for gallstones allows some considerations. Firstly, laparoscopic cholecystectomy is a procedure that must be correctly performed in all cases, without loss of stones and bile: The occurrence of "spillage", in case of unexpected cancer, significantly worsens the prognosis. In case of acute cholecystitis, or in any technically difficult case, as in the elderly, the surgeon should be cautious and eventually can convert the laparoscopy in a traditional laparotomy rather than possibly causing a tumor dissemination with inadequate maneuvers. The patients with UGBC should be treated by an experienced surgeon, preferably in a tertiary center specialized in hepatobiliary

surgery.

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Surgical palliation of gastric outlet obstruction in advanced malignancy

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Abstract

Gastric outlet obstruction (GOO) is a common problem associated with advanced malignancies of the upper gastrointestinal tract. Palliative treatment of patients'

symptoms who present with GOO is an important aspect of their care. Surgical palliation of malignancy is defined as a procedure performed with the intention of relieving symptoms caused by an advanced malignancy or improving quality of life. Palliative treatment for GOO includes operative (open and laparoscopic gastrojejunostomy) and non-operative (endoscopic stenting) options. The performance status and medical condition of the patient, the extent of the cancer, the patients prognosis, the availability of a curative procedure, the natural history of symptoms of the disease (primary and secondary), the durability of the procedure, and the quality of life and life expectancy of the patient should always be considered when choosing treatment for any patient with advanced malignancy. Gastrojejunostomy appears to be associated with better long term symptom relief while stenting appears to be associated with lower immediate procedure related morbidity.

Key words: Surgical palliation; Gastric outlet obstruction; Advanced malignancy; Gastrojejunostomy; Endoscopic stenting

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Core tip: Gastric outlet obstruction (GOO) is a common problem associated with advanced malignancies of the upper gastrointestinal tract. Palliative treatment of patients' symptoms who present with GOO is an important aspect of their care. Surgical palliation of malignancy is defined as a procedure performed with the intention of relieving symptoms caused by an advanced malignancy or improving quality of life. Palliative treatment for GOO includes operative (open and laparoscopic gastrojejunostomy) and non-operative (endoscopic stenting) options. Regardless of the treatment used for relief of symptoms all physicians having end of life conversations with patients should be adequately trained in end of life care to ensure that patients are getting the optimal treatment for their

particular circumstances.

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INTRODUCTION

Gastric outlet obstruction (GOO) is a common problem associated with advanced malignancies of the upper gastrointestinal tract. Symptoms can be severe and include nausea, vomiting, malnutrition and decreased quality of life. Due to the advanced stages of the underlying malignancies causing these symptoms many patients are not candidates for curative resection. However, palliative treatment of their symptoms is an important aspect of their care. Research has shown that symptoms of advanced gastric cancer can often be effectively managed with palliative interventions. One of the main symptoms of advanced gastric cancer is GOO. Treatment for GOO includes operative and non-operative options. Traditionally, open gastrojejunostomy was the treatment modality of choice to bypass the obstruction. However, in recent years endoscopic stenting has been used more frequently. While stenting is considered less invasive and associated with a quicker return to oral intake, it is associated with several disadvantages including a high rate of re-obstruction and stent migration^[1]. In this review, we discuss the incidence and presentation of GOO, the current data regarding the goals of palliative intervention, the success of palliative treatment of gastric cancer, the techniques used to treat GOO and the outcomes of those treatments (Figure 1).

INCIDENCE OF GOO

GOO is a common complication of both benign and malignant disease of the stomach, pancreas and duodenum. It is caused by occlusion of the lumen by intrinsic or extrinsic growth^[2]. Because up to 55% of gastric cancers and up to 75% of periampullary cancers are not resectable at the time of diagnosis, they represent the most common causes of malignant gastroduodenal obstruction^[1,3]. GOO can also be caused by lymphoma, biliary disease, metastasis to the duodenum or jejunum and extrinsic compression^[1,3]. Malignant gastroduodenal obstruction is associated with limited length of patient survival. Patients, on average, live 3-6 mo^[3-7]. Malignant obstruction is a serious problem for physicians to treat because it is associated with a marked reduction in quality of life in a group of patients who are already significantly medically compromised^[4]. In the setting of patients suffering from GOO, palliative interventions are often necessary to alleviate symptoms

and improve quality of life^[5].

The stomach has a significant capacity to distend allowing GOO to go unnoticed by the patient until high grade obstruction develops^[4]. The symptoms of GOO are often incorrectly ascribed to the patient's cancer or the therapies they are undergoing (including chemotherapy, radiation therapy or both). However, the diagnosis of GOO can be made by obtaining a good history of present illness from the patient. Patients present with symptoms of nausea, vomiting, malnutrition, reflux, abdominal distension and dehydration^[3]. Patients often present with vomiting undigested food hours after eating and the vomit is often described as bilious^[4]. As a result, these patients can develop "food fear" secondary to their debilitating emesis^[3]. Patients also describe a reduced quality of life, poor condition and poor performance status^[6]. Evaluation of patients who present with symptoms of GOO may require endoscopy and upper gastrointestinal series to evaluate severity and length of the stenosis. Because of the potential of an associated biliary obstruction, it is also important that the biliary system is evaluated prior to any surgical procedure. This workup can include a liver function panel, a right upper quadrant ultrasound, or a computed tomography scan with a "pancreas protocol".

Goals of palliative intervention

Substantial variation in the definition of palliative care has complicated the understanding of the role of palliative operations^[7]. The concept of "palliation" is often used by physicians to describe: (1) a patient with limited survival; (2) procedures performed in the presence of unresectable disease; or (3) as acknowledgment that a curative procedure is not an option^[7]. This suboptimal characterization of "palliation" has perpetuated imprecise interpretations of both palliative surgical indications and outcomes^[7]. In an attempt to standardize the role of palliative care, the World Health Organization has defined palliative care as "the total active care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. The goal of palliative care is the achievement of the best quality of life for patients and their families"^[7,8]. While these broad definitions of palliative care do provide a global understanding, they do not definitively explain the diverse goals of surgical palliation. For example, compare and contrast the patient who presents to the emergency room for an emergent laparotomy for a hemorrhagic tumor and the patient who presents to for an elective surgical biopsy to confirm advanced disease. The intent of these procedures is so dissimilar that it makes any meaningful evaluation of critical outcome measures imprecise^[7]. Even if one considers only those patients with known metastatic disease, they still present with such different clinical scenarios requiring surgery that it makes valid comparisons of outcomes difficult^[7]. In every case, ideal palliative care must emphasize the individual's specific

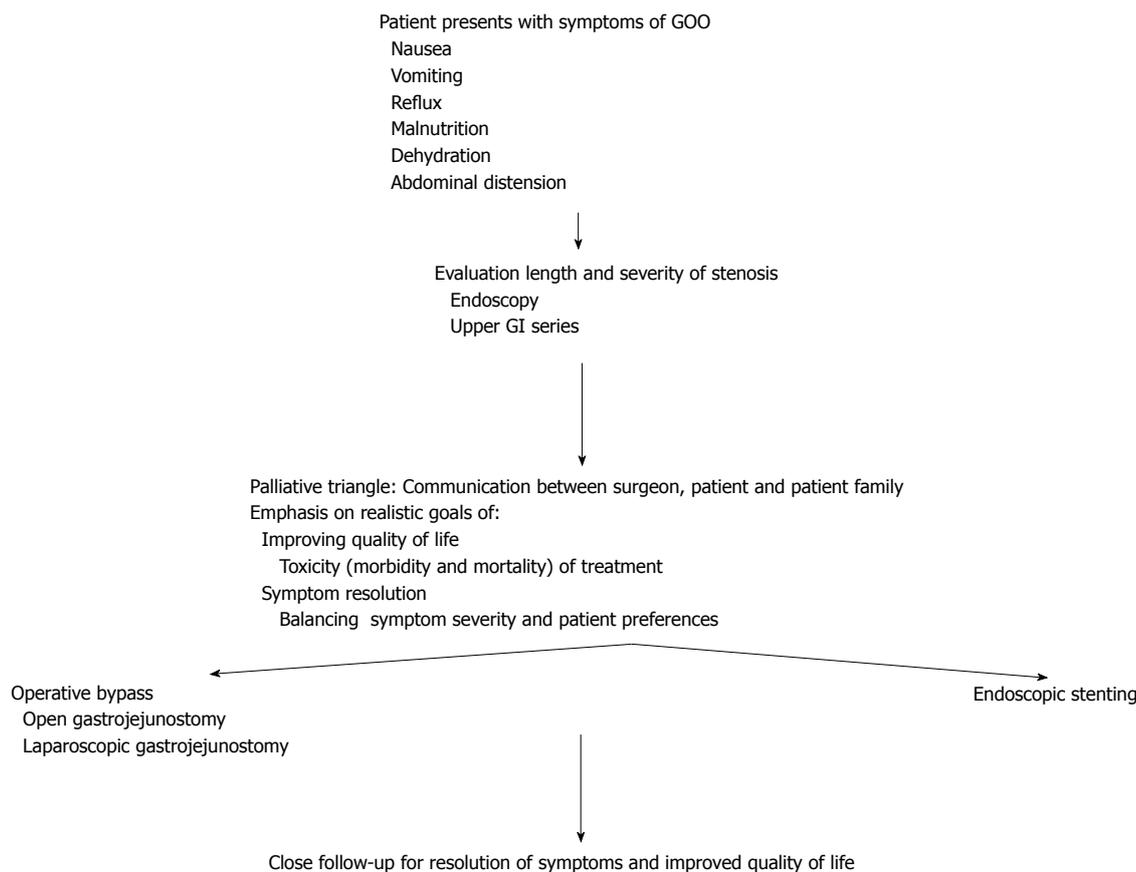


Figure 1 Flow diagram demonstrating workup and treatment for patients who present with gastric outlet obstruction from advanced malignancy. GI: Gastrointestinal; GOO: Gastric outlet obstruction.

values and needs and therefore, different indications and outcomes can be observed for essentially identical procedures^[7].

The best way to define surgical palliation of malignancy is as a procedure used with the primary intention of relieving symptoms caused by advanced malignancy or improving quality of life^[7,9-12]. It is important to note that a palliative procedure is not the opposite of curative procedure. Instead, each procedure has its own distinct goals and indications and need to be considered separately and independently. The performance status and medical condition of the patient, the extent of the cancer, the patients prognosis, the availability of a curative procedure, the natural history of symptoms of the disease (primary and secondary), the durability of the procedure, and the quality of life and life expectancy of the patient should always be considered when choosing treatment for any patient with advanced malignancy^[7,13]. The emphasis of palliative decision making should be placed on outcomes that can be realistically delivered with the goal of providing the patient with a good quality of life and symptom resolution^[10].

In order to successfully provide symptom relief at the end of life while also minimizing operative morbidity and mortality, careful patient selection is of critical importance^[14]. Appropriate decision making is enabled through effective interactions among the surgeon,

the patient, and their family members *via* a dynamic relationship described by the palliative triangle^[9,10,15]. This relationship allows the patients values, complaints, and social support to be considered against known surgical and medical alternatives^[16]. Through this triangle emphasis should be placed on outcomes that can realistically be delivered to the patient with the goal of providing: (1) symptom resolution; (2) a good quality of life; (3) technically superior palliative operations; (4) dignity; and (5) compassion. The dynamics of the palliative triangle help to moderate the different beliefs of each of its members and to guide the decision making to the best treatment for individual patient^[9,10,15]. Brown University studied the outcomes of patients with advanced malignancy that was managed by surgeons with the palliative triangle method. Patient reported symptom resolution or improvement after palliative intervention was noted in 117 of 129 procedures (90.7%) and this symptom relief occurred within 30 d after the operation. Palliative procedures were associated with 30 d postoperative mortality (3.9%) and morbidity (20.1%). Median survival was 212 d. The study suggests that palliative operations performed on patients selected using the palliative triangle approach have high rates of symptom improvement and low morbidity and mortality^[10]. It is important to note that in this study, either one or two meetings between the surgeon, the patient

and family lasting 60-90 min occurred before consensus was achieved on the appropriate palliative intervention. This fact highlights the complexity of the decision making involved when performing palliative procedures and the importance of understanding the core concepts of the palliative triangle^[10].

Excellent communication between patients, family and providers is essential to successful palliation whether surgery is performed or is not even offered^[10]. Effective communication between the patient and their doctor allows clinical problems to be identified more accurately, increases patient satisfaction with their care, improves patient compliance with treatment plans, alleviates feelings of distress and vulnerability by the patient and improves the patients overall well-being^[10]. At the end of life, patients and families are particularly vulnerable and they seek well developed interpersonal skills and communication from their physicians to guide them^[10].

PALLIATIVE INTERVENTION FOR GASTRIC CANCER-OPPORTUNITIES FOR SUCCESS

Patients with gastric cancer often present with an advanced stage and have a low cure rate, therefore palliative strategies are an essential and necessary component of gastric cancer management. Surgical palliation may include resection or bypass with or without endoscopic or percutaneous interventions. These interventions serve to eliminate potential complications (pain, obstruction, bleeding, debilitating ascites, perforation) and improve symptom control caused by the primary tumor^[7,17].

Research suggests that there may be a surgical benefit after palliative resection for patients with advanced gastric cancer^[18-20]. Keränen *et al*^[21] compared the safety, efficacy, and outcome of palliative stenting, palliative resection and gastrojejunostomy in patients with primary gastric cancer complicated by GOO. They concluded that palliative resection provides a surgical benefit and should be considered in patients suitable for surgery^[21]. A study from Memorial Sloan Kettering Cancer Center evaluated the outcomes of patients who underwent noncurative gastric resection with either palliative or nonpalliative intent^[7]. Three hundred and seven patients received a noncurative gastric resection between 1985 and 2001. Palliative operations were performed in 48% (147/307) and nonpalliative operations were performed in 52% (160/307) of patients^[7]. There was no difference in mean length of hospital stay [palliative (16.9 d) vs nonpalliative (18.9 d)], morbidity (54%) or mortality (6%) between the two groups^[7]. However, high-grade complications were less common in palliative [22% (32 of 147)] cases than in nonpalliative cases [29% (47 of 160), $P = 0.049$]^[7]. Additional palliative procedures were required in 24% (72 of 307) of patients, but their distribution was equal between the

two groups^[7]. Interestingly, many of the indications for repeat surgery were for treatment of distant disease and not for symptoms caused by the primary tumor. In both the palliative and nonpalliative groups, carcinomatosis caused gastrointestinal obstruction which required an intervention (either internal bypass, small bowel resection or colostomy) at similar rates^[7]. This study suggests that complication rates associated with noncurative procedures performed with palliative intent are lower than those performed with nonpalliative intent. Similarly, Saidi *et al*^[22] examined the role of palliative gastrectomy for patients with metastatic gastric cancer and evaluated its impact on survival. The study concludes that palliative gastrectomy with systemic therapy may improve survival in patients with stage IV gastric cancer^[22]. However, further research would need to be done to compare palliative gastrectomy plus systemic therapy to systemic therapy alone. Finally, Zhang *et al*^[23] attempted to summarize the outcome of patients undergoing palliative total gastrectomy for stage IV proximal gastric cancer. Between 1991 and 2005, clinical data of 197 patients undergoing palliative gastrectomy, 642 patients undergoing curative total gastrectomy, 102 patients undergoing explorative laparotomy, 78 patients undergoing jejunostomy and 152 nonsurgical patients, were enrolled. One-, three-, and five-year survival rates were significantly lower in the palliative gastrectomy group compared to the curative gastrectomy group^[23]. Interestingly, the median survival time in the palliative gastrectomy group was significantly longer than that in the laparotomy, jejunostomy and the no surgery. The postoperative mortality and complication rate were significantly higher in the palliative gastrectomy group compared to the curative gastrectomy group^[23]. The study concluded that palliative total gastrectomy for stage IV proximal gastric cancer is associated with prolonged survival time and decreased post-operative complications when compared to no surgery, laparotomy and jejunostomy procedures^[23]. The improvement in survival seen in the above studies may be due to the reduction in overall tumor burden^[24]. Together, this suggests that there may be a surgical benefit after palliative resection for patients with advanced gastric cancer.

Research regarding surgical treatment for advanced gastric cancer highlights the importance of appropriate patient selection. Samarasam *et al*^[25] retrospectively reviewed patients from 1999 to 2003 who underwent palliative surgery for gastric adenocarcinoma. One hundred and seven/one hundred and fifty-one (70.9%) underwent either subtotal gastrectomy (SG) or total gastrectomy (TG) to macroscopic free margins; the remaining 44/151 underwent laparotomy with or without gastrojejunostomy. All patients received adjuvant chemotherapy^[25]. Median survival was improved in resected patients (24 mo vs 12 mo, $P = 0.0003$); however the survival benefit decreased when a patient had more than one criteria for unresectability (T+, H+, P+, N+)^[25]. Median survival was similar between SG

and TG groups (24 mo and 20 mo, respectively)^[25]. This study suggests that patients with more than one criteria for unresectability may do better with less invasive procedures. Zhang *et al.*^[23] compared the clinicopathological factors and outcomes of palliative gastrectomy to exploratory laparotomy with or without bypass for noncurative gastric cancer^[26]. From 1988 to 2008, 365 patients underwent palliative gastrectomy and 151 patients underwent exploratory laparotomy or gastrojejunostomy for noncurative gastric cancer. One hundred and eighty-two of the patients were aged 70 years old and younger (group A) and 183 of the patients were older than 70 years old (group B). The overall survival of patients who underwent resection was 10.2 mo which was significantly longer than those patients who did not undergo resection (4.48 mo). Patients in the younger group (group A) were more likely to be female and had more aggressive tumors. Interestingly, the surgical morbidity was higher in both groups if the patients had comorbidities and the surgical morbidity and mortality was significantly higher in patients in the older age group (group B)^[26]. This data once again highlights the critical importance of appropriate patient selection and the terms of the palliative triangle.

While postoperative morbidity and mortality are important outcomes to consider for any surgical intervention the goals of palliative care emphasize quality of life and symptom relief. To better evaluate these important outcomes, one group performed a partitioned survival analysis, which assessed the state of health in relation to the patient's treatment, the treatment toxicity, and any patient relapse over time^[24,27]. Patient health state was defined in terms of "time without symptoms or toxicity" or (TWiST). Three hundred and seven non-curative resections were included in the analysis and 147 (48%) of them were performed with palliative intent. In the palliative group patients experienced an average of 8.5 mo in the TWiST state. Complications that reduced the time spent in TWiST included high-grade complications such as ICU admission, unplanned re-intervention, or permanent disability (2.1 mo, $P = 0.04$). Patients who presented with multiple sites of metastasis trended towards less time in the TWiST state (4.9 mo, $P = 0.08$). This data demonstrates the importance of appropriate patient selection. Pre-operative counseling between the surgeon, the patient and the family is critical in determining treatment goals and appropriate follow-up is necessary to ensure appropriate outcomes.

GASTROJEJUNOSTOMY SURGICAL TECHNIQUES

Understanding the anatomy of the stomach and small bowel in patients who have symptoms of GOO is an important aspect of choosing the right intervention.

Gastrojejunostomies can be performed in an antecolic or retrocolic fashion. The antecolic technique connects

the distal stomach to the jejunum. The retrocolic technique involves placement of the jejunal loop through the transverse colon mesentery^[28].

An incision is made in the upper midline of the abdomen. In an antecolic gastrojejunostomy the surgeon must identify a section of the distal stomach and a loop of jejunum distal to the ligament of Treitz that can be easily brought in close proximity to the stomach. Usually a location 15-20 cm distal to the ligament of Treitz is chosen. Care must be taken to identify the proximal jejunum when making a gastrojejunostomy, because anastomosing the ileum to the stomach is a rare complication associated with high morbidity. A posterior row of silk sutures is placed to connect the stomach and jejunum. Electro cautery is then used to open the jejunum and the stomach creating jejunal and gastric stomas respectively. The inner layer of the anastomosis is performed using a running full thickness absorbable suture which is carried anteriorly. Interrupted silk sutures are then placed to complete the anterior portion of the two layer gastrojejunostomy^[28].

A stapled anastomosis can also be performed in which case the enterotomy and gastrotomy are performed as described above to facilitate placement of the stapler. The opening should be large enough to allow entry of the staple device. The gastrointestinal anastomosis (GIA) stapling device is placed through the holes created in the stomach and the jejunal and the anastomosis is performed by firing the stapler. The enterotomy and gastroenterotomy are then closed together using a transanastomotic (TA) stapling device^[28].

If a retrocolic gastrojejunostomy is performed, the first step is again to identify the sites for the anastomosis of the stomach and jejunum. The transverse colon is lifted cephalad to visualize the mesentery and identify an avascular area through which the jejunal loop can pass through. A hand sewn anastomosis is performed in the same fashion described above for the antecolic approach using a two layer anastomosis with a posterior row of silk interrupted sutures. The jejunal and gastric stomas are created using electro cautery. The inner layer of the anastomosis is accomplished with a running full thickness absorbable suture. The retrocolic gastrojejunostomy is then completed using interrupted silk seromuscular sutures placed anteriorly^[28].

Similar techniques are used to perform the stapled anastomosis for a retrocolic gastrojejunostomy. The jejunal and gastric stomas are created using electro cautery. The retrocolic gastrojejunostomy is then completed using the GIA stapler and the openings created in the stomach and jejunum are closed together using a TA stapler. If a retrocolic approach is used most surgeons will loosely suture the edges of the mesentery to the jejunum to minimize the risk of herniation of the bowel loop^[28].

The midline incision is closed in the usual fashion regardless of whether an antecolic or retrocolic approach was used. A nasogastric tube is usually maintained

postoperatively on suction until bowel function returns and a diet can be initiated^[28].

LAPAROSCOPIC GASTROJEJUNOSTOMY SURGICAL TECHNIQUES

Understanding the anatomy of the stomach, liver, ligament of Treitz and esophagus are important details for the surgeon to understand before performing a laparoscopic gastrojejunostomy^[29]. It is necessary to identify the presence of hepatomegaly because a large left lateral segment may mean that the falciform ligament will need to be divided for optimal hepatic retraction and visualization^[29]. Again, accurate identification of the ligament of Treitz is imperative to ensure localization of the jejunum^[29].

Prior to surgery the patient is usually asked to undergo bowel preparation. After induction of anesthesia, a nasogastric tube (18 gauge) is placed to decompress the stomach. This will also be used during the creation of the gastrojejunostomy anastomosis and as an intraluminal stent to ensure patency of the newly created gastro-jejunal lumen. A urinary catheter is also placed to decompress the bladder.

The patient is placed in the supine position on the operating table. The arms are extended on arm boards and foot plates and safety straps are placed to secure positioning. The surgeon stands on the patient's right side while the assistant surgeon and camera operator are on the left side^[29]. The authors recommend an open Hassan technique to access the abdomen. A long 45 degree, 10 mm endoscope allows for optical visualization of the operative anatomy^[29]. Five ports are placed as follows: (1) one to the left of midline below the sternum to be used for liver retraction (an expandable liver paddle is used to bluntly retract the left lobe of the liver); (2) one to the right of midline to be used for the instrument in the surgeons left hand; (3) one to the right of the umbilicus for the instrument to be used in the surgeon's right hand; (4) one to the left of the umbilicus to be used for the camera; and (5) one in the left lower quadrant to be used for the instrument in the assistant's right hand^[30]. Laparoscopic gastrojejunostomy can be performed with a stapler or with a hand sewn technique.

For the hand sewn technique a needle driver for suturing and a left handed instrument, either blunt grasper or curved tip grasper, will be needed. To begin the construction of the gastrojejunostomy the left lobe of the liver must be fully retracted. To facilitate this, a nathanson retractor is placed in the epigastrium to elevate the liver and expose the gastro esophageal fat pad which is used to identify the gastro esophageal junction^[29,30]. The proximal end of the jejunal limb is carefully identified and brought into the upper abdomen (usually in an antecolic, antegastric manner). A running back wall suture line is created using a 2-0 Vicryl suture (approximately 20 cm in length). Two enterotomies are

made, one in the stomach and one in the jejunal limb, about 1.5 cm in length and a few millimeters away from the running back wall suture line^[30]. The suture is run from the patients left side corner to the right corner and the remaining suture and needle are saved. A second, inner running suture line is created using a 2-0 Vicryl which is started at the patients left side corner of the open enterotomy. Another 2-0 Vicryl suture is used to close the inner layer anteriorly. Prior to completion of the inner layer closure, a 34 French nasogastric (NG) or orogastric (OG) tube is passed across the anastomosis under direct visualization. The inner layer closure is completed by bringing the two sutures onto the anterior aspect of the anastomosis and tying them together. Needles are cut and removed. The previous outer layer Vicryl suture is then used to continue anteriorly to reinforce the inner layer. This can also be completed by starting a separate second suture beginning from the corner and tying in the middle of the anterior aspect gastrojejunostomy^[30].

A leak test is then performed. The patient is placed in the Trendelenburg position and the left upper quadrant is filled with normal saline to immerse the anastomosis^[30]. Air is introduced into NG tube until adequate inflation of the stomach and jejunal anastomosis is observed. A leak test can also be performed with methylene blue through the NG tube. If leakage is noticed the area is repaired with additional non absorbable sutures until no further air leak is seen^[30].

There are several of important techniques that should be used when performing a gastrojejunostomy to minimize postoperative complications. To minimize anastomotic ulcer and stricture formation, the inner layer is closed using absorbable sutures^[30]. The aperture of the anastomosis is regulated by closing the enterotomy defect over an NG or OG tube. Care must be taken to avoid suturing to the tube which can result in disruption of the closure^[30]. Back-hand suturing in the corners may allow more precise suturing if forehand stitching appears awkward in orientation^[30]. The tension on the running suture is maintained by the assistant throughout the closure process to avoid loosening of the closure and allowing potential leakage. Prior to tying the knots the entire suture must be cinched down to further eliminate potential gaps^[30].

A laparoscopic gastrojejunostomy can also be performed with stapling devices. First, the posterior wall of the stomach is cleared of adhesions and any vascular tissue with a Ligasure device. In preparation for a retrogastric anastomosis a gastrostomy is created and marked with a silk suture. An enterotomy is created in a carefully selected portion of the jejunum. A 30-mm long endoscopic gastrointestinal stapler is used to create a gastrojejunostomy by firing it across the common walls of the stomach and the jejunum for approximately 2 cm in length. Following stapling, anesthesia advances the NG tube under direct vision across the gastrojejunostomy^[29]. The gastrojejunostomy is closed over the NG tube with a running 2.0 silk suture. This layer is

carefully inspected to look for any gaps in the suture line. A second layer of 2-0 silk is paced circumferentially around the entire anastomosis. The gastrojejunostomy is tested for a leak and reinforced as appropriate. The NG tube must be advanced forward and pulled back to ensure that it has not been caught by on the sutures. The trocars are removed under direct visualization and the pneumoperitonium is released.

For both the hand sewn and stapling technique a suction drain may be left in the vicinity of the anastomosis for postoperative management. 3-0 absorbable suture is used for the subcuticular port site closure^[29]. Post operatively a nasogastric tube is usually maintained on suction until bowel function returns and a diet can be initiated^[29].

ENDOSCOPIC STENTING TECHNIQUES

It is important that the gastrointestinal stent morphology adapt to the anatomic curvature of the intestine to achieve appropriate function^[1]. There are currently two FDA approved duodenal stents and they include the Wallstent Enteral and the Wallflex Enteral duodenal Stent. The Wallstent Enteral from Boston Scientific is made from Cobalt-based alloy. It is uncovered and has a deployment diameter of 20-22 mm and a 40%-50% degree of shortening. The Wallstent Enteral features through the scope delivery and reconstrainability. The Wallflex Enteral duodenal Stent from Boston Scientific is made of Nitinol. It is uncovered and had a deployment diameter of 22 mm and a 30%-40% degree of shortening. The Wallflex Enteral duodenal Stent features proximal flaring, through the scope delivery and reconstrainability. These stents are self-expandable metal stents (SEMS)^[31]. They are both uncovered meaning that they embed into the stricture and surrounding tissue and can be placed through the working channel of a therapeutic endoscope. Uncovered SEMS are non-removable and migrate less often but tumor ingrowth frequently occurs causing a high rate of reobstruction^[31]. New stents are being developed with higher flexibility, less foreshortening and covers with the goal of reducing stent migration and tumor ingrowth. So far these stents have been found to be comparable to existing stents and may have a lower frequency of complications including decreased migration and tumor ingrowth^[4,32-36]. Other drug eluting or radioactive stents to help slow tumor growth are being developed but are currently not yet available.

Associated with GOO is sometimes so tight that it is difficult, if not impossible, to traverse the stricture with the therapeutic endoscope (the working channel of the scope needs to be greater than 3.8 mm)^[31]. In order to minimize risk of perforation, physicians should avoid attempting to aggressively dilate the stricture^[31]. However, patients with malignant duodenal obstruction are at a high risk for biliary obstruction. Therefore placing a biliary SEMS prophylactically before placing

the duodenal SEMS should be considered. Duodenal strictures are dilated (18-22 mm) only if biliary drainage is to be performed, because access to the papilla requires the use of a large diameter therapeutic duodenoscope^[31]. If, after assessing the status of the biliary tree, there is known or impending biliary obstruction an expandable metal biliary stent should be placed before the duodenal stent. To treat biliary obstruction after placement of a duodenal stent, a percutaneous transhepatic approach is usually required. Stenting of both the duodenum and the bile duct is the non-surgical equivalent of traditional double surgical bypass (gastrojejunostomy and choledochojejunostomy)^[31]. Due to these potential complications, duodenal stents generally are not used for benign disease only malignant disease.

Patients with GOO have high gastric residuals and suction of gastric contents should be performed prior to beginning the procedure to minimize aspiration risk and optimize visualization^[31]. If a patient is determined to be at high risk for aspiration then endotracheal intubation should be initiated prior to stent placement. The procedure should be performed under fluoroscopic or endoscopic guidance. Research suggests that the use of both modalities is important provide adequate visualization and get an idea of any distal obstruction^[3,37]. Patients should be in the supine or prone position to optimize fluoroscopic visualization. As mentioned above, the status of the biliary tree should always be assessed before gastro duodenal stent placement. Placement of the SEMS across the papilla will make endoscopic biliary access difficult. If the tumor is located in the proximal duodenum without involvement of the papilla a stent that is long enough to cross the lesion should be chosen but not excessively long which will prevent access to the papilla^[31]. Therefore, accurate assessment of the length and location of the malignant stricture is important^[31]. The stricture may be accessed with a standard biliary balloon catheter over a guide wire under fluoroscopic guidance. Injecting dye through the stricture may help delineate the length, geometry and extension of the structure. The selected stent should be about 4 cm longer than the stricture. Prior to patient discharge patients should be advanced to liquids and then to solids as tolerated. They should be told to avoid leafy vegetables which may result in stent occlusion.

OPEN GASTROJEJUNOSTOMY

OPERATIVE APPROACH OUTCOMES

Operative treatment options for GOO include NG placement, percutaneous gastrojejunostomy and gastrojejunostomy (open and laparoscopic).

While nasogastric and jejunostomy tubes are minimally invasive they have several disadvantages. Nasogastric tubes and gastrostomy tubes are used for decompression however they cannot be used for feeding. In contrast, jejunostomy tubes can be placed distal to the

obstruction so they can be used for hydration, enteral nutrition, and to provide medications^[4]. However these patients remain obstructed in their stomach and they often still have symptoms of nausea and vomiting. Percutaneous gastrojejunostomy tubes provide decompression of the stomach and distal enteral feeding. However these tubes can result in peritoneal leakage especially in the setting of ascites^[3]. The main disadvantage, however, of percutaneous tubes is the fact that patients are unable to resume oral feeding.

Surgical palliation is the standard treatment method for patients who present with symptoms of GOO^[38]. Gastrojejunostomy has been shown to be highly successful at relieving obstructive symptoms and allowing patients to return to oral eating^[4]. Research suggests that operative gastrojejunostomy may be preferable to endoscopic stent procedures due to its durability for providing symptom relief^[6,39,40]. However, due to the poor general condition and advanced malnutrition of these patients, surgical palliation with gastrojejunostomy can be associated with a high complication rate^[3,41]. The mortality rate associated with surgical bypass has been reported to be between 2%-36% and the complication rate to be between 13%-55%^[3,7,42,43]. The mean hospital stay is 11 to 15 d with a range of 5-80 d^[3,43,44]. Delayed gastric emptying is a common complication which has been reported to vary from 5 to 37 d^[3,38,43,45,46]. Patients who undergo palliative surgical gastrojejunostomy have been reported to have survival times between 35-293 d^[1,40,43-48]. The large range is likely due to the difference in the underlying extent of disease. There is no evidence to suggest a difference in mortality or survival between patients who undergo open surgical or endoscopic procedures^[45,46].

LAPAROSCOPIC GASTROJEJUNOSTOMY OPERATIVE APPROACH OUTCOMES

Laparoscopic gastrojejunostomy is another option for the relief of the obstructive symptoms associated with GOO^[49]. Laparoscopy is a less invasive procedure than open surgery. The hospital length of stay can be as low as 3 d and as high as 14 d^[41,42,44,50,51]. Laparoscopic procedures are associated with decreased blood loss compared to open procedures^[41,51]. However there is no research to suggest a difference in the amount of blood transfusion received^[42]. It is unclear as to whether laparoscopic gastrojejunostomy is associated with a delay in gastric emptying^[3,41]. Research shows no difference in mortality, operating time, or nonsteroidal and anti-inflammatory drug consumption between patients undergoing open vs laparoscopic bypass for GOO^[41,42]. There is inconclusive evidence regarding the difference in opiate analgesia and operative morbidity between laparoscopic and open procedures^[41,42]. The conversion to open surgery has been reported to range from 0% to 20%^[42]. The presence of malignant ascites is a relative contraindication for laparoscopic surgery.

ENDOSCOPIC STENTING APPROACH OUTCOMES

Nonoperative treatment options for the treatment of GOO include gastroduodenal stent placement. In the recent years there has been a decline in the number of patients undergoing surgical treatment of GOO because of the development of self-expanding metal stents^[4]. Stents have been found to be safe and effective in terms of palliation of symptoms especially in those patients who are too high risk to undergo surgery. Patients who have previously undergone a surgical procedure who later develop GOO are also good candidates for stent placement. However, it should be noted that because of the low durability and high re-obstruction rates of duodenal stents they are often not used for benign disease. A large systemic review found that in 6076 patients with malignant GOO, 97% underwent successful stent placement and 89% had relieve of symptoms and improvement in oral intake^[52]. Interestingly, patients who did not have relief of symptoms also suffered from side effects such as narcotic pain medication, anorexia or subsequent distal obstructive which may have been contributing to their symptoms^[52]. Advantages of stent placement include the following: less invasive, outpatient procedure, fewer complications, cost effective, rapid return to gastric emptying, shorter procedure time and improved quality of life^[3,4,45,53-55]. Patients may resume oral intake as quickly as post-operative day 1-5 of the procedure^[2-4,6,43,45,46]. It has been reported that 73%-87% of patients who have gastroduodenal stents placed resume oral food intake^[1,47]. The mean hospital discharge rate is short and has been reported to be 2.5-7.5 d. Survival has been reported to range from 63-189 d^[2,40,43,45-48]. Again, survival time is likely attributed to the advanced stages of the underlying disease.

Contraindications to stent placement include distal gastrointestinal obstruction, gastrointestinal perforation, and patients with multilevel bowel disease^[3]. The immediate complication rate of the procedure is low and has been reported to be 4%^[43]. However the rate of late adverse events has been found to be higher in patients who undergo stent placement compared to those who undergo gastrojejunostomy^[40]. The major disadvantages of stent placement include a high rate of stent migration and re-obstruction^[1,6,38,40]. Reobstruction rates have been found to occur more quickly than patients who undergo gastrojejunostomy^[40]. Another devastating complication is the concomitant or subsequent development of biliary obstruction which has been reported in up to 44% of cases^[4,56]. Other complications include bleeding and perforation^[4]. Interestingly, one study looked at the effect of endoscopic vs surgical palliative procedures for symptom relief in patients with metastatic or advanced loco regional cancer. They found that patients who underwent endoscopic procedures had fewer perioperative complications {endoscopic [18% (37/209)] vs patients who underwent operative

procedures [39% (205/522)], $P < 0.001$ }. The patients in the endoscopic group experienced a higher 30-d mortality {endoscopic [15% (38/247)]} when compared to the operative group [9% (54/576), $P = 0.017$]^[11]. Therefore, stenting is likely more beneficial for patients with a short anticipated survival, while gastrojejunostomy may provide more durable symptom improvement.

COST COMPARISON BETWEEN ENDOSCOPIC STENT AND GASTROJEJUNOSTOMY

Interestingly, one study compared the cost of stent placement and gastrojejunostomy for the treatment of malignant GOO. They found that food intake improved more rapidly after stent placement as opposed to after gastrojejunostomy. However, long term relief of obstructive symptoms was better after gastrojejunostomy. In addition they found that more major complications and more repeat interventions occurred after stent placement as opposed to after gastrojejunostomy. While the initial costs were higher for patients undergoing gastrojejunostomy there was no difference between the two procedures in follow-up costs. Total costs per patient were higher for gastrojejunostomy compared to stent placement. The incremental cost effectiveness ratio of the gastrojejunostomy compared to stent placement was 164 euros per extra day with gastric outlet obstruction scoring system adjusted for survival. They concluded that the medical effects were better after gastrojejunostomy despite the higher costs and that because the cost difference between the two groups was small that it should not play a role when deciding on the type of treatment to offer patients^[39].

CONCLUSION

Palliative treatments are offered to patients with the intent of relieving the symptoms of GOO and ultimately improving patient quality of life. Decisions regarding the use of surgical versus endoscopic procedures for GOO require the highest level of surgical judgment. Physicians must consider the individual patients quality and expectancy of life, the prognosis of the disease, the availability and the success of each treatment option^[9,14,15].

GOO can be effectively treated by both gastrojejunostomy and stenting. Gastrojejunostomy appears to be associated with better long term outcomes while stenting appears to be associated with better short term outcomes. New laparoscopic procedures and new technologies in endoscopic stents will likely continue to change the treatment recommendations for GOO. When it comes to palliative care, it is imperative that all physicians involved are adequately trained in end of life management to ensure that each patient gets the appropriate treatment for their particular circumstances.

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Restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: A narrative review

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Abstract

Restorative proctocolectomy with ileal pouch-anal

anastomosis (RP-IPAA) is the gold standard surgical treatment for ulcerative colitis. However, despite the widespread use of RP-IPAA, many aspects of this treatment still remain controversial, such as the approach (open or laparoscopic), number of stages in the surgery, type of pouch, and construction type (hand-sewn or stapled ileal pouch-anal anastomosis). The present narrative review aims to discuss current evidence on the short-, mid-, and long-term results of each of these technical alternatives as well as their benefits and disadvantages. A review of the MEDLINE, EMBASE, and Ovid databases was performed to identify studies published through March 2016. Few large, randomized, controlled studies have been conducted, which limits the conclusions that can be drawn regarding controversial issues. The available data from retrospective studies suggest that laparoscopic surgery has no clear advantages compared with open surgery and that one-stage RP-IPAA may be indicated in selected cases. Regarding 2- and 3-stage RP-IPAA, patients who underwent these surgeries differed significantly with respect to clinical and laboratory variables, making any comparisons extremely difficult. The long-term results regarding the pouch type show that the W- and J-reservoirs do not differ significantly, although the J pouch is generally preferred by surgeons. Hand-sewn and stapled ileal pouch-anal anastomoses have their own advantages, and there is no clear benefit of one technique over the other.

Key words: Ulcerative colitis; Total proctocolectomy; Ileal pouch; Anal anastomosis; Surgery; Laparoscopic

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Core tip: Restorative proctocolectomy with ileal pouch-anal anastomosis (RP-IPAA) is the preferred surgical treatment for ulcerative colitis. However, despite the widespread use of RP-IPAA, many aspects of this treatment still remain controversial, such as the approach (open or laparoscopic), number of stages of surgery, type of pouch,

and type of construction (*e.g.*, hand-sewn or stapled ileal pouch-anal anastomosis). Few large, randomized, controlled studies have been conducted, which limits the conclusions that can be drawn regarding controversial issues associated with RP-IPAA. It is suggested that prospective, randomized studies should be conducted in the future to compare the frequency of post-operative complications, cosmetic results, short- and long-term functional outcomes, and quality of life associated with the available techniques of RT-IPAA for the treatment of ulcerative colitis.

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INTRODUCTION

Ulcerative colitis is an inflammatory disease of the colon and rectum that affects millions of adults and children worldwide. Despite the progress of medical therapy, which has broadened the possible treatments after failure of corticosteroids, surgery is still required in 15%-35% of patients affected by ulcerative colitis^[1,2]. Surgery is indicated in the elective setting when dysplasia or cancer is present, the patient has a refractory disease, the side effects significantly impair the patient's quality of life, the patient develops steroid-dependence, or the patient is not compliant^[3,4]. In the acute setting, surgery is recommended in cases with hemorrhage, perforation, toxic megacolon, acute severe colitis, and a lack of improvement with second-line therapy. Surgeries are performed before these conditions worsen to avoid increased surgical morbidity and potential mortality^[3,4].

Since its introduction in 1978 by Parks *et al*^[5], the new gold standard surgical treatment of ulcerative colitis is restorative proctocolectomy with ileal pouch-anal anastomosis (RP-IPAA), which offers patients an unchanged body image with no stoma and a preserved anal route of defecation. It has been shown that RP-IPAA is common among older patients; one study revealed that the likelihood of requiring an end ileostomy decreased by 12% per year between 2005 and 2012 in patients aged 61 to 70 years compared with patients \leq 50 years of age [adjusted odds ratio (OR), 0.88 per year; $P = 0.021$]^[6].

However, despite the widespread use of RP-IPAA, many aspects of this treatment still remain controversial, including the type of approach (*i.e.*, open or laparoscopic), number of stages of surgery, type of pouch, and construction type (*i.e.*, hand-sewn or stapled ileal pouch-anal anastomosis) because few prospective, randomized studies have been designed

and performed.

The present narrative review aimed to define the controversies associated with the use of RP-IPAA in patients affected by ulcerative colitis. An electronic literature search of PubMed, MEDLINE, EMBASE, and the Cochrane Database of Collected Reviews was performed for the dates from January 1978 to March 2016. The search included the following terms: "Inflammatory bowel disease", "colitis", "colectomy", and "ileal pouch-anal anastomosis".

OPEN OR LAPAROSCOPIC RP-IPAA

Laparoscopic surgery in the treatment of ulcerative colitis has become very popular in the last decade. An analysis of the American College of Surgeons National Surgical Quality Improvement Program database (ACS-NSQIP, 2005-2008) for all ulcerative colitis patients who underwent a colectomy showed that the laparoscopic approach was used in 29.2% of cases, with rates increasing 8.5% each year (18.5% in 2005 to 41.3% in 2008, $P < 0.001$)^[7].

Recently, three meta-analyses^[7-9] compared open and laparoscopic RP-IPAA conducted for ulcerative colitis and familial adenomatous polyposis with respect to operative (duration of surgery, blood loss) and short-term (intraoperative mortality and post-operative complications) outcomes. One meta-analysis also compared functional outcomes (number of bowel movements in 24 h and per night, use of pads during the day and during the night, incontinence, and use of anti-diarrheal medications). As shown in Table 1, all of the meta-analyses reported that laparoscopic surgery requires a longer operative time and produces significantly less blood loss. The post-operative complications were also similar between the two procedures (with the exception of the incidence of wound infection, which was shown to be lower with laparoscopic surgery in the meta-analysis conducted by Singh *et al*^[7]). Functional outcomes were also similar between laparoscopic and open RP-IPAA in the meta-analysis of Singh *et al*^[7].

It should be noted that these meta-analyses were conducted on studies that were published many years ago (with the most recent study dated March 2012), included numerous types of interventions, and were essentially executed during the ascending phase of the learning curve of laparoscopic surgery. However, there are several more recent studies highlighted in Table 2. One of these studies showed that there was no significant difference between laparoscopic and open IPAA with respect to estimated blood loss, blood transfusions, postoperative narcotic usage, total complications, return of bowel function, length of stay, and hospital readmission rates^[10]. However, this study also reported that patients in the laparoscopic IPAA group underwent ileostomy closure an average of 24.1 d sooner than patients in the open group ($P = 0.045$).

Table 1 Meta-analyses comparing the intra-operative, short-term, and functional outcomes of open *vs* laparoscopic restorative proctocolectomy with ileal pouch-anal anastomosis

Ref.	Number of studies included/N of RCTs	Number of patients	Operative time	Blood loss	Intra-operative mortality	Hospital stay	Post-operative complications	Functional outcomes
Tilney <i>et al</i> ^[9]	10/1	Open: 178 LS: 175	Higher in LS by 86 min ^b	Lower in LS by 84 mL ^b	Not reported	No significant differences	No significant differences	No significant differences ¹
Ahmed Ali <i>et al</i> ^[8]	11/1	Open: 354 LS: 253	Higher in LS by 92 min ^b	Lower in LS by 138 mL	No significant differences	Shorter in LS by 2.12 d	Total Open: 41.5 LS: 37.6 Severe Open: 7.8 LS: 5.1	LS: Shorter time to bowel movement (-1.96 d); no significant difference in daytime and overnight continence, soiling, or urge incontinence
Singh <i>et al</i> ^[7]	27/1	Open: 1331 LS: 1097	Higher in LS by 70.1 min ^b	Lower in LS by 89.1 mL ^b	Not reported	Shorter in LS by 1 d	No significant differences with the exception of wound infection (lower in LS)	LS led to fewer nocturnal bowel movements and reduced pad usage during the day

¹Data based on only 2 studies; ^b*P* < 0.001. RCT: Randomized controlled trial; LS: Laparoscopic surgery.

Table 2 Studies comparing the intra-operative, short-term, and functional outcomes of open *vs* laparoscopic restorative proctocolectomy with ileal pouch-anal anastomosis

Ref.	Type of study	Number of patients	Operative time (min)	Blood loss (mL)	Mortality (%)	Hospital stay (d)	Post-operative complications (%)	Functional outcomes
Fajardo <i>et al</i> ^[10]	Retrospective	Open: 69 LS: 55	Open: 187 ± 52 LS: 266 ± 55 ^e	Open: 284 ± 146 LS: 294 ± 274	Open: 0 LS: 0	Open: 7.8 ± 4.9 LS: 8.4 ± 6.0	Open: 59.4 LS: 50.1	Open: 5.1 ± 2.8 LS: 4.9 ± 4.9 ²
Fleming <i>et al</i> ^[11]	Retrospective	Open: 339 LS: 337	Patients with an operative time > 336 min Open: 13.7% ^e LS: 36.6% ^e	Patients with transfusion Open: 8% ^a LS: 3.9 ^a	Open: 0.6 LS: 0.5	Open: 7.9 ± 4.8 LS: 7.3 ± 4.3	Major Open: 29.7 ¹ LS: 16.8 ⁴ Minor Open: 18.4 ³ LS: 10.6 ³	Not reported
Causey <i>et al</i> ^[12]	Retrospective	Open: 148 LS: 299	Not reported	Not reported	Open: 0 LS: 0	Not reported	Open: 18.2 ^b LS: 29.8 ^b	Not reported
Schiessling <i>et al</i> ^[13]	PRT ¹	Open: 21 LS: 21	Open: 200 ± 53 LS: 313 ± 52 ^e	Open: 228 ± 119 LS: 261 ± 195	Open: 0 LS: 0	Open: 19.6 ± 20.5 LS: 12.3 ± 5.8	Open: 5 LS: 9.5	Open: 3.5 ± 2.5 LS: 3.4 ± 2.5 ²
Tajti <i>et al</i> ^[15]	Retrospective	Open: 22 LS: 23	Open: 185 ± 17 ^{1,c} LS: 245 ± 51 ^{1,c}	Units of blood transfusion Open: 3 ± 1.9 LS: 2 ± 1.7	Open: Not reported LS: Not reported	Open: 11.6 ± 3.4 LS: 11.5 ± 3.8	Sepsis Open: 27 ¹ LS: 0 ^d	Open: 7.83 ± 3.28 ⁵ LS: 7.81 ± 3.31 ⁵
Benlice <i>et al</i> ^[14]	Retrospective	Open: 238 LS: 119	Higher in LS		Not evaluated		Similar incidence of incisional hernia and small bowel obstruction	

¹Included patients with ulcerative colitis and familial adenomatous polyposis; ²Days to first ingestion; ³Based on a multivariate analysis: OR = 0.44 (0.27-0.70) (*P* = 0.01); ⁴Based on a multivariate analysis: OR = 0.67 (0.45-0.99) (*P* = 0.04); ⁵Number of stools per day. ^a*P* = 0.02; ^b*P* = 0.008; ^c*P* = 0.040; ^d*P* = 0.007; ^e*P* < 0.0001. LS: Laparoscopic surgery; PRT: Prospective randomized trial.

The study by Fleming *et al*^[11], which included 339 laparoscopic and 337 open IPAA procedures, showed that the laparoscopic approach was associated with a lower rate of major (OR = 0.67, 95%CI: 0.45-0.99, *P* = 0.04) and minor (OR = 0.44, 95%CI: 0.27-0.70, *P* = 0.01) complications. Accordingly, results from

the American College of Surgeons National Surgical Quality Improvement Program database (ACS-NSQIP, 2005-2008) for all ulcerative colitis patients who underwent colectomy demonstrated that a laparoscopic approach was associated with lower morbidity and mortality (IPAA complication rate: Laparoscopic =

18.2% and open = 29.9%, $P = 0.008$)^[12]. Interestingly, a prospective, randomized study comparing laparoscopic and open IPAA for the treatment of ulcerative colitis and familial adenomatous polyposis was recently conducted by German researchers^[13]. Unfortunately, the study was stopped prematurely due to insufficient patient recruitment, and data for only 21 patients in each arm were reported. The available results revealed that there was no difference in the amount of blood loss between the two groups, as well as that laparoscopic surgery was superior with respect to the length of skin incision, whereas the open approach was superior in the operative duration. However, there were no discrepancies in the length of hospital stay, postoperative pain, bowel function, and quality of life between the approaches. The retrospective cohort study (conducted from January 1992 through December 2007) by Benlice *et al.*^[14] examined 238 open and 119 laparoscopic IPAAs and showed that open and laparoscopic operations were associated with similar incidences of incisional hernia (8.4% vs 5.9%; $P = 0.40$), small-bowel obstruction requiring hospital admission (26.1% vs 29.4%; $P = 0.50$), and small-bowel obstruction requiring surgery (8.4% vs 11.8%; $P = 0.31$). The small study by Tajti *et al.*^[15] showed that there was no difference between laparoscopic and open IPAA regarding the rate of early postoperative complications, whereas the rates of intestinal obstruction (8.7% vs 45%) and sepsis (0% vs 27%) were significantly lower in the laparoscopic group. Conversely, the study by Inada *et al.*^[16], which included only 24 patients, revealed that the percentage of patients requiring a transfusion and having postoperative complications was lower in the laparoscopic group.

A cross-sectional study carried out in 3 university hospitals in the Netherlands and Belgium compared the time to first spontaneous pregnancy between 23 young patients who had undergone open RP-IPAA and 27 young patients who had undergone laparoscopic RP-IPAA. Patient characteristics were similar in both groups. Indications for surgery were ulcerative colitis in 37 patients, familial adenomatous polyposis in 12 patients, and colonic ischemia in 1 patient. A Kaplan-Meier survival analysis was conducted to assess the time to first spontaneous pregnancy and revealed a higher pregnancy rate after laparoscopic IPAA (Log-Rank test, $P = 0.023$). Similarly, a subsequent survival analysis of all the patients with ulcerative colitis showed an increased pregnancy rate in the laparoscopic group (Log-Rank test, $P = 0.033$)^[16]. This result is probably due to the reduced formation of adhesions after laparoscopic colectomy^[17].

Finally, a recent systematic review showed that the incidence of wound infection and intra-abdominal abscess is significantly lower in laparoscopy than in open emergency subtotal colectomy performed in patients with severe acute colitis^[18].

Overall, it appears that there is no clear evidence

that laparoscopic RP-IPAA offers significant advantages over open surgery. Nevertheless, more recent studies indicate that laparoscopic surgery is associated with fewer complications than open surgery. However, the scarcity of randomized, controlled trials makes any definitive conclusions impossible to draw.

ONE- VS TWO-STAGE RP-IPAA

One-stage surgery consists of RP-IPAA without ileostomy and aims to reduce the potential impact of surgery on a patient's quality of life. Many surgeons prefer to perform the entire RP-IPAA operation without the ileostomy^[19-21]. However, other surgeons consider the ileostomy to be useful and mandatory because the rate of complications and number of subsequent laparotomies is higher when diversion is not performed^[22-24].

The large retrospective study by Remzi *et al.*^[25] compared data from patients at a single institution who underwent RP-IPAA either with ($n = 1725$) or without ($n = 277$) a diverting ileostomy. They observed that there were no differences between the two groups with respect to septic complications, quality of life, and functional outcomes and concluded that in patients with stapled anastomosis, tension-free anastomosis, intact tissue rings, normal hemostasis, absence of air leaks, malnutrition, toxicity, anemia, or prolonged consumption of steroids should be considered for one-stage RP-IPAA because the one-stage procedure is safe for these patients and is associated with similar results to those of the 2-stage RP-IPAA. Conversely, a meta-analysis reviewing 17 independent studies and including a total of 1486 patients yielded different results^[26]. Essentially, the study showed that the incidence of anastomotic leakage and pouch-related sepsis was significantly greater in the group without a protective ileostomy. According to the authors of this review, the exclusion of a protective stoma may only be appropriate for specific patients undergoing RP-IPAA, such as those in whom a pouch may be technically easier to perform (*e.g.*, young women not taking corticosteroids and without comorbidities).

It appears that one-stage RP-IPAA may be safe in selected patients and that adequate, randomized studies are necessary to clarify whether protective ileostomy is needed in patients undergoing RP-IPAA.

TWO- VS THREE-STAGE RP-IPAA

Two-stage surgery consists of RP-IPAA and ileostomy during the initial operation, followed by ileostomy closure, whereas the three-stage surgery consists of a subtotal colectomy and ileostomy, proctectomy and pouch creation, and ileostomy closure. The usage rate of a 3-stage RP-IPAA is extremely variable, ranging from 19% to 69%^[27-29]. Data from the ACS-NSQIP have shown that the usage rate of a 3-stage approach remained stable in the United States between 2007 and

Table 3 Studies comparing the mortality and morbidity of 2-stage and 3-stage restorative proctocolectomy with ileal pouch-anal anastomosis

Ref.	Type of study	Number of patients 2- vs 3-stage	Mortality (%)	Post-operative complications (%)	Sepsis/septic shock (%)	Pouch leak (%)	Wound infection (%)	Intra-abdominal abscess (%)	Bowel obstruction (%)	Pouch failure (%)
² Nicholls <i>et al</i> ^[27]	Retrospective	2-stage: 57 3-stage: 95	2-stage: 2 3-stage: 0	2-stage: 49 3-stage: 51	2-stage: 20 3-stage: 17	2-stage: 10.3 3-stage: 3.6	2-stage: 9 3-stage: 12	2-stage: 2 3-stage: 1	2-stage: 9 3-stage: 15	2-stage: 2 ^a 3-stage: 9 ^a
Pandey <i>et al</i> ^[28]	Retrospective	2-stage: 68 3-stage: 50	2-stage: 1.47 3-stage: 0	2-stage: 55.2% 3-stage: 52.2%	Unknown	2-stage: 13.2 3-stage: 8	2-stage: 8.8 3-stage: 7	2-stage: 16.2 3-stage: 6	2-stage: 11.8 3-stage: 9	Unknown
Hicks <i>et al</i> ^[29]	Retrospective	2-stage: 116 3-stage: 28	2-stage: 0 3-stage: 0	Mean number of complications: 1.18 vs 1.29	Unknown	2-stage: 10.3 3-stage: 3.6	Unknown	2-stage: 21.6 3-stage: 21.4	2-stage: 20.8 3-stage: 3.6 ^c	2-stage: 6.7 3-stage: 3.6
Bikhchandani <i>et al</i> ^[30]	Retrospective	2-stage: 1452 3-stage: 550	2-stage: 0.4 3-stage: 0	2-stage: 11.5% 3-stage: 9.4%	2-stage: 9.1 3-stage: 7.4	2-stage: 9.4 3-stage: 6.7 ¹	2-stage: 10.5 3-stage: 13.1 ¹	Unknown	Unknown	Unknown

Differences are not significantly different. ¹Reported as deep organ space infection; ²Studies including patients affected by ulcerative colitis and familial adenomatous polyposis; ^a $P < 0.05$; ^c $P = 0.03$.

2011, with approximately 25% of patients affected by ulcerative colitis in a non-emergent setting undergoing a 3-stage RP-IPAA^[28].

The two-stage RP-IPAA has the advantages of avoiding an additional operation, a shorter hospital stay, administration of less anesthetic, and a shorter time with a stoma compared with the three-stage procedure. The three-stage procedure allows the patients to improve their nutritional status, withdraw from immunosuppressive medications, and resolve any anemia before the pelvic dissection for pouch construction and IPAA, as well as avoid a complex pelvic dissection in the setting of systemic inflammation.

All of the studies that compared 2- and 3-stage RP-IPAA are retrospective (Table 3)^[27-30]. Usually, in these studies, patients who underwent either 2- or 3-stage surgery differed significantly with respect to clinical and laboratory variables as well as the use of steroids and anti-TNF agents^[27-30]. In 1989, Nicholls *et al*^[27] reviewed data from 152 consecutive patients undergoing RP-IPAA (57 two-stage and 95 three-stage) and showed that the anastomotic leakage rate was 10.3% in the 2-stage group and 3.6% in the 3-stage group, with long-term pouch failure rates of 2% and 9%, respectively ($P < 0.05$). The frequency of defecation, frequency of night evacuation, and need for anti-diarrheal medication were reduced in patients who underwent the 3-stage procedure compared with those who underwent the 2-stage procedure. Although a higher proportion of patients in the 3-stage group had emergency surgery compared with the 2-stage group (32% vs 2.6%; $P < 0.01$), there was no advantage to the 3-stage procedure except when urgent surgery was required for the following: (1) a patient had complications of ulcerative colitis; (2) malignancy or Crohn's disease could not be

ruled out; and (3) a patient taking oral steroids with active colitis had a combination of a low hemoglobin value and low serum albumin levels. In the study by Pandey *et al*^[28], 68 ulcerative colitis patients were in the 2-stage group and 50 were in the 3-stage group. The patients in the 3-stage group were more likely to have received aggressive medical therapy, antitumor necrosis factor therapy, and systemic corticosteroids. The overall complication rates were similar between the groups, but infectious complications were significantly higher in the 2-stage group.

Conversely, in the study by Bikhchandani *et al*^[30], the records of 2002 patients (2-stage = 1452 and 3-stage = 550) from the ACS-NSQIP were reviewed, and the 30-d morbidity and mortality rates were found to be similar between the two approaches. Unfortunately, the incidence of anastomotic leakage was not reported. However, the authors reported that the rate of deep organ space infections (which were presumed to be due to a postoperative leak) did not differ between the two approaches. Interestingly, the patients who underwent a 3-stage surgery in this study had more favorable clinical features at the time of IPAA, including decreased preoperative sepsis, corticosteroid use, weight loss, and hypoalbuminemia. Finally, the study by Hicks *et al*^[29] revealed that the 3-stage procedure was associated with a higher frequency of emergency status, greater intraoperative hemodynamic instability, and a lower use of immunomodulators compared with the 2-stage procedure, but the two procedure types were similar with regard to the number of comorbidities and use of either steroids or anti-TNF agents. The patients who underwent the 2-stage surgery had a lower risk of anal stricture but a comparable risk of fistula or abscess formation or pouch failure over the long term compared

with the patients who underwent the 3-stage procedure.

One recent retrospective study showed that a modified 2-stage RP-IPAA (subtotal colectomy with end ileostomy, followed by completion proctectomy and IPAA without diverting ileostomy) compared with the conventional 2-stage RP-IPAA was associated with a significantly lower rate of anastomotic leakage following pouch creation (4.6% vs 15.7%, $P < 0.01$; multivariate analysis: OR = 0.27, 95%CI: 0.12-0.57)^[31].

TYPE OF POUCH

An IPAA can be constructed with an S-reservoir, a J-reservoir, or a W-reservoir. The J-pouch, unlike the S-pouch and W-pouch, can be formed by stapling and requires less time; for this reason, the J-pouch is generally preferred by surgeons.

The meta-analysis conducted by Lovegrove *et al.*^[32] compared the short- and long-term outcomes of J, W, and S ileal reservoirs using data from 18 studies published between 1985 and 2000, with a total of 1519 patients with ulcerative colitis and familial adenomatous polyposis (689 J-pouch, 306 W-pouch, and 524 S-pouch). There were no significant differences between the groups with regard to total postoperative complications, anastomotic leakage, anastomotic stricture, wound infection, pelvic sepsis, pouchitis, and pouch failure. However, the patients with either an S- or W-pouch had a lower frequency of defecation and a reduced need for antidiarrheal medications compared with the patients with a J-pouch, whereas patients with a J-pouch were significantly less likely to require intubation than patients with either an S- or a W-pouch.

However, two recent studies demonstrated that the J- and W-pouches have the same long-term functional results^[32,33]. In the study by Røkke *et al.*^[33], which only included patients with ulcerative colitis, the functional results of the W- and J-reservoir were similar in the middle (2.5 years) and long (11.5 years) term. Similarly, McCormick *et al.*^[34] reported that 24-h bowel movement frequency, daytime frequency, and nocturnal function did not differ between the W- and J-pouch groups at the 9-year follow-up appointments.

Some surgeons prefer the S-pouch because the efferent limb fits well into the anal canal and the body lies on the levators, whereas the blunt end of a J-pouch may be distorted because it is forced into the muscular tube of the stripped anus. In this regard, the retrospective study by Wu *et al.*^[35] showed that patients with an S-pouch, compared with patients with a J-pouch, had fewer bowel movements, less frequent pad use, and a lower fecal incontinence severity index, suggesting that, when constructing the IPAA with the hand-sewn technique, the S-pouch is preferable.

HAND-SEWN OR STAPLED ILEAL POUCH-ANAL ANASTOMOSIS

Two types of pouch-anal anastomoses can be performed

in RP-IPAA: A hand-sewn IPAA (with or without a mucosectomy) of the rectal stump and a stapled pouch-anal anastomosis with conservation of the rectal mucosa.

In 2006, two different meta-analyses were published that compared these two techniques^[36,37]. The meta-analysis by Lovegrove *et al.*^[36] included 4183 patients with ulcerative colitis and familial adenomatous polyposis who underwent formation of an ileal pouch reservoir (2699 patients with a hand-sewn pouch and 1484 patients with a stapled pouch) between 1983 and 2000. Patients with hand-sewn and stapled anastomoses showed similar early postoperative outcomes (anastomotic leak: 8.8% vs 5.2%, $P = 0.42$; pelvic sepsis: 7.2% vs 4.7%, $P = 0.21$; pouch-related fistula: 5.9% vs 2.2%, $P = 0.31$; pouchitis: 2.2% vs 5%, $P = 0.81$; stricture of the anastomosis: 18.2% vs 12.5%, $P = 0.20$; pouch failure: 5.3% vs 2.3%, $P = 0.06$). In addition, the two techniques were similar with regard to stool frequency per 24 h, defecation at night, use of antidiarrheal medication, seepage during the daytime, and daytime pad usage. However, in the hand-sewn group, seepage at night and incontinence of liquid stool occurred more frequently, and the use of pads overnight was more common. The improved nocturnal continence observed in the hand-sewn group was correlated with higher anorectal physiological measurements. Unfortunately, there were insufficient data from the included studies to perform a quantitative and comparative analysis on the incidence of dysplasia in the anal transition zone.

The meta-analysis by Schluender *et al.*^[37], which included four prospective, randomized trials published between 1994 and 2006 that included 180 ulcerative colitis and familial adenomatous polyposis patients, clearly demonstrated that there were no significant differences in functional outcomes between hand-sewn and stapled IPAA, as well as in the resting and contracting sphincter pressures. Based on these results, the authors concluded that, given the potential for persistent cuffitis and/or dysplasia/cancer development in the incompletely removed rectal mucosa after stapled IPAA, the hand-sewn IPAA appears to be preferable.

The large, retrospective study by Kirat *et al.*^[38], which included patients affected by ulcerative colitis and familial adenomatous polyposis, compared 474 hand-sewn and 2270 stapled ileal pouch-anal anastomoses performed at a single institution. Overall, patients with a stapled IPAA had better outcomes and quality of life compared with those with a hand-sewn IPAA. The frequencies of anastomotic stricture, septic complications, bowel obstruction, and pouch failure were significantly lower among the patients who received a stapled anastomosis. In addition, stapled anastomosis was associated with a lower frequency of incontinence, seepage, and pad usage, as well as reduced dietary, social, and work restrictions. Kirat *et al.*^[38] concluded that as long as there are no contraindications (dysplasia, presence of cancer in the rectum or colon), stapled anastomosis is the superior technique with respect to short-, mid-, and long-term outcomes. Nevertheless, the same study analysis

demonstrated that preservation of the anal transitional zone did not lead to the development of cancer in patients monitored for a minimum of ten years^[39].

More recently, a small retrospective study that included patients only affected by ulcerative colitis showed that postoperative complications did not differ significantly between the two pouch groups, with the exception of a greater incidence of postoperative anal fistula in the stapled group ($P = 0.03$). Functional outcomes and long-term quality of life were similar between patients who had received either hand-sewn or stapled IPAA^[40].

CONCLUSION

Regarding the use of RT-IPAA for the treatment of ulcerative colitis, there are few large, randomized, controlled studies, which makes it impossible to draw definitive conclusions regarding controversial issues such as the use of either the open or laparoscopic approach, number of stages of surgery, type of pouch, and pouch construction (*i.e.*, hand-sewn or stapled pouch). The available data from retrospective studies suggest that laparoscopic surgery has no clear advantages over open surgery and that one-stage RP-IPAA may be indicated in qualifying cases. With regard to the 2- and 3-stage RP-IPAA, the fact that patients who underwent 2- and 3-stage surgeries differed significantly with regard to their clinical and laboratory variables makes any comparison extremely difficult. Regarding pouch type, the long-term results show that W- and J-reservoirs do not differ significantly. Finally, the hand-sewn and stapled ileal pouch-anal anastomoses have their own advantages, but there is no clear benefit of one technique over the other. It is suggested that adequate prospective, randomized studies should be conducted in the near future to compare the frequency of post-operative complications, cosmetic results, short- and long-term functional outcomes, and quality of life between the available RT-IPAA techniques for the treatment of ulcerative colitis.

Currently, it is important to emphasize that the choice of the type of surgery should be based on the experience and skills of the performing surgeons in the hospital as well as on each individual case.

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Surgical approach to right colon cancer: From open technique to robot. State of art

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Abstract

This work is a topic highlight on the surgical treatment of the right colon pathologies, focusing on the literature state of art and comparing the open surgery to the different laparoscopic and robotic procedures. Different laparoscopic procedures have been described for the treatment of right colon tumors: Totally laparoscopic right colectomy, laparoscopic assisted right colectomy, laparoscopic facilitated right colectomy, hand-assisted right colectomy, single incision laparoscopic surgery colectomy, robotic right colectomy. Two main characteristics of these techniques are the different type of anastomosis: Intracorporeal (for totally laparoscopic right colectomy, single incision laparoscopic surgery colectomy, laparoscopic assisted right colectomy and robotic technique) or extracorporeal (for laparoscopic assisted right colectomy, laparoscopic facilitated right colectomy, hand-assisted right colectomy and open right colectomy) and the different incision (suprapubic, median or transverse on the right side of abdomen). The different laparoscopic techniques meet the same oncological criteria of radicalism as the open surgery for the right colon. The totally laparoscopic right colectomy with intracorporeal anastomosis and even more the single incision laparoscopic surgery colectomy, remain a technical challenge due to the complexity of procedures (especially for the single incision laparoscopic surgery colectomy) and the particular right colon vascular anatomy but they seem to have some theoretical advantages compared to the other laparoscopic and open procedures. Data reported in literature while confirming the advantages of laparoscopic approach, do not allow to solve controversies about which is the best laparoscopic technique (Intracorporeal vs Extracorporeal Anastomosis) to treat the right colon cancer. However, the laparoscopic techniques with intracorporeal anastomosis for the right colon seem to show some theoretical advantages (functional, technical, oncological and cosmetic advantages) even if all studies conclude that further prospective randomized trials are necessary.

Robotic technique may be useful to overcome the problems related to inexperience in laparoscopy in some surgical centers.

Key words: Mini-invasive right colectomy; Robotic right colectomy; Intracorporeal anastomosis; Extracorporeal anastomosis; Totally laparoscopic right colectomy

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Core tip: We report a topic highlight of the mini-invasive treatment of the right colon pathologies, focusing on the Literature State of Art and comparing the open surgery *vs* the different laparoscopic and robotic procedures. We try to analyze the different current approaches to right colon cancer treatment focusing in particular light and shadows of totally laparoscopic right colectomy compared to other mini-invasive (single incision laparoscopic colectomy, laparoscopic assisted right colectomy, laparoscopic facilitated right colectomy, hand-assisted right colectomy, robotic right colectomy) and open procedure. The two main characteristics of these techniques are the different type of anastomosis: Intracorporeal or extracorporeal and the different incision (suprapubic *vs* median *vs* transverse on right side of abdomen). The different laparoscopic techniques meet the same oncological criteria of radicalism as the open surgery for the right colon. The laparoscopic techniques with intracorporeal anastomosis for the right colon remain a technical challenge but they seem to have some theoretical advantages compared to the other laparoscopic and open procedures described in our study even if further prospective randomized trials are necessary to confirm it.

Fabozzi M, Cirillo P, Corcione F. Surgical approach to right colon cancer: From open technique to robot. State of art. *World J Gastrointest Surg* 2016; 8(8): 564-573 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i8/564.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i8.564>

INTRODUCTION

The laparoscopic treatment for benign and malignant pathologies of the left colon and rectum is actually accepted and validated. Laparoscopy advantages are widely demonstrated in term of: Post-operative pain reduction, early resumption of the intestinal function, decreasing in hospital stay, time to return to work and better cosmetic results. The oncologic outcomes are the same than open surgery^[1]. These results are also achieved thanks to the development of Kehlet "Fast-Track" recovery protocols. The laparoscopic technique for the right colon instead, had a slower diffusion probably for the complexity of right colon laparoscopic anatomy and the variability of the vascular peduncles that require a greater laparoscopic experience than left

colon and rectum surgery. For these reasons, many surgeons consider the laparoscopic approach to right colon an useless and complex waste of time^[2].

Different laparoscopic hybrid procedures developed but there are not sure evidences which is the best one and also the role of laparoscopy itself in the right colon treatment remains controversial.

The aim of the study is to critically analyze the literature state of art on right colectomy, focusing on the lights and shadows of laparoscopic and robotic approach in relation to open surgery and comparing the different laparoscopic procedures.

MINI-INVASIVE PROCEDURE FOR RIGHT COLON CANCER

Right colectomy is indicated for malignant pathologies involving the intestinal tract between the ileocecal Bahuino valve and the colonic hepatic flexure. Laparoscopic resection must respect the same oncologic criteria as the open approach including: "no-touch isolation technique", isolation and ligation of the vascular pedicles at the origin, oncologic lymphadenectomy and "distal and radial clearance" of the neoplasm from resection margins^[3,4].

Different laparoscopic procedures have been described for the treatment of right colon tumors: (1) totally laparoscopic right colectomy (TLC) which provides all steps conducted in laparoscopy including Intracorporeal ileo-colic Anastomosis (IA)^[5]; (2) single incision laparoscopic surgery (SILS) for right colon (SILC) allows to perform the intervention laparoscopically (with intracorporeal anastomosis) through larger multichannel single (about 3 cm diameter) trocar and curved instruments^[6,7]; (3) laparoscopic assisted right colectomy (LAC) which provides laparoscopic vessel ligations and right colon mobilization but the ileo-colic Anastomosis is performed extracorporeally by open incision (EA)^[8,9]; (4) laparoscopic facilitated right colectomy (LFC), a variant of laparoscopic assisted, which provides only the laparoscopic right colon mobilization while the vessels ligation and anastomosis are extracorporeally (EA)^[10]; (5) hand-assisted right colectomy (HAC) with laparoscopic mobilization of colon by hand help through a right side minilaparotomy and extracorporeal anastomosis^[11,12]; and (6) robotic right colectomy (RRC) with manual intracorporeal anastomosis^[13].

The two main characteristics of these techniques are the different type of anastomosis and minilaparotomies. The anastomosis may be performed in intracorporeal way for TLC, SILC and RRC or extracorporeally for LAC, LFC, HAC and open right colectomy. The minilaparotomy is generally performed in suprapubic region (a Pfannes-tiel of about 5-6 cm) in the TLC, SILC^[14,15] and RRC for the specimen extraction while it is performed median in periumbilical site or transverse in right side of abdomen (about 10-12 cm of length) in LAC, LFC, HAC and open surgery to extract the specimen and to make the EA.

Table 1 Laparoscopic vs open right colectomy: Comparison of short term outcomes

Ref.	Patient number LS/OS	Mean operative time (min) LS/OS	Blood loss (mL) LS/OS	Harvested nodes LS/OS	First flatus/defecation (d) LS/OS	P.O. Complications (patients) LS/OS	Hospital stay LS/OS	Mortality LS/OS
Ramacciato <i>et al</i> ^[20]	33/33	251/222.9 ¹	135/404 ¹	12.7/18 ¹	3.15/3	1/4 ¹	11.2/13.8 ¹	0/0
Khan <i>et al</i> ^[21]	89/75	120/NR	NR	15/13	NR	0/4 ¹	4/8 ¹	0/4 ¹
Veldkamp <i>et al</i> ^[22]	627/621	145/115 ¹	100/175 ¹	NS	3.6/4.6 ¹	NS	8.2/9.3 ¹	NS
Lohsiriwat <i>et al</i> ^[23]	13/20	207.7/104.5 ¹	120/107	29.2/18.8	2.4/2.6	1/0	6.2/7.1	0/0
Guillou <i>et al</i> ^[24]	484/253	NR	NR	12/35	5/6	NR	9/11	21/13
Abdel-Halim <i>et al</i> ^[25]	22/34	187/130 ¹	NR	23.8/21.2	3/4 ¹	4/9	6/10 ¹	1/2
Zhao <i>et al</i> ^[26]	119/101	170.7/244.4	100/150 ¹	22.3/21.8	2.7/3.2 ¹	11.8/17.6%	11.4/12.8 ¹	1/1

¹Data are statistically significant ($P < 0.05$). NS: Data are not statistically significant; NR: Data are not reported; LS: Laparoscopy; OS: Open surgery.

In the SILC, the specimen extraction can also be performed through the umbilicus eventually used to make the anastomosis extracorporeally^[16].

SHORT AND LONG TERM OUTCOMES: LAPAROSCOPY VS OPEN SURGERY

Several studies including meta-analysis demonstrated the advantages of laparoscopic vs open approach for the treatment of right colon cancer in short term outcomes (Table 1): Minimal invasiveness, reduced blood loss, less postoperative pain, earlier first flatus, shorter hospital stay and reduced rate of wound infections and incisional hernias. No differences, instead, were found between the two techniques for other complications such as: pneumonia, anastomotic leaks, ileus, deep venous thrombosis or pulmonary embolism^[17]. The number of nodes taken out, the post-operative (p.o.) mortality and cancer recurrence were not statistically different in the two groups^[17-26].

In some studies, the operative time was statistically longer in laparoscopy (LS) and it is connected to the learning curve^[27].

The limits of the studies reported in literature are related to the lack of double blinded randomized clinical trials which determines selection bias, to the different experience of the Surgical Centers which cannot be judged by a single paper and to different patient's management. Consequently, more randomized clinical trials with same standardized preoperative and postoperative enhanced protocols for patient's management must be conducted by High Specialized Surgical Centers.

About long term outcomes, the study of Guerrieri *et al*^[28] reported in the open surgery group an increased risk of local recurrence, metastasis and cancer-related mortality, while a meta-analysis of Reza *et al*^[29] showed no difference between LS and open surgery (OS) groups for cancer related mortality or disease recurrence during five-year follow-up. Han *et al*^[30] confirmed the same results with no statistically difference between LS and OS groups for overall survival at 1-, 3- and 5-year follow-up for all tumor stages.

LAPAROSCOPIC COLECTOMY SHORT AND LONG TERM OUTCOMES: INTRACORPOREAL (TLC) VS EXTRACORPOREAL ANASTOMOSIS (LAC, LFC AND HAC)

A recent meta-analysis of Feroci *et al*^[31] compares the intracorporeal and extracorporeal anastomosis considering short term outcomes. The two techniques do not show significant differences in term of mortality, surgical and non surgical complications. In Fabozzi *et al*^[32] study, the TLC (with IA) group presents some advantages about post-operative recovery in particular regarding: Earlier first flatus, earlier food intake, reduced analgesic consumption, shorter hospital stay vs LAC (with EA) group (Figure 1). These better results may be explained by the less intestinal manipulation in the IA group thanks to the lesser dissection (lesser p.o. adhesions) and mobilization of transverse colon at the cost of longer operative time and higher laparoscopic experience^[32-34].

On the contrary, some authors (Table 2) reported different results: shorter operative time and hospital stay in LAC vs TLC group, remarking the necessity of further controlled studies^[9,32,33,35-38].

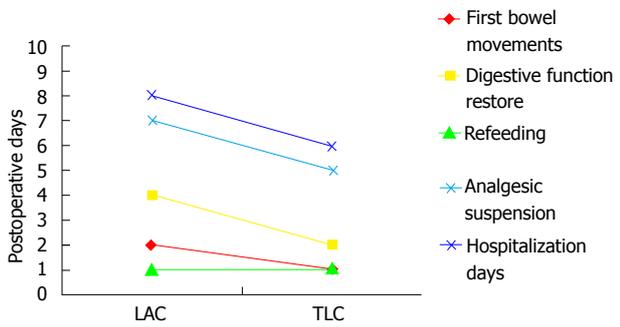
All authors, fortunately, agree about the absolute indication to TLC with IA in obese patients, who present some factors interfering with EA: Greater wall thickness, shorter and thick mesentery causing the necessity of enlarging minilaparotomy to perform the colonic resection and EA.

The goal of treatment in colon cancer outcomes should be the number of lymph nodes harvested: This is similar in TLC (IA) and LAC (EA) groups because the vessel ligation was conducted in the same intracorporeal way (Table 2). The lymph nodes removal, in fact, is influenced by the level of vessel ligation which must be performed at the origin from Superior Mesenteric Artery. This technical point explains why it is more difficult to obtain a sufficient number (at least 12) of lymph nodes through a right sided abdominal small

Table 2 Totally laparoscopic right colectomy vs laparoscopic assisted right colectomy: Comparison of short term outcomes

Ref.	Patient number TLC/LAC	Length of skin incision (mm) TLC/LAC	Mean operative time (min) TLC/LAC	Blood loss (mL) TLC/LAC	Harvested nodes TLC/LAC	First flatus/defecation (d) TLC/LAC	P.O. Complications (patients) TLC/LAC	Hospital stay TLC/LAC	Mortality TLC/LAC
Roscio <i>et al</i> ^[33]	42/30	48.2/71 ¹	176.5/186.3	31.2/43.3	25.9/22	2.9/3.4 ¹	1/2	6.2/7.2 ¹	0/1
Fabozzi <i>et al</i> ^[32]	50/50	60/120 ¹	78/92 ²	NR	16/17	1.3/2.6 ¹	0/14 ¹	5.3/7.6 ¹	0/0
Scatizzi <i>et al</i> ^[35]	40/40	50/40	150/150	NR	30/26	0/1	3/3	5/5	0/0
Hellan <i>et al</i> ^[36]	23/57	40/50 ¹	190/180	50/100	18/17	NS	6/14	4/4	0/1
Magistro <i>et al</i> ^[9]	40/40	55/72 ¹	230/203 ¹	NR	22/20	2.2/2.6 ¹	7/8	6.3/6	0/1
Chaves <i>et al</i> ^[37]	35/25	NR	226/208 ¹	NR	20.6/14.2	3/4 ¹	7/5	6/8 ¹	1/1
Grams <i>et al</i> ^[38]	54/51	NR	190/156 ¹	NS	NR	2/2.4	6/15	3.2/3.8 ¹	1/1

¹Data are statistically significant ($P < 0.05$). NS: Data are not statistically significant; NR: Data are not reported; TLC: Totally laparoscopic right colectomy; LAC: Laparoscopic assisted right colectomy.



Fabozzi *et al.* Surg Endosc (2010)

Figure 1 Comparison between laparoscopic assisted right colectomy and totally laparoscopic right colectomy. From Fabozzi *et al*^[32].

incision of the LFC and HAC.

The right colon dissection with the median to lateral approach in TLC in fact, consents to achieve a good exposure of all colonic vessels: The ileo-colic trunk, the right colic artery, the right branch of the median colic artery (Figure 2A). The most difficult step is the nodal dissection at the origin of the median colic vein and of the Henle's trunk that could increase a risk of bleeding, so a great expertise and laparoscopic skill are requested^[39].

TLC provides a mechanical (stapled side to side anastomosis) IA (Figure 2B) while EA procedures can have a stapled or hand-sewn anastomosis. A recent Cochrane systematic review reported a lower rate of anastomotic leakage in stapled ileo-colic anastomosis compared to hand-sewn anastomosis^[40]. The safety of both types of side to side anastomosis (hand-sewn running suture anastomosis vs stapled EA) is well known but the advantages of mechanical anastomosis could be due to the standardization of anastomosis (60 mm blue cartridge) and the faster performance that do not depend from the ability of surgeon^[31].

In Fabozzi *et al*^[32] TLC has better postoperative recovery outcomes such as shorter hospital stay, faster bowel movements and also better aesthetic results thanks to the minor size and site of minilaparotomy (in suprapubic region) (Figure 2C) which also determines less post-operative pain and p.o. analgesia and less

risk of incisional hernias. The suprapubic incision (in IA procedures) in fact, is subjected to less abdominal pressure (compared to right sided abdominal incision in EA procedures) and it is not influenced by diaphragmatic movements that can increase the p.o. pain. Moreover, the pain of the right side incision (Figure 2D) can also reduce diaphragmatic and respiratory movements determining a higher risk of pulmonary infections (Table 3)^[31,32].

Other studies compare transverse vs midline incision showing better outcomes in term of p.o. morbidity, hospital stay and incisional hernia in the first one^[33,41,42].

The cost of procedures is lower in case of EA (Open, LAC, LFA) compared to IA of TLC and RRC due to longer operative time and use of instruments but the cost of drugs is significantly higher in EA than IA group related to duration of p.o. use of analgesics^[31]. The only one study published on the long term results is by Lee *et al*^[43], reporting no difference in survival and disease free survival at 3 years follow-up between the two groups (IA vs EA).

The limits of literature data depend on the large amount of non-randomized studies which leads to a bias giving preferential choice to the more difficult technique (TLC with IA).

Open questions remain the operating time that is related to the learning curve to reach the laparoscopic suture skill, and the oncological long term results connected to a correct nodal clearance for which there is lacking of high grade evidences.

SILC VS MULTIPORT LAPAROSCOPIC RIGHT COLECTOMY

Single incision laparoscopic surgery is a recently introduced mini-invasive procedure performed through single skin access of 3-4 cm using a larger multichannel port. It was first used for laparoscopic colecistectomy and appendectomy and later it has been tested for other procedures^[16]. Colorectal SILS was first performed in 2008^[44]. The umbilicus is the most common access for the SILS procedures (in particular for right colon) but some surgeons prefer to use other

Table 3 Comparison between different minilaparotomies in right colectomies

Laparotomy	Suprapubic	Right hypocondrium
Dimension	↓	↑
Wound infection	↓	↑
Incisional hernia	↓	↑
P.O. pain	↓	↑
Respiratory function	↓	↑

From Fabozzi *et al*^[32].

sites (such as the right side of abdomen) for example when a diverting stoma is planned^[7,16]. The SILC port is generally composed by 3 or 4 channel (depending on type): 1 of 10 mm for the 30° camera, 1 of 12 mm for stapler or other instruments and other 1 or 2 channels of 5 mm for specific curved instruments to allow the inverse triangulation and to facilitate the movements in operative field^[15,16]. The specimen was generally removed through a suprapubic incision or enlarging (if necessary) the umbilical incision^[7,15,16]. Despite the experience in SILS is recently improved and many papers are appeared in literature, the technical difficulties of procedure, the prolonged learning curve and the oncological results are still object of discussion^[16,45].

Recent study of Yun *et al*^[46] reported same oncologic results in SILS compared to conventional laparoscopy for colon cancer.

A systematic review on 881 patients (389 SILC vs 492 Multiport) of Vettoretto *et al*^[47] reported no statistical difference between the two techniques in morbidity and mortality, number of lymphnodes harvested and disease free survival at 24 mo. Other outcomes such as operative time, post-operative analgesic use, blood loss, anastomotic leaks rate, first flatus and hospital stay were not analyzed due to the lack of data.

A randomized clinical trial of Poon *et al*^[48] on 25 patients reported a reduced p.o. pain and hospital stay in SILS procedure even if further randomized clinical trials are necessary.

In the SILS specimen extraction can be performed through the umbilicus, also used to make the anastomosis extracorporeally. The extracorporeal anastomosis allows shorter operative time, so some surgeons prefer it especially in their early experience. Instead, the minilaparotomy can be performed in suprapubic region to extract the specimen when intracorporeal anastomosis is made^[47].

A certain benefit of SILS is the better cosmetic result comparing to the other mini-invasive and open procedures even if some authors think that cosmetic evaluation must be made after the complete wound healing^[49].

Another metanalysis of Yang *et al*^[50] reported smaller incisions, less blood lost and more lymphnodes removed with same results in p.o. morbidity and operative time.

With the progressive diffusion of the SILS and the improvement of surgeons experience, its cost became

almost the same of conventional laparoscopy^[49].

SOMETHING ABOUT LS VS RS

The major spreading of EA techniques depends on their major feasibility compared to IA of TLC. The use of Robot (Da Vinci System™) has simplified the laparoscopic procedure allowing the surgeons who do not make laparoscopy to overcome the learning curve of minimally invasive surgery. The robotic technique plays the same steps of open surgery with the advantages of the minimally invasiveness (including the better vision) but it is easier than laparoscopy.

According to Trastulli *et al*^[13] the use of Robot facilitates an extended lymphadenectomy through a complete mesocolon excision if compared to laparoscopy.

Robotic surgery is safe and could be an effective alternative to conventional LS. Like laparoscopy, it avoids the big incision, reduces pain, allows early mobilization, and diminishes general (respiratory and circulatory) and local complications (wound infection and incisional hernia). Global morbidity and mortality rate is generally lower than all types of corresponding open interventions.

Moreover, the Da Vinci Intuitive Xi™ Robotic System could allow interventions to be more effective and reliable than traditional laparoscopic techniques and faster in terms of operative but not total time because it includes the time for system setup too. Robotic surgery, restoring the hand-eye coordination and three-dimensional view lost in laparoscopic surgery, filtering hand tremors, giving more freedom degrees to instruments and amplifying different motion scale, could allow to perform complex procedures with greater precision and better results^[51,52]. Thus, difficult laparoscopic interventions may become easier to perform, and the indications for robotic and minimal invasive surgery could be generally extended despite the long setup time.

A recent meta-analysis of Xu *et al*^[53] reports the advantages of robotic approach compared to laparoscopy in treatment of right colon cancer. In particular, RRC seems to be associated with lower blood losses, reduced p.o. complications and a faster restore of bowel functions despite a long operative time. In literature the benefits of laparoscopy vs open surgery in the treatment of colorectal surgery are well known: Smaller incision, less blood loss, less p.o. pain, early resume to normal diet and intestinal function, short hospital stay and quickly return of the patients to daily life activities. On the other side, the laparoscopic approach for the right colon shows some technical difficulties connected to the lack of fixed anatomical landmarks (as we mentioned before) and to the laparoscopy itself such as the lack of three dimensional vision, the complex dissection and suturing, so it is performed only by expert surgeons with good results. The Da Vinci Xi Robot System™ allows to overcome all laparoscopic technical difficulties (three dimensional vision, easy

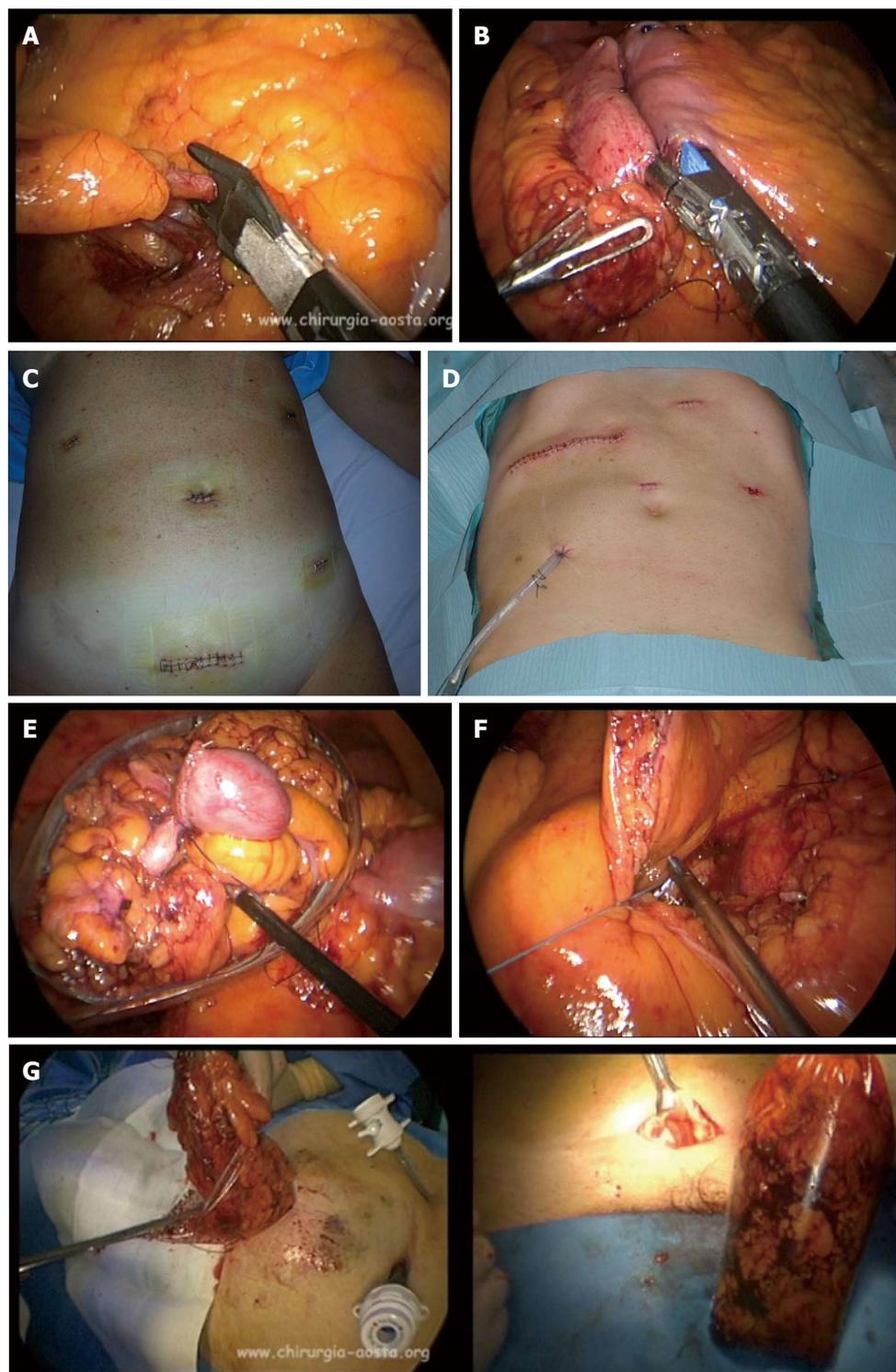


Figure 2 The right colon dissection. A: Ileo-colic artery and vein laparoscopic ligations; B: Ileo-colic mechanical anastomosis in totally laparoscopic right colectomy (TLC); C: Trocar sites and minilaparotomy site of TLC; D: Trocar sites and minilaparotomy site of laparoscopic assisted right colectomy (LAC); E: Right colon positioning in endobag during TLC; F: Mesentery laparoscopic suturing; G: Right colon removal by endobag in TLC.

suturing, filtering tremor movements with surgeon comfortable sitting) combining the advantages of minimally invasive surgery and open surgery^[53].

Actually, the higher costs of the robotic surgical instruments, as compared with the cost of the laparoscopic instruments, represent the real disadvantage of

this new technique.

However, the absence of a sufficient number of patient follow-up in the literature does not allow having data on long term results.

A schematic representation of the advantages or disadvantages of each technique is reported in Table

Table 4 Comparison between open right colectomy, laparoscopic assisted right colectomy, totally laparoscopic right colectomy, single incision laparoscopic Surgery for right colon and robotic right colectomy

Parameters	Open right colectomy	LAC	TLC	SILC	RRC
Laparotomy site and dimension	Transverse (on right side) Median (10-12 cm)	Transverse (on right side) (7-13.5 cm)	Suprapubic (48-13 cm)	Suprapubic Umbilical (median) (3-4.5 cm)	Suprapubic (4-6 cm)
Type of anastomosis	EA	EA	IA	IA/EA	IA
3D vision	Yes	No	No	No	Yes
Surgeon hand tremor filtering	No	No	No	No	Yes
High-precision movements and suturing	No	No	No	No	Yes
Technical difficulty	↓	↑	↑↑	↑↑↑	↓
Surgeon's comfort (dock station)	↓	↓	↓	↓↓↓	↑
Patient's comfort	↓	↓	↑↑	↑↑	↑↑
Costs	↓	↑	↑	↑	↑↑↑

LAC: Laparoscopic assisted right colectomy; TLC: Totally laparoscopic right colectomy; SILC: Single incision laparoscopic surgery for right colon; RRC: Robotic right colectomy.

4^[13,14,16,29,32,33,41,47,51,52].

CONCLUSION

The different laparoscopic techniques meet the same oncological criteria of radicalism as the open surgery for the right colon: Absence of tumor manipulation (“no touch techniques”), section at the origin of the right vascular peduncles and the “distal and radial clearance” of the neoplasm margins^[54]. The TLC and even more the SILC with IA remain a technical challenge due to the complexity of procedures (especially for the SILC) and the particular right colon vascular anatomy but they seem to have some theoretical advantages than the other mini-invasive and open procedures^[26,32,33,46].

Oncologic advantages

The extraction of the operative specimen by 15 cm endobag through a suprapubic incision prevents the tumor squeezing and neoplastic cells spreading (Figure 2E and G).

Technical advantages

The closure of mesentery by non-absorbable running suture (Figure 2G) especially in obese patients is easier in laparoscopic procedures with IA thanks to its better vision and exposure. The laparoscopic suturing of mesentery reduces the risks of internal hernia and avoids traction on vascular and nervous peduncles (as it could happen in case of EA) which is one of the cause of the delayed canalization.

Functional advantages

The suprapubic incision (a little Pfannestiel) for the specimen removal is smaller (about 5 cm) than other laparoscopic techniques (about 8 cm) and open technique (about 10 cm) (Figure 2C and D). The smaller dimension and the site of incision reduce the post-operative pain with less assumption of analgesic drugs, promoting early mobilization of patients and recovery of intestinal function, better respiratory exchanges,

better tissue (and anastomotic) oxygenation, faster healing and coming back to ordinary life. In fact, the major dimensions and right sided abdomen (or median) incision of non totally laparoscopic and open techniques with muscles section cause greater pain, reducing the respiratory excursions especially in the elder and favouring pulmonary complications with prolonged hospitalization and higher risk of incisional hernias as reported by some authors^[32,33,36,41,42] (Table 3).

Cosmetic advantages

The smaller dimension and the suprapubic (TLC, SILC) or umbilical (SILC) site incision determine better aesthetic results than other mini-invasive and open right colon techniques (larger incision on the right side of the abdomen).

Although some good short term outcomes, TLC and SILS with IA have the limitation of a minor tactile feedback and a steep learning curve (longer in SILS)^[16,45]. Despite advances in technologies and devices, the laparoscopic procedures require dexterity and technical skill. In a study of Tekkis *et al*^[27] the evidences demonstrated that colorectal surgeons with an experience of 0-25 procedures have a significant higher risk of conversion to open surgery respect to surgeons with over 175 procedures. Surgeons with a 25 laparoscopic colectomies experience employed a median of 180 min for procedure, while at the 175th procedure the median operating time is 115 min. To reach good results with TLC, it is mandatory to overcome specific technical steps (laparoscopic intracorporeal running suture, mechanical stapler use, correct bowel orientation) supported by expert staff assistance and advanced technology.

After these assumptions, TLC may be considered feasible and safe techniques, even if it requires a great experience not only in laparoscopy but also in open surgery to ensure better p.o. results, better comfort for the patients and similar oncological outcomes to the open surgery^[27,32,55].

The SILC may be considered a valid alternative

to TLC thanks to similar p.o. outcomes but a longer learning curve than TLC is required in addition to a great experience in laparoscopic and open surgery. It seems to report better cosmetic results, even if in TLC, the suprapubic scare would be also covered by the brief. It not clear instead, if it has an higher incisional hernia rate or p.o pain due to the median site of incision compared to suprapubic incision (of TLC) and right sided incision of other procedures^[32,36,41,42,47].

Recently, an early experience of Robotic SILC reported a longer operative time, higher conversion rate and 27% of p.o. complications rate (in particular: Wound hematomas, infections and incisional hernias of the umbilicus)^[56].

The LAC instead, could be considered an alternative to both TLC and SILC for the surgeons with early experience in laparoscopic advanced procedures or to avoid a primary open surgery of the right colon or a conversion to open surgery due to technical problems related to difficult anatomy, surgical experience or intraoperative complications untreatable in laparoscopy^[57].

Some authors report that HAC procedure has not advantages respect to LAC in term of clinical and oncological results but it could have some advantages in case of bulky tumors treatment^[11].

Data reported in literature while confirming the advantages of laparoscopic approach, do not allow to solve controversies about which is the best laparoscopic technique (IA vs EA) to treat the right colon cancer: some authors consider a mini-invasive right colectomy with IA as "a triumph of technique over the common sense" while for others is "an illogical waste of time". For these reasons, all the studies reported in literature conclude that further prospective randomized trials are necessary.

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Can the prognosis of colorectal cancer be improved by surgery?

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Abstract

Surgical resection is the only curative treatment modality

for colorectal cancer limited locally. Evidence for the kind of resection procedure that is effective for improving prognosis is insufficient. Prognosis improvement is expected with the no-touch isolation technique (NTIT), making it the most important resection procedure. We are conducting a multicenter randomized controlled trial (RCT) to confirm the efficacy of NTIT in patients with colorectal cancer. The present review serves as a preface to our trial, as it focuses on basic and clinical studies that support the efficacy of NTIT. The detection ratios of circulating tumor cells (CTCs) of peripheral blood indicate the progress and prognosis of colorectal cancer. In a rabbit liver tumor model, metastases increased after surgical manipulation. Also, CTCs increased during the radical excision of colorectal cancer. However, NTIT decreased the detection of CTCs of intraoperative portal vein blood in patients with colorectal cancer. Although these aforementioned results support the use of NTIT, a previous controlled prospective trial was not able to confirm the clinical benefit of NTIT, as it had an insufficient sample size and many patients were lost to follow-up. Therefore, we initiated a large-scale high-quality RCT to confirm the efficacy of NTIT for colorectal cancer.

Key words: Colorectal cancer; General surgery; No-touch isolation technique; Circulating tumor cells; Randomized controlled trial

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Core tip: Currently, we are conducting a multicenter randomized controlled trial to confirm the efficacy of the no-touch isolation technique (NTIT) in patients with colorectal cancer. A previous controlled prospective trial was not able to confirm the clinical benefit of NTIT, as it had an insufficient sample size and many patients were lost to follow-up. However, basic and clinical studies have supported the use of NTIT for treating colorectal cancer. The present review serves as a preface to our

trial, as it provides background information on whether the prognosis of colorectal cancer is improved by surgery.

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INTRODUCTION

Surgical resection is the only curative treatment for colorectal cancer limited locally. The purpose of surgical resection of primary colon cancer is complete removal of the tumor, major vascular pedicles, and lymphatic system of the affected colonic segment^[1]. Total mesorectal excision^[2-5] and complete mesocolic excision (CME)^[6] for colon and rectal cancers, respectively, reduce tumor recurrence after curative resection. Furthermore, Japanese D3 dissection is similar to CME^[7]. However, evidence for the kind of resection procedure that is effective for improving prognosis is insufficient. The no-touch isolation technique (NTIT) is the most important resection procedure, because prognosis improvement is expected. NTIT was first proposed in the 1950s^[8]. In this technique, central vascular ligation is the first priority, and it is followed by mobilization of the tumor-bearing segment of the colon. This technique aims to reduce cancer cells flowing from the primary tumor site into the liver and other organs by ligating the blood vessels first. A retrospective study showed improvement in prognosis with this technique^[9], but a randomized controlled trial (RCT) failed to prove its efficacy with statistical significance^[10]. Therefore, NTIT is not regarded as a standard technique in current guidelines^[1]. Currently, we are conducting a multicenter RCT to confirm the efficacy of NTIT in patients with colorectal cancer undergoing open surgery^[11]. In this trial, the conventional technique gives first priority to mobilization of the tumor-bearing segment of the colon, which is followed by central vascular ligation and ligation of other vasculature. Conversely, NTIT gives first priority to central vascular ligation, which is followed by mobilization of the tumor-bearing segment of the colon. This trial is designed to confirm the superiority of NTIT over the conventional technique in terms of disease-free survival. We hypothesize that the 3-year disease-free survival of the NTIT arm will be greater than that of the conventional technique arm (75%) by 6%. According to the method of Schoenfeld and Richter, the sample size will be 840 patients (420 patients per arm) with a one-sided alpha level of 5% and power of 80%, and 259 events are expected to occur within 3 years of accrual and 3 years of follow-up. Considering that some patients will be lost to follow-up, the total target sample size is set at 850 patients. We secured statistically sufficient cases in this

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RCT, and we described the quality control of the follow-up and the surgery in the protocol. The present review serves as a preface to our trial, as it focuses on basic and clinical studies that support the benefit of NTIT for colorectal cancer.

DISCUSSION

Does the detection ratio of circulating tumor cells of peripheral blood indicate the progress and prognosis of cancer?

Numerous articles have been published about the relationship between cancer-bearing patients and circulating tumor cells (CTCs), but two meta-analyses have generalized this point well.

In the first meta-analysis^[12], five studies reported on the incidence of CTCs in lymph node involvement positive and negative groups, and three of those studies showed a statistically significant increase in the lymph node involvement positive groups compared with that in the lymph node involvement negative groups. A meta-analysis of all the studies showed a significantly higher incidence of CTCs in the lymph node involvement positive groups (50%) than in the lymph node involvement negative groups (21%). Five studies reported the rate of hepatic metastases at maximal follow-up in patients who were CTC positive and negative, and two of those studies demonstrated a statistically significant hepatic metastases rate in patients who were CTC positive compared with that in those who were CTC negative. A meta-analysis of all the studies indicated a significantly increased hepatic metastases rate of 21% in patients who were CTC positive compared with 8% in those who were CTC negative. Three studies reported the incidence of CTCs in different stages, and no study showed a significant difference between CTC positive and negative groups. A meta-analysis of all the studies showed a significantly lower incidence of CTCs in stage I and II groups (17%) than in stage III groups (32%). When stage I and stage II tumors were compared, the incidence of CTCs was higher in stage II (19%) than in stage I (12%), but this was not statistically significant. Three studies reported disease-free survival with data extracted at 1-3 years. Disease-free survival was significantly higher in the CTC negative groups than in the CTC positive groups at 1 year, 2 years, and 3 years after resection.

In the second meta-analysis^[13], 36 studies (3094 patients) were eligible for the final analyses. Pooled analyses showed that the detection of CTCs in the peripheral blood compartment was a statistically significant prognostic factor of recurrence-free survival [HR = 3.06 (95%CI: 1.74-5.38) and overall survival (OS) = 2.70 (1.74-5.38)].

Do metastases increase after surgical manipulation of the tumor?

Nishizaki *et al.*^[14] perform and experiment on liver tumors in a rabbit model and reported the results. In

this experiment, they inoculated carcinoma in a rabbit liver, and they separated the rabbits into two groups according to the presence or absence of manipulation before hepatectomy. Then they compared the number of tumors in the hepatic vein, number of metastases in the lung, and prognosis between the two groups. The incidence of vascular permeation of liver tumor cells into the hepatic vein was significantly higher in the manipulation group than in the non-manipulation group ($P < 0.01$). On the fourteenth day after tumor resection, the number of metastatic nodules in the lung was significantly increased in the manipulation group compared to that in the non-manipulation group ($P < 0.01$). The survival of rabbits after tumor resection was significantly shorter in the manipulation group than in the non-manipulation group ($P < 0.01$).

Do CTCs increase during the radical excision of colorectal cancer?

Weitz *et al.*^[15] used cytokeratin 20 reverse transcription polymerase chain reaction (RT-PCR) to detect CTCs in the peripheral vein preoperatively, intraoperatively, and postoperatively. Blood samples were taken from 65 patients who were undergoing resection of primary colorectal cancer. As the depth of tumor invasion deepened, the rate of detection of CTCs increased. Also, as the lymph node metastatic degree advanced, the rate of detection of CTCs increased. In addition, regarding the timing of the measurement, the rate of detection of CTCs was the highest intraoperatively. These data indicate that surgery enhances the release of CTCs into circulation.

Do CTCs increase during the resection of colorectal cancer liver metastasis?

Koch *et al.*^[16] also used cytokeratin 20 RT-PCR to detect CTC in the central vein preoperatively, intraoperatively, and postoperatively. Blood samples were taken from 37 patients who were undergoing resection of liver metastases. Concerning the timing of the measurement, the rate of detection of CTCs was highest intraoperatively. This was similar to the finding of colorectal cancer primary tumor surgery. When CTCs were detected during the resection of liver metastasis, the prognosis was poor.

Does NTIT decrease the detection of CTCs in intraoperative portal vein blood?

Hayashi *et al.*^[17] measured CTCs of portal vein blood using the mutant-allele-specific amplification method. They examined a ratio of CTCs of intraoperative portal vein blood by comparing the conventional technique and NTIT. For the conventional technique, CTCs were confirmed in 73% of cases, but for NTIT, CTCs were only confirmed in 14% of cases. As the use of NTIT reduces CTCs during surgical manipulation, they concluded that this technique may be effective for preventing metastases in those with colorectal cancer.

Was the clinical use of NTIT proven in the controlled prospective trial that compared NTIT and the conventional technique?

Wiggers *et al.*^[10] conducted a controlled prospective trial to assess the effect of NTIT on the treatment of colon cancers. This trial is the only RCT that has been published on this topic. Two hundred and thirty-six patients were prospectively and randomly assigned to undergo NTIT or the conventional technique. OS did not differ significantly between the two groups. This RCT failed to prove the efficacy of NTIT with statistical significance. After the results of this trial were published, NTIT was not regarded as a standard technique in current guidelines. However, there was a trend of good survival and disease-free survival in the NTIT group in the RCT. After a detailed review of the RCT, we concluded that the RCT could not show the superiority of NTIT because it had an insufficient sample size and many patients were lost to follow-up. Therefore, we initiated a large-scale RCT to confirm the efficacy of NTIT in patients with colorectal cancer^[11]. Furthermore, we considered a collateral study to obtain basic proof for this clinical trial. We thought that significant data would be needed to confirm the presence or absence of CTCs in the portal vein blood or peripheral blood intraoperatively or postoperatively. However, we were unable to establish this accompaniment study because of cost.

CONCLUSION

Although the results of basic and clinical studies support the benefit of NTIT, a previous controlled prospective trial was not able to confirm the clinical efficacy of NTIT, but it had an insufficient sample size and many patients were lost to follow-up. Therefore, we are currently conducting a large-scale high-quality RCT to confirm the efficacy of NTIT in patients with colorectal cancer.

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Retrospective Study

Hand-assisted laparoscopic restorative proctocolectomy for ulcerative colitis

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Abstract

AIM

To evaluate the utility of hand-assisted laparoscopic restorative proctocolectomy (HALS-RP) compared with the conventional open procedure (OPEN-RP).

METHODS

Fifty-one patients who underwent restorative total proctocolectomy with rectal mucosectomy and ileal pouch anal anastomosis between January 2008 and July 2015 were retrospectively analyzed. Twenty-three patients in the HALS-RP group and twenty-four patients in the OPEN-RP group were compared. Four patients who had purely laparoscopic surgery were excluded. Restorative total proctocolectomy was performed with mucosectomy and a hand-sewn ileal-pouch-anal anastomosis. Preoperative comorbidities, intraoperative factors such as blood loss and operative time, postoperative complications, and postoperative course were compared between two groups.

RESULTS

Patients in both groups were matched with regards to patient age, gender, and American Society of Anesthesiologists score. There were no significant differences in extent of colitis, indications for surgery, preoperative comorbidities, and preoperative medications in the two groups. The median operative time for the HALS-RP group was 369 (320-420) min, slightly

longer than the OPEN-RP group at 355 (318-421) min; this was not statistically significant. Blood loss was significantly less in HALS-RP [300 (230-402) mL] compared to OPEN-RP [512 (401-1162) mL, $P = 0.003$]. Anastomotic leakage was noted in 3 patients in the HALS-RP group and 2 patients in the OPEN-RP group (13% *vs* 8.3%, NS). The rates of other postoperative complications and the length of hospital stay were not different between the two groups.

CONCLUSION

HALS-RP can be performed with less blood loss and smaller skin incisions. This procedure is a feasible technique for total proctocolectomy for ulcerative colitis.

Key words: Hand-assisted laparoscopic surgery; Ulcerative colitis; Laparoscopic surgery; Proctocolectomy

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Core tip: This is a retrospective study to evaluate the utility of hand-assisted laparoscopic restorative proctocolectomy (HALS-RP) for ulcerative colitis (UC). Fifty-one patients underwent restorative proctocolectomy, and twenty-three patients in the HALS-RP were compared with twenty-four patients in the conventional open surgery group (OPEN-RP). The mean operative time for the HALS-RP group was not different to OPEN-RP group, but blood loss was significantly less in HALS-RP compared to OPEN-RP. HALS is a feasible procedure for restorative proctocolectomy for UC with small skin incision.

Shimada N, Ohge H, Yano R, Murao N, Shigemoto N, Uegami S, Watahani Y, Uemura K, Murakami Y, Sueda T. Hand-assisted laparoscopic restorative proctocolectomy for ulcerative colitis. *World J Gastrointest Surg* 2016; 8(8): 578-582 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i8/578.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i8.578>

INTRODUCTION

Laparoscopic surgery (LAP) was introduced in 1991 by Jacobs *et al.*^[1] for colorectal cancer, and is now the standard of care in many colorectal operations. Numerous studies have shown the benefits of LAP for colorectal cancer including less blood loss, less postoperative pain, earlier return of bowel function, and shorter length of hospital stay^[2-4]. LAP for patients with ulcerative colitis (UC) was reported in 1992 by Peters^[5], but it has not been widely accepted because of the complexity of the surgeries and long operative times^[6]. Hand-assisted laparoscopic (HALS) was introduced in the mid-1990s as a hybrid technique^[7]. Surgeons can provide direct retraction, perform the dissection, and control bleeding with one hand placed into the abdominal space through a small incision. HALS is a minimally invasive surgery and has been reported

as an acceptable technique for total proctocolectomy (TPC). HALS is reported to be as minimally invasive as LAC^[8], but there have been few reports comparing HALS and open surgery for UC. The aim of this study was to assess the utility of hand-assisted laparoscopic restorative proctocolectomy (HALS-RP) compared with the traditional open approach (OPEN-RP) performed by colorectal surgeons for patients with UC in a single institution.

MATERIALS AND METHODS

A total of 95 patients underwent restorative TPC with mucosectomy and hand-sewn ileal-pouch anal anastomosis (IPAA) for UC in Hiroshima University Hospital from January 2008 to July 2015. Fifty-one patients who underwent a 2-staged procedure were included in this retrospective study. Those patients were divided into the HALS-RP group ($n = 23$) and the OPEN-RP group ($n = 24$) based on three surgeons' preferences. Patients diagnosed with indeterminate colitis, or those who underwent pure laparoscopic surgery ($n = 4$), were excluded. Patient's demographics, preoperative clinical information, intraoperative factors such as operative time and blood loss, postoperative complications, and postoperative course were compared. The patients were preoperatively categorized according to American Society of Anesthesiologists (ASA) classifications. Data are shown as the median with the interquartile range (IQR) in parentheses or means with standard deviations (SD) for continuous variables, and frequencies for categorical variables. Continuous data with a Gaussian distribution was showed as means and SD, and analyzed with the Student's *t* test. In the case of a non-Gaussian distribution, continuous data were expressed as median and IQR and analyzed with the Wilcoxon rank-sum test. For categorical variables, the Pearson's χ^2 test was performed, and Fisher's exact test was used when the data set was small (expected cell counts were < 5). A *P* value < 0.05 was considered statistically significant. Statistical evaluation was carried out using the JMP version11 software (SAS institute Japan).

HALS surgical technique

Transanal mucosectomy was performed in the jack-knife position. During this procedure, the anterior wall of the rectum was separated from the prostate gland or vaginal wall. The posterior wall of the rectum could be separated from the sacrum *via* transmesorectal excision. Patients were then placed in the lithotomy position. A 7-cm vertical incision below the umbilicus was made for the hand port and the wound protector was inserted. Mobilization of the right side colon and sigmoid colon was performed, and the terminal ileum was resected through the small incision under direct vision. Two trocars were placed in the upper umbilical region for the laparoscope and the left mid-abdomen for the surgeon's right hand (Figure 1). A hand-assist device (Gel Port[®] system) was assembled within the

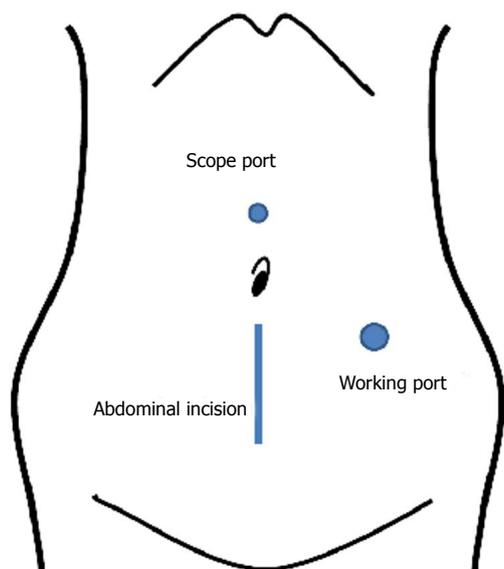


Figure 1 Skin incision for hand-assisted laparoscopic restorative proctocolectomy. A 7-cm vertical incision below the umbilicus was made for the hand port. Two trocars were placed in the upper umbilical region for the laparoscope and the left mid-abdomen for the surgeon's right hand. A hand-assist device (Gel Port® system) was assembled within the wound protector.

wound protector. Pneumoperitoneum was initiated and the greater omentum was dissected from the transverse colon. The left colon including the splenic flexure was mobilized, and the mesentery was divided outside of the marginal artery of colon. A vessel sealing system (LigaSure®; Valleylab) was used for this purpose. After pneumoperitoneum, mobilization of the rectum was performed through the incision. A J-pouch was constructed at the terminal ileum with linear staplers, and hand-sewn to the anal verge.

RESULTS

Twenty-three cases in the HALS-RP group and 24 cases in the OPEN-RP group were matched in regards to patient age, gender, and ASA score (Table 1). However, body mass index (BMI) in the HALS-RP was 20.8 ± 3.1 , which was significantly less than that of the OPEN-RP group (22.6 ± 3.3 , $P = 0.043$). There were no significant differences in extent of colitis, indications for surgery, preoperative comorbidities, and preoperative medications in the two groups. Preoperative leukocyte count was higher in the HALS-RP group than OPEN-RP group (7486 ± 478 vs 5661 ± 410 , $P = 0.002$). The amount of total-corticosteroid and C-reactive protein was also higher than the OPEN-RP group; this was not significantly different.

The operative outcomes and complications are summarized in Table 2. The mean operative time for the HALS-RP group was slightly longer, but this was not significantly different [HALS-RP 369 (320-420) min vs OPEN-RP 355 (318-421) min]. Blood loss was significantly lower in the HALS-RP group (300 (230-402) mL vs 512 (401-1162) mL, $P = 0.003$). IPAA

Table 1 Comparison of patients' characteristics *n* (%)

	HALS-RP (<i>n</i> = 23)	OPEN-RP (<i>n</i> = 24)	<i>P</i> value
Age, mean	42.7 ± 12.7	50.9 ± 18.1	NS
Sex (male/female)	15/8	18/6	NS
BMI, kg/m ²	20.8 ± 3.1	22.6 ± 3.3	0.043
ASA score			NS
1	1 (4.3)	1 (4.2)	
2	22 (95.7)	23 (95.8)	
3	0 (0)	0 (0)	
Disease duration (month, median)	132 (66-216)	136 (36-256)	NS
Extent of colitis			NS
Pancolitis	17 (73.9)	16 (76.1)	
Left side colitis	6 (26.1)	4 (19.0)	
Rectal colitis	0 (0)	1 (4.8)	
Indication for surgery			NS
Cancer/dysplasia	6 (26.9)	10 (41.6)	
Stricture	4 (17.4)	2 (8.33)	
Refractory to medication	13 (56.5)	10 (41.6)	
Others	0 (0)	2 (4.26)	
Preoperative medication			
Corticosteroid (mg, median)	4400 (1000-8700)	950 (0-4462)	NS
L-CAP/G-CAP	10 (43.4)	12 (50)	NS
CyA, Tarolimus	3 (8.7)	0 (0)	NS
Biologics	2 (8.7)	3 (12.5)	NS
Preoperative comorbidity			NS
HT	3 (13)	4 (16.7)	
DM	1 (4.3)	3 (12.5)	
Preoperative laboratory data (average ± SD)			
Leukocyte	7486 ± 478	5661 ± 410	0.002
Hemoglobin	11.8 ± 0.74	13.05 ± 0.28	NS
Serum albumin	3.96 ± 0.11	4.16 ± 0.221	NS
CRP	1.42 ± 0.749	0.29 ± 0.104	NS

HALS-RP: Hand-assisted laparoscopic restorative proctocolectomy; OPEN-RP: Restorative proctocolectomy with open surgery; CyA: Cyclosporine A; L-CAP: Leukocyte apheresis; G-CAP: Granulocyte apheresis; CRP: C-reactive protein; NS: No significance.

anastomotic leakage was noted in 3 patients in the HALS-RP group and 2 patients in the OPEN-RP group (13% vs 8.3%, NS). Rates of surgical site infection were not significantly different. Superficial and deep surgical site infections developed in 3 cases in the HALS-RP group (13.0%) and 3 cases in the OPEN-RP group (12.4%, NS). Organ space infections were noted in 5 cases in the HALS-RP group (21.7%) and 4 in the OPEN-RP group (16.7%, NS). Other postoperative complications such as small bowel obstruction, venous thrombosis, and neurologic bladder dysfunction were also similar.

Return of bowel function, which was estimated by bilious output from the ileostomy, was similar between the two groups (1.5 ± 0.13 d and 1.8 ± 1.4 d, $P = 0.26$). Tolerance of liquid diet was 1.3 ± 0.13 d and solid diet was 5.26 ± 0.75 d in the HALS-RP group; these were similar to the OPEN-RP group (1.29 ± 1.75 d and 3.62 ± 0.29 d). The length of hospital stay after surgery was not different between the two groups 20 (16-26) d in HALS-RP, 18 (14-29) d in OPEN-RP, $P = 0.408$.

Table 2 Comparison of surgical outcome and complications

	HALS-RP (n = 23)	OPEN-RP (n = 24)	P value
Surgical outcome			
Operation time (min, median)	369 (320-420)	355 (318-421)	NS
Blood loss (mL, median)	300 (230-402)	512 (401-1162)	0.003
Bowel movement (d, mean)	1.5 ± 0.13	1.8 ± 1.4	NS
Toleration of liquids	1.3 ± 0.13	1.29 ± 1.75	NS
Toleration of solid diet	5.26 ± 0.75	3.62 ± 0.29	NS
Length of stay (d)	20 (16-26)	18 (14-29)	NS
Complications, n (%)			
IPAA anastomotic leak	3 (13.04)	2 (8.33)	NS
Surgical site infection			
Superficial wound infection	3 (13.04)	1 (4.17)	NS
Deep wound infection	0 (0)	2 (8.3)	NS
Organ space infection	5 (21.7)	4 (16.67)	NS
Small bowel obstruction	6 (26.0)	4 (16.6)	NS
Venous thromboembolism	2 (8.7)	3 (6.38)	NS
Neurogenic bladder dysfunction	0 (0)	1 (4.17)	NS
Hemorrhage	0 (0)	1 (4.17)	NS

HALS-RP: Hand-assisted laparoscopic restorative proctocolectomy; OPEN-RP: Restorative proctocolectomy with open surgery; IPAA: Ileal-pouch anal anastomosis; NS: No significance.

DISCUSSION

Laparoscopic surgery is common practice in segmental resection for colorectal disease namely because it provides a good field of view in the abdominal cavity. Furthermore, smaller skin incisions and faster recovery of bowel function are achieved using this technique. However, laparoscopic TPC for patients with UC is still not widely accepted as it is a longer and more complex surgery, and difficult to handle inflamed bowel laparoscopically without causing injury. In terms of avoidance of bowel edema, shorter operative times are preferred for ileal-pouch and anal anastomosis healing. On the other hand, patients with UC are relatively young and often prefer small skin incisions for cosmetic reasons. Recently, HALS for colorectal surgery was compared with conventional LAP, and showed that a HALS approach shortened operative time, but overall morbidity, time to return of bowel function, and length of hospital stay were similar to those of LAP^[8-10]. While we adopted HALS in 2008, there have been few studies comparing it with traditional open surgery for TPC with mucosectomy. In this study, we aimed to compare HALS-RP and traditional open surgery over the last 8 years in a single institution.

In terms of operative time, one study showed that HALS reduced time by 33 min in sigmoid/left colectomy, and 57 min in total colectomy compared with a conventional LAP technique^[9]. Aalbers *et al.*^[11] reported that the most important advantage of HALS in TPC was reduction in operating time, making the operation more efficient. In our series, HALS-RP was successfully completed without significant increase of operative time compared with OPEN-RP. Operative time of 374 min in this study series was still longer than previous studies, which reported times ranging from 210 to 356 min^[6,12-15]. We speculate that this was because we

started the trans-anal procedure with a mucosectomy in the jack-knife position and the time required for position change to modified lithotomy position was included. All told, this was approximately 70 min before the abdominal incision. Moreover, we chose a hand-sewn IPAA for all cases, which takes longer than a stapled IPAA, the most common technique reported in previous studies. HALS-RP showed significantly less blood loss than OPEN-RP. We attribute this to the good view of the splenic flexure as compared to that with open surgery.

Nakajima *et al.*^[14] reported that HALS maintains the early postoperative benefit of minimally invasive surgery as well as a totally laparoscopic approach for TPC. However, we are of the opinion that a HALS approach may hasten return of bowel function given there is direct manipulation of the intestine with the operator's hand. Accordingly, in this study, an advantage of the return of postoperative bowel function in the HALS-RP group was not shown. The median length of hospital stay in this study was also the same in both groups [20 (16-26) d in HALS-RP, 18 (14-29) d in OPEN-RP]. Although both were longer than in other studies^[6,14], diet advancement was done in a traditional step-wise fashion, and time was devoted to patient education regarding ileostomy care and medical control of diarrhea.

Total length of skin incisions for HALS-RP at our institution was 8 cm, with a 7-cm midline incision, and two 0.5 cm incisions for trocars. Laparoscopic TPC uses a total incision length of 4.1 to 8.2 cm for trocars and construction of the ileal-pouch^[11,13]. Thus, regarding total skin incision length, there are few cosmetic advantages of totally laparoscopic TPC.

Currently we use three different approaches for TPC: Open surgery, HALS, and LAP. Choice of technique is tailored to the individual patient. For young women, LAP may be appropriate. For patients with prior surgery, open surgery should be considered. HALS has the benefit of having the view of laparoscopic surgery but the time saving of open surgery, which may reduce surgeon stress.

This study has several limitations. Our case numbers are small. This is a nonrandomized comparison between two groups in a retrospective fashion. Surgical methods were not selected in accordance with any definitive criteria, but rather by surgeons' preferences, which could introduce some element of bias.

HALS for TPC affords the good operative view of laparoscopic surgery as well as the tactile feedback of open surgery. It is an acceptable alternative to conventional open surgery.

COMMENTS

Background

Total proctocolectomy (TPC) with mucosectomy for patients with ulcerative colitis (UC) is a complex, lengthy procedure. Traditional laparoscopic surgery (LAP) for UC has taken long operation time. The authors hypothesize that hand-assisted laparoscopic restorative proctocolectomy (HALS-RP) is superior to LAP for this disease.

Research frontiers

Although some study report about HALS-RP compared with LAP, there have been few studies comparing it with traditional open surgery for TPC.

Innovations and breakthroughs

This study indicated that HALS-RP is acceptable with less blood loss, and without increase of operative time and postoperative complications compared with open procedure (OPEN-RP).

Applications

HALS-RP is useful technique for TPC for UC with small skin incision and affords the operative good view.

Peer-review

This is a retrospective single-center study. Twenty-three patients in the HALS-RP group and 24 cases in the OPEN-RP group were matched in regards to patient age, gender, and anesthesiologists score. The study demonstrates that the rates of other postoperative complications and the length of hospital stay were not different between the two groups, with less blood loss and smaller skin incisions in the HALS-RP group.

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Observational Study

Pancreaticoduodenectomy: A study from India on the impact of evolution from a low to a high volume unit

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Abstract

AIM

To analyse the impact of turning of our department from a low to a high volume provider of pancreaticoduodenectomy (PD) on surgical outcome.

METHODS

A retrospective collection of data was done for patients who underwent PD. According to the number of PDs undertaken per year, we categorized the volume into low volume (< 10 PDs/year), medium volume (10-24 PDs/year) and high volume (> 25 PDs/year) groups.

RESULTS

From 2002 to 2013, 200 patients underwent PD. The annual number of PD increased from 4 in 2002 to 34 in 2013. The mean operative time, operative blood loss and need for intraoperative blood transfusion decreased considerably over the volume categories ($P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively). Increased procedural volume was associated with a lower morbidity ($P = 0.021$) and shorter length of hospital stay ($P < 0.001$). Similarly the rate of mortality dropped from 10% for the low volume group to 2.2% for the medium volume group and 0.0% for the high volume group ($P = 0.007$).

CONCLUSION

The transformation from a low volume to a high volume provider of PD resulted in most favourable outcomes favouring the continued centralization of this high risk procedure.

Key words: Pancreaticoduodenectomy; High volume centre

Core tip: Due to the complexity and challenging nature of pancreaticoduodenectomy, it is likely that both short- and long-term outcomes strongly depend on the cumulative number of cases performed by the surgeon as well as by the hospital. Strong evidence exists for volume-outcome relationship in which high volume centres have reduced perioperative morbidity and mortality. High volume hospitals are assumed to have structural characteristics associated with better quality of care, and providers in these hospitals are thought to improve their processes of care through experience in providing complex care. While the findings of this study are presented in terms of high, medium, and low volume periods, an important point exists regarding the volume-outcome relationship that must be emphasized. Thus for patients seeking to identify a hospital at which to have their surgery, the best strategy if all other factors are equal is to choose the hospital that performs pancreatic surgery most frequently.

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INTRODUCTION

Pancreaticoduodenectomy (PD) is a complex, high risk surgical procedure usually performed for malignancy of the pancreatic head or periampullary region. Before 1980, PD has been associated with a high rate of morbidity (40%-60%) and a high mortality rate up to 20%^[1]. Since that time, the in-hospital mortality rate has decreased substantially with high-volume tertiary care centers reporting in-hospital mortality rate of 4% or less^[2,3]. Luft *et al*^[4] provided the empirical relationship between higher surgical volume and lower postoperative mortality, which led to centralization of high risk operations to improve the outcome. Various studies have demonstrated that high volume tertiary centers have significantly lower (< 5%) in-hospital mortality rates for PD than low volume centres (> 10%)^[5,6]. The majority of data regarding centralization of PD were obtained from multi-institutional comparisons and there are few studies describing the effects of increased caseload of PD within the same unit. Although the trend of centralization has been slow as demonstrated by a nationwide survey of PD in the United States^[7], no information is available regarding volume-outcome association in India.

The purpose of this study was to explore the effect of centralization of PD on perioperative outcome at a tertiary care center in Northern India during the period

2002-2013 and analyse the impact of turning our department from a low to a high volume provider of PD.

MATERIALS AND METHODS

Through retrospective collection of data from a prospectively maintained database at the Department of Surgical Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Kashmir (India), medical records of patients who underwent PD for pancreatic or periampullary benign or malignant lesions were identified. Patient's demographics, surgical parameters and post-operative events were recorded and analysed. After performing PD (classical or pylorus preserving) with or without associated organ resection, pancreaticojejunostomy was achieved by anastomosing the pancreatic remnant to the end of the jejunal loop by either mucosa to mucosa or dunking method. All the surgical procedures were performed by the senior surgeon OJS with a senior assistant (SAB). The present study also included patients who were a part of previous publications from the department^[8-10]. Clavien-Dindo classification^[11] was used to grade the complications, and complications requiring either intervention under local or locoregional or general anaesthesia, ICU management or causing death were considered as major (grades 3-5). Besides recording the annual departmental volume, according to the number of PD performed per year we categorized the volume into low volume (< 10 PDs/year); medium volume (10-24 PDs/year); and high volume (\geq 25 PDs/year) as described earlier^[12].

Pancreatic fistula was categorized according to the International Study Group on Pancreatic Fistula criteria^[13]. Inability of a patient to return to a standard diet by the end of the first postoperative week necessitating prolonged nasogastric intubation of the patient was treated as delayed gastric emptying (DGE) as defined by the International Study Group on Pancreatic Surgery (ISGPS)^[14], bile leak was defined as bilious drain with raised bilirubin level, and culture positive purulent collection was treated as intra-abdominal abscess.

Postpancreatectomy haemorrhage (PPH) was defined according to the ISGPS based on the time of onset, site of bleeding, severity and clinical impact^[15]. Overall morbidity included all major complications including infections, cardiopulmonary and gastrointestinal complications; the primary endpoint was operative mortality defined as death occurring during the period of hospital stay or within 30 d of surgery. Secondary endpoints were postoperative morbidity rate, occurrence of pancreatic fistula, DGE and length of hospital stay. Follow-up for infection and non-infectious complications was carried out for 30 d after hospital discharge. Readmission rate (within 30 d after discharge) was also recorded.

Statistical analysis

Statistical analyses were performed using χ^2 and Fishers exact tests for categorical variables and ANOVA for

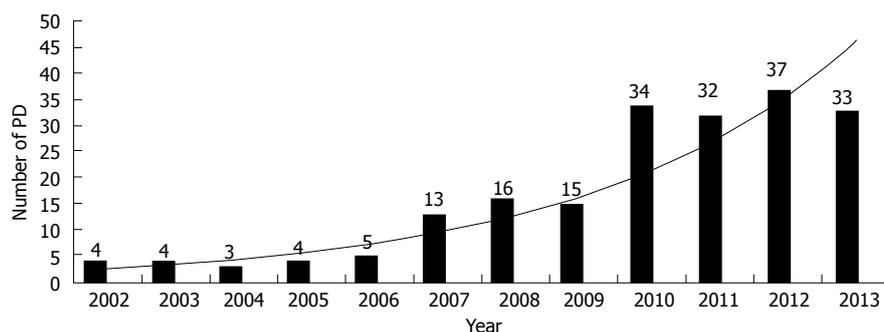


Figure 1 Yearly distribution of number of pancreaticoduodenectomies. PD: Pancreaticoduodenectomies.

Table 1 Histopathological type

Variable	n (%)
Pancreatic adenocarcinoma	85 (42.5)
Ampullary adenocarcinoma	57 (28.5)
Distal cholangiocarcinoma	23 (11.5)
Duodenal adenocarcinoma	10 (5.0)
Neuroendocrine tumors	7 (3.5)
Serous cystadenoma	3 (1.5)
Chronic pancreatitis	3 (1.5)
Mucinous cystadenoma	2 (1.0)
Intra-ductal papillary mucinous neoplasm	2 (1.0)
Pancreatoblastoma	2 (1.0)
Gastrointestinal stromal tumors	2 (1.0)
Pancreatic sarcoma	1 (0.5)
Duodenal leiomyoma	1 (0.5)
Angiomyolipoma	1 (0.5)
Mucinous cystoadenocarcinoma	1 (0.5)

Table 2 Demographic characterization

Variable	Low volume (< 10 PDs/yr), n = 20	Medium volume (10-24 PDs/yr), n = 44	High volume (≥ 25 PDs/yr), n = 136	P value
Gender (male/female)	12/8	25/19	80/56	0.963
Age (yr), mean ± SD	58.95 ± 10.44	59.22 ± 10.29	62.58 ± 9.05	0.059
BMI, mean ± SD	21.00 ± 2.55	21.59 ± 2.76	21.45 ± 2.50	0.691
ASA score, n (%)				
1	3 (15.0)	6 (13.6)	16 (11.8)	
2	12 (60.0)	26 (59.2)	78 (57.4)	
3	4 (20.0)	10 (22.7)	34 (25.0)	0.996
4	1 (5.0)	2 (4.5)	8 (5.8)	
Jaundice, n (%)	16 (80.0)	32 (72.7)	105 (77.2)	0.770
Abdominal pain, n (%)	7 (35.0)	15 (34.1)	40 (29.4)	0.776
Vomiting, n (%)	4 (20.0)	7 (15.9)	24 (17.6)	0.920
Cholangitis, n (%)	3 (15.0)	6 (13.6)	26 (19.1)	0.674
Diabetes, n (%)	3 (15.0)	9 (20.5)	23 (16.9)	0.825
CV disease, n (%)	3 (15.0)	7 (15.9)	18 (13.2)	0.898
Cold, n (%)	2 (10.0)	4 (9.1)	8 (5.9)	0.659
Preoperative Hb (mg/dL), mean ± SD	9.37 ± 1.19	9.73 ± 1.44	9.62 ± 1.19	0.558
Preoperative albumin (mg/dL)	3.33 ± 0.52	3.52 ± 0.58	3.56 ± 2.68	0.914
Serum bilirubin (mg/dL), mean ± SD	9.48 ± 5.38	8.56 ± 4.00	9.11 ± 5.38	0.754
Preoperative biliary stenting, n (%)	3 (15.0)	8 (18.2)	19 (14.0)	0.794

continuous variables. Post hoc tests were applied to look for inter-group differences. Statistical analyses were performed using SPSS 20 Chicago (United States). P values of 0.05 or less were considered statistically significant.

RESULTS

During the 12-year period from January 2002 to December 2013, 200 PDs were performed in the department. Across the study period, the annual average number of PD increased from 4 in 2002 to 34 in 2013 (Figure 1). The most common indications for surgery were pancreatic adenocarcinoma (n = 85, 42.5%), ampullary adenocarcinoma (n = 57, 28.5%) and distal cholangiocarcinoma (n = 23, 11.5%) (Table 1). The various demographic features between the low volume (group A), medium volume (group B) and high volume (group C) categories revealed no statistical change during the study period (Table 2). In group C, PD included portal vein resection (4 patients) and right hemicolectomy (6 patients) (Table 3).

In groups A, B and C the mean duration of surgery (246.3 ± 20.6 min, 227.7 ± 47.5 min, 125.5 ± 16.1 min, P ≤ 0.001), operative blood loss (1098.5 ± 163.8 mL, 932.3 ± 207.5 mL, 415.9 ± 82.7 mL, P ≤ 0.001), mean blood units transfused (1.3 ± 0.4 UI, 1.3 ± 0.6 UI, 0.2 ± 0.4 UI, P ≤ 0.001) and the requirement of feeding jejunostomy (75%, 59.1%, 7.4%, P ≤ 0.001)

decreased significantly with increasing hospital volume (Table 4). There was a progressive regression in the rate of overall complications across the volume groups (group A, 50.0%; group B, 45.5% and group C, 27.2%, P = 0.021).

The most common complications were DGE and occurrence of pancreatic fistula. Both these types of complications showed a significant difference in rates across the volume groups (pancreatic fistula rate of 15.0% in group A, 15.9% in group B and 3.6% in group C; P = 0.011), whereas DGE was observed at a rate of 20.0% in group A; 18.2% in group B and 5.9% in group C (P = 0.018; Table 5). The rate of PPH was 10.0% in group A; 2.2% in group B and 0% in group C (P = 0.007; Table 4). Five patients required reoperative surgery (2 postoperative haemorrhage, 2 pancreatic fistula and 1 DGE). The reoperative rate significantly decreased when comparing the volume groups (in low volume 10.0%; in medium volume 4.5% and in high volume 0.7%,

Table 3 Comparative analyses of features in the perioperative period during the progress from a low to a high volume PD centre, *n* (%)

Variable	Low volume (< 10 PDs/yr), <i>n</i> = 20	Medium volume (10-24 PDs/yr), <i>n</i> = 44	High volume (≥ 25 PDs/yr), <i>n</i> = 136
Preoperative			
Triple phase CECT abdomen/pelvis	10 (50)	40 (90.9)	136 (100)
CA 19.9	10 (50)	44 (100)	136 (100)
Operative			
Classical Whipple	14 (70)	12 (27.3)	4 (2.9)
PPPD	6 (30)	32 (72.7)	132 (97.1)
With portal vein resection	0 (0)	0 (0)	4 (2.9)
With right hemicolectomy	0 (0)	2 (4.5)	6 (4.4)
Pancreaticojejunostomy			
Duct to mucosa	17 (85)	5 (11.4)	0 (0)
Dunking	3 (15)	39 (88.6)	136 (100)
Use of pyloric dilatation	0 (0)	32 (72.7)	132 (97.1)
Use of omental flap ^[8]	0 (0)	10 (22.7)	136 (100)
No of abdominal drains			
1 drain	4 (20)	39 (88.6)	136 (100)
2 drains	16 (80)	5 (11.4)	0 (0)
Feeding jejunostomy	15 (75)	26 (59.1)	10 (7.4)
Ocreotide 0.1 mg S/C × 3 times for 1 wk	15 (75)	10 (22.7)	0 (0)
Postoperative			
Fast track approach ^[10]	0 (0)	16 (36.4)	126 (92.6)

CA 19.9: Carbohydrate antigen 19.9; PPPD: Pylorus preserving pancreaticoduodenectomy.

P = 0.029). Occurrence of intraabdominal infections and rate of bile leak also decreased when comparing the volume categories, but did not reach statistical significance.

A consistent decrease in the mean length of hospital stay was noticed for the high volume group of patients and differences across groups were statistically significant (11.8 ± 3.4 d, 11.3 ± 2.9 d and 7.9 ± 1.7 d for low, medium and high volume periods, respectively; *P* ≤ 0.001). The consistency of the stepwise inverse relation between volume and in-hospital mortality was notable (0%, 2.2% and 10.0% for high, medium and low volume groups, respectively).

DISCUSSION

More than 30 years ago, Luft *et al*^[4] introduced the empirical relationship between higher surgical volume and lower postoperative mortality. This led to the concept of centralization of complex surgical procedures to improve outcome. This relationship of hospital volume and surgical mortality for complex surgical procedures including PD was amply described by Birkmeyer *et al*^[16]. Despite improvements due to regionalization, PD remains a complex procedure associated with high perioperative morbidity and potential mortality. Strong evidence exists for volume-outcome relationship where high volume centers have reduced perioperative morbidity and mortality, although the exact mechanism (surgeon

Table 4 Operative details

Variable	Low volume (< 10 PDs/yr), <i>n</i> = 20	Medium volume (10-24 PDs/yr), <i>n</i> = 44	High volume (≥ 25 PDs/yr), <i>n</i> = 136	<i>P</i> value
Duration of surgery in minutes, mean ± SD	246.3 ± 20.6	227.7 ± 47.5	125.5 ± 16.1	< 0.001
Operative blood loss in millilitre, mean ± SD	1098.5 ± 163.8	932.3 ± 207.5	415.9 ± 82.7	< 0.001
Intraoperative blood transfusion required, no of patients (%)	20 (100)	41 (93.2)	23 (16.9)	< 0.001
Mean blood units transfused, mean ± SD	1.3 ± 0.4	1.3 ± 0.6	0.2 ± 0.4 (0-1)	< 0.001
Pancreatic texture, <i>n</i> (%)				
Soft	4 (20.0)	11 (25.0)	30 (22.1)	0.925
Intermediate	11 (55.0)	20 (45.5)	72 (52.9)	
Firm	5 (25.0)	13 (29.5)	34 (25.0)	
Pancreatic duct diameter at neck, <i>n</i> (%)				
< 3 mm	7 (35.0)	12 (27.3)	46 (33.8)	0.700
≥ 3 mm	13 (65.0)	32 (72.7)	90 (66.2)	
Feeding jejunostomy, <i>n</i> (%)	15 (75.0)	26 (59.1)	10 (7.4)	< 0.001

PD: Pancreaticoduodenectomy.

related factors vs system related factors) behind it remains unclear. For example, an experienced surgeon working in a low volume institution may be technically proficient at PD; however, the system support for diagnosis and treatment of postoperative complications may be inadequate. Conversely a high volume center with intensive care, interventional radiologic and gastroenterological expertise could provide superior support to a surgeon with lesser PD experience. Previous publications have clearly demonstrated that mortality, survival and overall life expectancy are improved when PD is performed in high volume centers^[17-20].

SKIMS is the only tertiary care hospital available for the population (about 10 million) of Kashmir valley. SKIMS, the regional provider, developed interest in the PD procedure and developed a focussed team dedicated to caring for these patients. This included formulation of treatment protocols and critical care ways, as well as standardizing diagnostic workups, operative details and management of postoperative complications. Further information regarding provider capabilities and surgical results were disseminated locally, regionally and nationally. This resulted in an increased number of referrals to the institution, resulting in regionalization. In the first period of the study (January 2002 to September 2006), the annual average number of PD was about 4. It went up to 14/year in the next three and a half years, and in the last phase of this study the figure was 34. There was a significant drop in the operative parameters like operative time (246.3 ± 20.6 min, 227.7 ± 47.5 min to 125.5 ± 16.1 min, *P* ≤ 0.001),

Table 5 Postoperative complications and outcome

Variable	Low volume (< 10 PDs/ yr), $n = 20$	Medium volume ($10-24$ PDs/yr), $n = 44$	High volume (≥ 25 PDs/yr), $n = 136$	<i>P</i> value
Pancreatic fistula, n (%)	3 (15.0)	7 (15.9)	5 (3.6)	
Grade A	1 (33.3)	3 (42.8)	2 (40.0)	0.011
Grade B	1 (33.3)	3 (42.8)	2 (40.0)	
Grade C	1 (33.3)	1 (14.3)	1 (20.0)	
Delayed gastric emptying, n (%)	4 (20.0)	8 (18.2)	8 (5.9)	
Grade A	2	6	7	0.018
Grade B	1	2	1	
Grade C	1	0	0	
Hemorrhage, n (%)	2	1	0	0.007
Grade A	1	0	0	
Grade B	0	1	0	
Grade C	1	0	0	
Intra-abdominal infection, n (%)	1 (5.0)	2 (4.5)	1 (0.7)	0.175
Bile leak, n (%)	1 (5.0)	2 (4.5)	2 (1.5)	0.395
Total morbidity, n (%)	10 (50.0)	20 (45.5)	37 (27.2)	0.021
Major morbidity (Clavien grade III, IV)	3 (15.0)	2 (4.5)	3 (2.2)	0.024
Reoperation, n (%)	2 (10.0)	2 (4.5)	1 (0.7)	0.029
Mortality, n (%)	2 (10)	1 (2.2)	0	0.007
Postoperative length of hospital stay (d), mean \pm SD	11.8 \pm 3.4	11.3 \pm 2.9	7.9 \pm 1.7	< 0.001

PD: Pancreaticoduodenectomy.

operative blood loss (1098.5 \pm 163.8 to 932.3 \pm 207.5 mL to 415.9 \pm 82.7 mL, $P \leq 0.001$), requirement and mean blood units transfused (1.3 \pm 0.4 UI to 1.3 \pm 0.6 UI to 0.2 \pm 0.4 UI, $P \leq 0.001$). Similarly the occurrence of complications like pancreatic fistula (15.0% to 15.9% to 3.6%, $P = 0.011$), DGE (20.0% to 18.2% to 5.9%, $P = 0.018$) and PPH (10% to 2.2% to 0%, $P = 0.007$) decreased significantly with the increase in procedure volume and increased experience.

Surgeon volume has been less emphasized in the literature and until more recently, it has been linked to mortality and may explain a significant part of an institution's volume effect^[21]. A learning curve in pancreatic surgery has been hypothesized and modelled, suggesting that after 60 PDs surgeons improved the perioperative outcomes of estimated blood loss, operative time and length of hospital stay in patients undergoing PD for periampullary adenocarcinoma^[22]. Few elective surgical procedures are associated with higher operative risk.

Numerous studies show a consistent trend towards hospital case volume predicting better outcome in pancreatic surgery. These studies offer the most compelling support of the hospital case volume: Better outcome concept because of their size and diversity of the study design. In 1995 Gordon *et al.*^[23] published a retrospective study on 501 patients who underwent pancreatic resection at one of 39 hospitals in Maryland. Hospital mortality rate was significantly lower at the

high-volume regional medical center compared to all other hospitals (2.2% vs 13.5%).

The persistent increase in the number of PD not only resulted in gross reduction of overall morbidity (50.0% to 45.5% to 27.2%, $P = 0.021$), but also significantly decreased the length of hospital stay (11.8 \pm 3.4 d to 11.3 \pm 2.9 to 7.9 \pm 1.7, $P = 0.001$). It is worth to mention that hospitals with 11 years of experience performing one Whipple's procedure per year have a predicted mortality rate that is lower than for very low volume hospitals with only 1 year of experience, although the difference is not statistically significant. Moreover, very low volume hospitals with 11 years of experience have a predicted mortality rate that is significantly different and almost three times higher than that for hospitals with 11 years of experience that perform 10 or more Whipple's procedures per year (9.2% vs 3.4%)^[17]. Thus experience does little to mitigate the difference in mortality observed between low and high volume hospitals. During the time of the study, the mortality rate dropped significantly from 10% to 0%. These results suggest that achieving a procedure volume of 25 PDs or more per year may be sufficient for minimizing inpatient mortality. The influence of institutional volume has also been reflected on late survival after PD for cancer. Birkmeyer *et al.*^[24] investigated this possible effect and concluded higher 3-year survival rate at high volume hospitals (37%) than at those with medium (29%), low (26%) or very low volume (25%) ($P < 0.0001$). These findings indicate that hospital volume also influences both perioperative risk and long-term survival after PD for cancer.

It has been clearly stated that the volume-outcome relationship usually is stronger for hospital volume than for surgeon volume. This has been ascribed to the "experience effect" of the whole team taking care of the patient. There are two competing explanations for the observed association between volume and outcome. The first, "practice makes perfect", hypothesizes that institutions have better outcome because their case load and experience allow them to improve their systems and techniques. The second, "selective referral", hypothesizes that institutions with better outcomes have larger volumes because their excellence is known and thus more patients come to be cared for in these institutions. Which hypothesis is correct has not been established.

This study clearly demonstrates that regionalization can benefit the population of a state through the reduction of in-hospital mortality. In spite of the fact that this study was not able to examine the functional status, quality of life or the length of survival, in-hospital mortality rate is an important objective measurement and of great interest and concern to consumers. Although this study has several possible limitations like the retrospective nature, lack of information on cancer staging, unavailability of data on quality of life and long term survival, the major strength of this

study is that volume groups were compared within the same surgical unit and this eliminates several biased variables affecting inter-hospital comparisons. Further individual patient variables and clinical course which previous volume outcome studies lack were described based on administrative data and not medical records. The results of this study support the beneficial effects of regionalization by which health care services should result in optimization of outcomes for complex, high risk elective surgeries. Further research should be directed to identify procedures for which regionalization is most likely to have a beneficial effect and to determine how best to achieve the regionalization.

COMMENTS

Background

Pancreaticoduodenectomy (PD) is a complex, high risk surgical procedure usually performed for malignancy of the pancreatic head or periampullary region. PD has been associated with a high rate of morbidity (40%-60%) and a high mortality rate up to 20%. High volume tertiary centers have significantly lower (< 5%) in-hospital mortality rates for PD than low volume centres (> 10%). This led to the concept of centralization of complex surgical procedures to improve outcome.

Research frontiers

The purpose of this study was to explore the effect of centralization of PD on perioperative outcome at a tertiary care center in Northern India during the period 2002-2013 and analyse the impact of turning the authors' department from a low to a high volume provider of PD. Although the trend of centralization has been slow as demonstrated by a nationwide survey of PD in the United States, no information is available regarding volume outcome association in India.

Innovations and breakthroughs

It has been clearly stated that the volume-outcome relationship usually is stronger for hospital volume than for surgeon volume. This has been ascribed to the "experience effect" of the whole team taking care of the patient. High volume hospitals are assumed to have structural characteristics associated with better quality of care, and providers in these hospitals are thought to improve their processes of care through experience in providing complex care. While the findings of this study are presented in terms of high, medium, and low-volume periods, an important point exists regarding the volume-outcome relationship that must be emphasized.

Application

The results of this study support the beneficial effects of regionalization by which health care services should result in optimization of outcomes for complex, high risk elective surgeries. Further research should be directed to identify procedures for which regionalization is most likely to have a beneficial effect and to determine how best to achieve the regionalization.

Terminology

PD is associated with a high morbidity and mortality and a constant effort at improving this, among many, has led to the concept of centralization. The concept of centralization stresses the importance of high volume centers that are assumed to have structural characteristics associated with better quality of care, and providers in these hospitals are thought to improve their processes of care through experience in providing complex care.

Peer-review

The majority of data regarding centralization of PD are obtained from multi-institutional comparisons and there are few studies describing the effects of increased caseload of PD within the same unit. Numerous studies show a consistent trend towards hospital case volume predicting better outcome in

pancreatic surgery. These studies offer the most compelling support of the hospital case volume: Better outcome concept because of their size and diversity of the study design. In India no information is available regarding volume outcome association.

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Open abdomen in gastrointestinal surgery: Which technique is the best for temporary closure during damage control?

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Abstract

AIM

To compare the 3 main techniques of temporary closure of the abdominal cavity, vacuum assisted closure (vacuum-assisted closure therapy - VAC), Bogota bag and Barker technique, in damage control surgery.

METHODS

After systematic review of the literature, 33 articles were selected to compare the efficiency of the three procedures. Criteria such as cost, infections, capacity of reconstruction of the abdominal wall, diseases associated with the technique, among others were analyzed.

RESULTS

The Bogota bag and Barker techniques present as advantage the availability of material and low cost, what is not observed in the VAC procedure. The VAC technique is the most efficient, not only because it reduces the tension on the borders of the lesion, but also removes stagnant fluids and debris and acts at cellular level increasing cell proliferation and division. Bogota bag presents the higher rates of skin laceration and evisceration, greater need for a stent for draining fluids and wash-ups, higher rates of intestinal adhesion to the abdominal wall. The Barker technique presents lack of efficiency in closing the abdominal wall and difficulty on maintaining pressure on the dressing. The VAC dressing can generate irritation and dermatitis when the drape is applied, in addition to pain, infection and bleeding, as well as toxic shock syndrome, anaerobic sepsis and thrombosis.

CONCLUSION

The VAC technique, showed to be superior allowing a better control of liquid on the third space, avoiding complications such as fistula with small mortality, low infection rate, and easier capability on primary closure

of the abdominal cavity.

Key words: Trauma; Damage control; Abdominal compartment syndrome; Temporary abdominal closure

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Core tip: The authors reviewed several manuscripts published in the last 20 years evaluating the management of the open abdomen. Several techniques have been described and the most popular ones were analyzed. The vacuum assisted closure (vacuum-assisted closure therapy), Bogota bag and Barker technique are currently the most used. The authors evaluate, for each technique, efficiency, complications, mortality and wound control.

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INTRODUCTION

Throughout history surgical principles were based on anatomical repairs with the goal to make primary and definite organic repair. In the last decade, a greater importance has been given in repairing physiological features of the surgical patient. This resulted in the concept of damage control surgery with special emphasis on the need for open abdominal maintenance (laparotomy)^[1].

Laparostomy comprises a surgical approach where the abdominal wall is not sutured by plans and left open, allowing a regular inspection and drainage of intracavitary content^[2,3]. Its usage is indicated in cases of abdominal trauma, damage control surgery, sepsis of abdominal origin, severe acute pancreatitis, the need for new laparotomy, hemodynamic instability, retroperitoneal hematomas and necrotizing fasciitis, allowing a continuous evaluation of intra-abdominal pressure in order to avoid the development of abdominal compartment syndrome^[2,4-7].

According to the consensus carried out by the World Society of the Abdominal Compartment Syndrome (WSCAS - 2004), abdominal compartment syndrome is defined as a condition where organ dysfunction is caused by sustained intra-abdominal hypertension above 20 mmHg. However, it is known that values below this (> 12 mmHg) will also cause organ dysfunction, but to a lesser degree. Abdominal hypertension is divided in degrees^[2]: (1) 12-15 mmHg; (2) 16-20 mmHg; (3) 21-25 mmHg; and (4) > 25 mmHg.

In 2013, the WSACS concluded that intra-abdo-

Table 1 Etiologies for abdominal compartmental syndrome

Primary	Secondary
Abdominopelvic causes ^[5] :	Extra-abdominal causes ^[5] :
Complex abdominal trauma ^[5]	Sepsis ^[5]
Ruptured Aneurysm aorta ^[5]	Acidosis (pH < 7.2) ^[5]
Hemoperitoneum ^[5]	Hypothermia ^[5]
Pancreatitis ^[5]	Politransfused (> 10 IU of packed red blood cells in 24 h) ^[5]
Peritonitis ^[5]	Coagulopathies (platelets < 55000/mm ³ or aPTT > 2x/normal or TAP < 50% - INR > 1.5) ^[5]
Retroperitoneal bleeding ^[5]	Great chest, vascular and orthopedic trauma ^[5]
Hepatic transplants ^[5]	Great burnt ^[5]
Primary closure under tension ^[5]	Vigorous hydration (> 5 U/24 h) ^[5]

minimal pressure must be measured in patients who have at least two risk factors for hypertension, which are correlated with the pathology that triggered the abdominal injury. This pressure must be measured every 4-6 h, using preferentially the bladder and in cases of contraindication, other *via* as abdominal, rectal and vaginal may also be used^[2,5]. The compartmental syndrome may also be classified according to their etiology (Table 1)^[5].

Complications arise from the current shock, which leads to the involvement of multiple systems causing renal perfusion decrease, decline in glomerular filtration rate (oliguria and acute renal insufficiency); ischemia of the intestinal wall and its mucosa, liver failure by portal flow decrease, cerebral hypoperfusion, among others^[5].

During the period in which the abdomen is open, the aponeurosis can laterally retract and lose the possibility of closure, creating then a ventral incisional hernia. These, with subsequent formation of adhesions make future abdominal surgeries more complicated, increasing morbidity and mortality^[8]. This can be avoided by applying temporary closure techniques, such as Bogota bag, Barker technique, vacuum assisted closure therapy (VAC), among others that allow closing the abdominal cavity with less stress^[9].

The aim of this review article is to compare the 3 main techniques of temporary abdominal cavity closure, vacuum closure (VAC), Bogota bag and Barker technique, after damage control laparotomy. In this study, we analyzed efficiency, financial costs, risks and benefits for each of the most common available methods.

MATERIALS AND METHODS

This paper is a review of manuscripts published in the literature from 1996 to 2016. Search was performed in MEDLINE, PUBMED, Scielo e Lilac's with the following keywords: VAC technique, Bogota bag and Barker techniques, traumatic abdominal injuries. The papers should have addressed effectiveness of each technique,

Table 2 Comparison of the advantages of each technique

Bogota bag	Allows greater number of reviews of the abdominal cavity than the direct synthesis; better control of septic focuses by easy access; abdominal decompression; and functional restoration of the abdominal wall; has low cost; immediate availability; flexibility and high resistance; is not adhered to the tissues; does not cause allergic or inflammatory reactions; has quick and easy installation; can be used in any part of the body; allows the visualization of organs; is used in trauma, cancer surgery, and various abdominal surgeries; is a protector against water loss and heat
Barker technique	It is an inexpensive technique; uses material found in the surgical center and easily applicable; has moderate fluid control; allows closure of the abdominal wall with less tension; has low rates of complications
Vacuum-assisted closure therapy	It prevents contamination; allows dissection of the wound; protects the wound from external injuries; reduces the interstitial pressure; increases blood flow to the lesion; reduces the expression of matrix metalloproteinases in chronic wounds; promotes wound healing; removes stagnant fluids and debris; increases proliferation and cell division rates; induces granulation tissue formation; and brings greater comfort to the patient with infrequent complications. In selected cases it can be used as an outpatient procedure; allows shorter hospital stay and better quality of life

Table 3 Comparison between the disadvantages of each technique

Bogota bag	Use of more drains and rinses; presents a certain risk of eviscerations and difficulty in mobilizing the patient; it can cause skin lacerations; bowel adhesion to abdominal wall; it needs gas sterilization of the bag; there is a difficult control of the third space; leaks under the bag can wet the bed increasing the risk of hypothermia
Barker technique	In some cases, it does not allow adequate approach of the abdominal wall; it has moderate fluid control; greater difficulty in detecting complications that occur with bleeding and the maintaining of continuous pressure
Vacuum-assisted closure therapy	High cost; it can cause skin irritation due to the use of the adhesive; it can cause pain, infection and bleeding; it can lead to toxic shock syndrome (rare) and can cause thrombosis

cost, associated infections, readiness on abdominal wall reconstruction and diseases associated with the technique. Only articles in English and Portuguese and performed in humans were selected. Thirty-three articles met the selection criteria.

RESULTS

The Bogota bag technique presents as advantages (Table 2) the availability to material access, lower cost, fast and easily executed, and not dependent on a great experience from the surgeon. For allowing a great visibility and entrance in the abdominal cavity, it promotes greater control of the septic spots and enables several revisions. Moreover, it allows abdominal decompression, does not cause inflammatory reactions or allergies, being used in several parts of the organism and in any kind of surgery, from traumas to tumor removal. However, it presents higher rates of eviscerations and skin lacerations, implying greater need for abdominal drainage and wash-ups, higher rates of intestinal adhesion to the abdominal wall, difficulty in controlling the third space and leaks. Thus, it requires sterilization of the bag by gas preventing its availability (Table 3).

The technique proposed by Barker presents positive factors, such as easy assembly at a low cost, since it uses hospital material already used for other functions (Table 2). Since acquiring these materials is easy, the technique application becomes simple. The closure of the abdominal cavity is done with less stress, preventing complications associated with moderate control of the fluid produced by the body. One disadvantage is the lack of efficiency in approaching the abdominal wall when the injury is extensive and important. There is a deficiency on maintaining pressure, which must be

continuous and properly maintained in order to make the organs act in the recovery. In complicated cases with abdominal bleeding, it may take a while to detect this bleeding while draining the fluid (Table 3).

The temporary closure technique by negative pressure, the VAC, among all of them has a more effective action on closing the abdominal cavity because it reduces the tension on the injury borders and works at cellular level increasing cell proliferation and division. Furthermore, it induces the formation of granulated tissue, reducing the aspect of matrix metalloproteinase on chronic wounds (Table 2). There is an increase of blood flow at the site of the injury. At the same time protects the wound from external injuries to progress and removes stagnant fluids and debris, avoiding cavity contamination, reducing the interstitial pressure and bacterial proliferation. Thus, it promotes healing of the wound and decreases complication rates and hospital stay providing a better quality of life. Among all techniques, VAC presents a significant higher cost. It can generate irritation and contact dermatitis, when the drape is applied, in addition to pain, infection and bleeding. Among the complications, the most severe ones are toxic shock syndrome and anaerobic sepsis (Table 3).

DISCUSSION

Open abdomen as a damage control procedure has been recommended since 1979. The technique allows extensive drainage of pus through the wall opening and it also facilitates the washing of the peritoneal cavity through scheduled surgeries or on demand as required^[8]. In this procedure, the lining of the abdominal wall is not completely aligned, allowing a regular inspection on the



Figure 1 Bogota bag.



Figure 2 Barker technique.

condition of the handles and drainage of the intra-cavity content^[8]. This procedure is indicated in situations such as severe pancreatitis, severe sepsis, abdominal trauma among others.

In cases of pancreatitis, it is indicated in the presence of acute abdomen signs, entero-mesenteric infarction, presence of pancreatic necrosis and abdominal compartment syndrome. Surgical intervention comprises exploratory laparotomy with pancreatic necrosectomy, debridement and washing of the peripancreatic tissue with subsequent laparostomy, associated with antibiotic therapy in infected cases, presenting in general an unfavorable clinical course^[10].

When we refer to cases of severe sepsis of abdominal origin, this therapy is necessary in the presence of necrotizing soft tissue infections (necrotizing fasciitis), intra-abdominal abscess, infected pancreatic necrosis, intestinal infarction, fecal peritonitis, when there is no possibility of closing the abdomen due to edema of the abdominal viscera, and when the complete eradication of the infectious origin is not possible^[11].

For the open abdomen to be feasible, various techniques of temporary closure of abdominal cavity have been studied. The ideal technique needs to protect the abdominal content, prevent from evisceration (opening of the abdominal layer), preserve the fascia, minimize visceral damage, allow quantification of fluid losses to the third space allowing selective plugging, minimize domain loss, decrease bacteria amount, infection and inflammation, and keep patient dry and intact^[8].

Bogota bag

Initially described in 1984, plastic bags utilized to contain parenteral solutions were used to coat the abdominal opening on the patient for a second surgical intervention^[12]. Afterwards, the polyvinyl chloride (plastic bag) was adopted to maintain the abdomen open, technique initially called as Bogota bag or Borraez's bag^[12]. It consists of a sterilized (by gas) plastic bag used for closure of abdominal wounds, being sutured to the skin or fascia of the anterior abdominal wall^[13] (Figure 1). Variations of this treatment have already been described, and one of them is the use of a big bag,

inside the peritoneal cavity, loose and that covers all of the abdominal viscera. Afterwards, the bag is placed under the skin and another plastic bag is inserted. That avoids many handle collisions from inside the abdominal cavity, adhesions between the viscera and parietal peritoneum, diminishing the risk of lesions and enabling cavity washing and its closure^[12].

In general, it is very used in association with the polypropylene screen (as a reinforcement and contention), that is sutured to the skin, together with the edge of the collecting bag. This is done due to evisceration and difficulty in mobilizing the patient, consisting in the arising issues with the treatment^[1].

However, it is a procedure that will require a larger use of stents and wash-ups, presenting a certain risk of eviscerations and difficulty in mobilizing the patient^[12]. In addition, it generates skin lacerations, adherence of the intestine to the abdominal wall, difficulty in reproaching the abdomen and the need to gas sterilize the bag before its use, harder control of third space with minimum loss and any leak from under the bag can wet the bed increasing the risk of pneumonia^[13,14].

Vacuum-pack

The technique developed by Barker *et al*^[15] was described in 1995 using vacuum dressings for temporary closure of the abdominal cavity and since then it has been called "vacuum-pack" and became the most indicated for several conditions^[16] (Figure 2). It was developed to be used with material found in the surgical rooms, presenting low cost and simple technique^[15,17].

The vacuum-pack consists in an open polyethylene sheet between the abdominal viscera and anterior parietal peritoneum; a humid surgical dressing over the sheet with two suction drains. Then, an adhesive sheet throughout the wound, including a wide margin on the surrounding skin is placed. The stents are then connected to a suction device that enables 100-150 mmHg of continuum negative pressure^[18]. This technique prevents damage to the abdominal wall due to the absence of sutures, preserving it to future approaches or definite closure, maintaining integrity of the fascia for later closure, allowing a quick approach to the



Figure 3 Vacuum-assisted closure.

abdominal cavity. The material utilized in contact with the abdominal viscera - the polyethylene sheet - is not adherent, and the vacuum-pack allows a better control of fluid quantity produced^[17].

Regarding rates of fascial closure achieved with this technique, in 1997 a study obtained results of 61% of success. The patients, who were trauma victims and were subjected to Barker's technique, had primary fascial closure on the 2nd laparotomy, being close to the achieved average^[15]. Other studies had rates of 29%-100%^[16,19-21]. The definite closure of the abdominal cavity after the 8th post-operative day from laparotomy was associated with a higher rate of complications^[22].

Barker *et al.*^[23] showed their experience by using this technique in intestinal lesions submitted to resection in a study that lasted 11 years. There was no difference between patients who used this or other types of wound dressings regarding fistulas or leaks. Other studies reported fistula rates from 3% to 5%^[19,23-25].

A study combining trauma victims and other cases of open abdomen, reports as existing complications: Abdominal abscess/infection, abdominal compartment syndrome, dehiscence, anastomotic leakage, coagulopathy, deep venous thrombosis, fascial necrosis, gastrointestinal ischemia, intestinal fistula, intestinal obstruction, pulmonary embolism and multiple organ failure^[25]. In this study, it was not explained if these complications were directly related to the use of vacuum-pack. The complication rates related by Barker *et al.*^[15] are 15%.

VAC system

The VAC, called VAC therapy or system is also known as negative pressure therapy (TPN), or sub atmospheric pressure (PTE) or as vacuum packing (TVV). Argenta and Morykwas^[26] published an experimental work with VAC system, using acute wound in pigs, in 1997. In this work, they postulated that this system has a multimodal action mechanism. Since then, the clinical results observed in a variety of wounds were the best seen in comparison with the usual methods. The VAC therapy worked as a catalyst for the development of a series of studies^[24,26]. Its efficiency in severe traumatic wounds helped to develop an area that belonged to plastic and reconstructive surgery^[24].

To apply this type of therapy, equipment made of reticulated foam is used and placed at the region and sealed in with the use of a patch (Figure 3). This foam can be made of polyurethane or polyvinyl alcohol, which generally presents 400-600 μm pores; it is cut to adjust perfectly along the wound before getting applied. If needed, several pieces of foam can be used to cover the gaps of the wound^[24,27]. The foam is patched in with a drape that remains stuck on the skin with a 3 to 5 cm margin from the wound. In this sticker, a small 2 cm diameter hole is made in the center and a TRAC sticker (device that leads secretion to the tank) is linked to it. Then, a pump is connected to the foam (vacuum) that generates continuous sub atmospheric pressure (VAC-KCI, San Antonio, Texas, United States). Usually, putting an intermittent cycle of pressure for five minutes of suction and two minutes turned off. The pressure, in general, is adjusted to 125 mmHg and is distributed evenly throughout the wound through sponge pores. A plastic sticker is applied over the sponge to allow wound sealing^[24,27-29].

Firstly, VAC removes stagnant fluid and debris and then is constantly optimizing blood supply and matrix deposition. Therefore, the partial oxygen pressure within the tissue increases and bacterial proliferation is reduced. Secondly, VAC leads to increased local interleukin-8 and vascular endothelial growth factor concentrations, which may trigger the accumulation of neutrophils and angiogenesis. With the cyclical application of sub atmospheric pressure, VAC alters the cytoskeleton of cells in the wound bed, triggering a cascade of intracellular signals that increase the rates of cell proliferation and division, and subsequent formation of granulation tissue^[30].

The VAC system can be utilized for treatment of surgical infected wounds, trauma wounds, pressure ulcers, bone wounds and exposed hardware, diabetic foot ulcers and venous stasis ulcers. In addition, it can be used in reconstructing wounds, allowing elective planning of definite reconstructive surgery, without compromising the wound or the result. Furthermore, it increased significantly the success rate for skin graft when utilized as a cushion over the grafted wound^[27].

Complications of VAC therapy are not frequent when the system is used correctly. Complication rates mostly described in literature are due to patient's comorbidities and skin irritation caused by the drape. Other complications such as pain, infection or bleeding are not easily seen. Severe complications, such as toxic shock syndrome, anaerobic sepsis or thrombosis are described as well but rare^[27].

The timing of primary conclusion with the vacuum assisted closure therapy is not always the fastest because it depends on each case, with the exception for patients with cardiovascular disease and/or diabetes. A portable VAC system (VAC freedom) is available in the market and it's a regular size bag that has helped treating wounds carefully at home; this shows that VAC therapy improves quality of life because it reduces the

length of hospital stay^[31].

The total cost for VAC therapy is not significantly lower than the others; however, after analyzing time involvement and costs with nursing team, there is a considerable cut. Comfort for patients and nursing team are described in many cases as a relevant factor for choosing this therapy^[31].

Comparison between the different techniques for damage control surgery

Comparing the use of VAC to other methods for temporary closure of the abdominal cavity, several studies showed that VAC performs better. A prospective study conducted by Batacchi *et al.*^[32] in 2009 compared patients who were abdominal trauma victims treated with the Bogota bag and VAC, during the abdominal cavity temporary closure. The VAC treatment was more effective in controlling intra-abdominal pressure ($P < 0.01$), normalization of serum lactate ($P < 0.001$), as well as less time needed for ventilation, faster abdominal closure and consequently shorter time at the intensive care unit and hospital stay. The results of the "Sequential Organ Failure Assessment" and mortality rate were not significantly different. Another study, conducted by Bee *et al.*^[33] compared polyglactin 910 (MESH) and VAC on temporary closure of the abdominal cavity after damage control surgery or compartment abdominal syndrome on a randomized study. In their results, VAC presented a 31% rate against 26% for the MESH group of late primary closure. The fistulas rates on the VAC group were 26% while on MESH, it was 5%. The differences presented in this study were not statistically different.

Kaplan *et al.*^[13] in 2005 concluded that VAC is the one to supply the ideal material for temporary closure on with greater satisfaction. From the 17 articles evaluated that had as object of study the 3 alternatives discussed in this article, the Bogota bag exhibited mortality rates of 53%, the vacuum-pack and VAC, 31% and 30%, respectively. Regarding complications such as fistulas, the VAC presented a rate of 2.6% against 7% of vacuum-pack and 13% of Bogota. Fascial closure was reached in 79% of patients subjected to VAC, while 58% was reached in vacuum-pack and Bogota bag reached only 18%^[13].

Regarding intra-abdominal pressure (PIA), control Batacchi *et al.*^[32] in 2009, comparing the Bogota bag and VAC system, concluded that VAC was more effective on PIA control ($P < 0.01$) and on serum lactate ($P < 0.001$) during the first 24 h after surgical decompression^[30]. The patients subjected to VAC had a faster abdominal closure and consequently stayed a shorter time at the intensive care unit; nevertheless, mortality rates were not different between the two groups.

Cheatham *et al.*^[25] in a 2013 study that compared VAC and vacuum-pack showed that both techniques present similar complication rates such as the development of abdominal compartment syndrome (8%) and fistulas (4%). VAC was associated with a bigger

rate for primary fascial closure longer than 30 d (73% against 27% of vacuum-pack) and smaller mortality rate on the same period for patients who needed open abdomen for at least 48 h. The difference in mortality between VAC and vacuum-pack increased significantly during the first 30 d due to the posterior development of multiple organ failure subjected to vacuum-pack and due to better peritoneal fluid removal rich in cytosines (increases organ dysfunction) through VAC^[25]. Bruhin *et al.*^[34], in a recent study compared several techniques looking at contamination, fistula, and mortality rates, among others. Higher rates of primary fascial closure after VAC application in combination with "dynamic closure" technique (using traction, suture of dynamic retention or ABRA) were obtained. Moreover, patients who were not contaminated had a closure rate of 81%, followed by the exclusive use of VAC with rates of 72% and home-made (Barker technique) of 58%, taking into account that the Bogota bag data were inadequate^[32]. Contaminated lesions were noticed, and resulted on higher rates of abdominal closure (74.6%), followed by its exclusive use (48%), Barker technique (35%) and Bogota bag (27%). In relation to the presence of fistulas and the mortality rate, the VAC technique had the lowest rate, being the highest value (40% of mortality rate) obtained by the Barker technique^[32].

In conclusion, the treatment for open abdomen patients has evolved greatly in the last decades, with great improvement of the existing techniques and the emerging of new ones. Its main objective is to maximize tissue perfusion and to minimize potential intra-abdominal complications, such as fistulas and hernias, enabling early closure of the abdominal cavity. VAC therapy showed to be superior in relation to the other techniques, such as Bogota bag and vacuum-pack, allowing a better control of the third space fluid, avoiding complications such as fistula; it has lower mortality and infection rates, and better capacity in primary closure of the abdominal cavity. On the other hand, the Bogota bag technique was the least efficient, even though it is still very much used due to its low cost, easy access to material that is generally already present in the surgical room.

COMMENTS

Background

Laparostomy comprises a surgical approach where the abdominal wall is not sutured by plans and left open, allowing a regular inspection and drainage of intracavitary content. Its usage is indicated in cases of abdominal trauma, damage control surgery, sepsis of abdominal origin, severe acute pancreatitis, the need for new laparotomy, hemodynamic instability, retroperitoneal hematomas and necrotizing fasciitis, allowing a continuous evaluation of intra-abdominal pressure in order to avoid the development of abdominal compartment syndrome.

Research frontiers

The different techniques available for the temporary closure presents several benefits as well as limitations for its use and today there is a tendency to use the properties of negative pressure to ensure a faster recover of the patient

increasing the rate definite closure of the abdominal wall.

Innovations and breakthroughs

There are mainly three basic approaches for the maintenance of an open abdomen are: The Bogota bag technique presents as advantages the availability to material access, lower cost, fast and easily executed, and not dependent on a great experience from the surgeon. For allowing a great visibility and entrance in the abdominal cavity, it promotes greater control of the septic spots and enables several revisions. Moreover, it allows abdominal decompression, does not cause inflammatory reactions or allergies, being used in several parts of the organism and in any kind of surgery, from traumas to tumor removal. However, it presents higher rates of eviscerations and skin lacerations, implying greater need for abdominal drainage and wash-ups, higher rates of intestinal adhesion to the abdominal wall, difficulty in controlling the third space and leaks. Thus, it requires sterilization of the bag by gas preventing its availability. The technique proposed by Barker presents positive factors, such as easy assembly at a low cost, since it uses hospital material already used for other functions. Since acquiring these materials is easy, the technique application becomes simple. The closure of the abdominal cavity is done with less stress, preventing complications associated with moderate control of the fluid produced by the body. One disadvantage is the lack of efficiency in approaching the abdominal wall when the injury is extensive and important. There is a deficiency on maintaining pressure, which must be continuous and properly maintained in order to make the organs act in the recovery. In complicated cases with abdominal bleeding, it may take a while to detect this bleeding while draining the fluid. The temporary closure technique by negative pressure, the vacuum-assisted closure therapy (VAC), among all of them has a more effective action on closing the abdominal cavity because it reduces the tension on the injury boarders and works at cellular level increasing cell proliferation and division. Furthermore, it induces the formation of granulated tissue, reducing the aspect of matrix metalloproteinase on chronic wounds. There is an increase of blood flow at the site of the injury. At the same time protects the wound from external injuries to progress and removes stagnant fluids and debris, avoiding cavity contamination, reducing the interstitial pressure and bacterial proliferation. Thus, it promotes healing of the wound and decreases complication rates and hospital stay providing a better quality of life.

Applications

The treatment for open abdomen patients has evolved greatly in the last decades, with great improvement of the existing techniques and the emerging of new ones. Its main objective is to maximize tissue perfusion and to minimize potential intra-abdominal complications, such as fistulas and hernias, enabling early closure of the abdominal cavity. VAC therapy showed to be superior in relation to the other techniques, such as Bogota bag and vacuum-pack, allowing a better control of the third space fluid, avoiding complications such as fistula; it has lower mortality and infection rates, and better capacity in primary closure of the abdominal cavity.

Terminology

Laparostomy comprises a surgical approach where the abdominal wall is not sutured by plans and left open, allowing a regular inspection and drainage of intracavitary content. Abdominal compartment syndrome is defined as a condition where organ dysfunction is caused by sustained intra-abdominal hypertension above 20 mmHg. However, it is known that values below this (> 12 mmHg) will also cause organ dysfunction, but to a lesser degree. The Bogota bag technique presents as advantages the availability to material access, lower cost, fast and easily executed, and not dependent on a great experience from the surgeon. For allowing a great visibility and entrance in the abdominal cavity, it promotes greater control of the septic spots and enables several revisions. The Barker's technique presents positive factors, such as easy assembly at a low cost, since it uses hospital material already used for other functions such as surgical towels, sterile plastic bag and surgical drapes commercially available connected to the wall vacuum. The closure of the abdominal cavity is done with less stress, preventing complications associated with moderate control of the fluid produced by the body. The temporary closure technique by negative pressure, the VAC, reduces the tension on the injury boarders and works at cellular level increasing cell proliferation and division. Furthermore, it induces the formation of granulated tissue, reducing the aspect of matrix metalloproteinase on chronic wounds. At the same time protects the wound from external injuries to progress and removes stagnant fluids and debris using a continuous negative

pressure applied by the system, avoiding cavity contamination, reducing the interstitial pressure and bacterial proliferation.

Peer-review

This article is a review about three different techniques of laparostomy, a technique that is nowadays very often utilized above all during damage control surgery. The subject of the review is quite interesting for emergency and trauma surgeons.

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Update on medical and surgical options for patients with acute severe ulcerative colitis: What is new?

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Abstract

Acute severe ulcerative colitis (UC) is a highly morbid condition that requires both medical and surgical management

through the collaboration of gastroenterologists and colorectal surgeons. First line treatment for patients presenting with acute severe UC consists of intravenous steroids, but those who do not respond require escalation of therapy or emergent colectomy. The mortality of emergent colectomy has declined significantly in recent decades, but due to the morbidity of this procedure, second line agents such as cyclosporine and infliximab have been used as salvage therapy in an attempt to avoid emergent surgery. Unfortunately, protracted medical therapy has led to patients presenting for surgery in a poorer state of health leading to poorer post-operative outcomes. In this era of multiple medical modalities available in the treatment of acute severe UC, physicians must consider the advantages and disadvantages of prolonged medical therapy in an attempt to avoid surgery. Colectomy remains a mainstay in the treatment of severe ulcerative colitis not responsive to corticosteroids and rescue therapy, and timely referral for surgery allows for improved post-operative outcomes with lower risk of sepsis and improved patient survival. Options for reconstructive surgery include three-stage ileal pouch-anal anastomosis or a modified two-stage procedure that can be performed either open or laparoscopically. The numerous avenues of medical and surgical therapy have allowed for great advances in the treatment of patients with UC. In this era of options, it is important to maintain a global view, utilize biologic therapy when indicated, and then maintain an appropriate threshold for surgery. The purpose of this review is to summarize the growing number of medical and surgical options available in the treatment of acute, severe UC.

Key words: Acute severe ulcerative colitis; Colectomy; Corticosteroids; Infliximab; Cyclosporine; Ileal pouch-anal anastomosis

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Core tip: The numerous avenues of medical and sur-

gical therapy have allowed for great advances in the treatment of patients with ulcerative colitis. In this era of options, it is important to maintain a global view, utilize corticosteroids and rescue therapy when indicated, and then maintain an appropriate threshold for surgery. Colectomy remains a viable and often life-saving treatment and should not be viewed as the "therapy of last resort".

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INTRODUCTION

Acute severe ulcerative colitis (UC) is an exacerbation of a chronic condition characterized by inflammation of the colonic mucosa extending from the rectum proximally to varying portions of the large intestine. UC is a highly morbid condition that requires both medical and surgical management. Prior to the 1950's and the implementation of urgent colectomy and systemic steroids, mortality rates were as high as 70% in patients with severe UC^[1]. In recent years, mortality rates have dropped to less than 1% with the combination of medical therapy, rescue therapy, and timely total abdominal colectomy (TAC) when indicated^[2,3]. Despite the introduction of rescue therapies such as cyclosporine (calcineurin inhibitor) and infliximab [tumor necrosis factor (TNF) monoclonal antibody] in the treatment regimen of patients with severe UC, colectomy rates have remained stable (27%) for the past thirty years^[4].

Historically, severe UC has been defined as the passage of at least six daily bloody stools, along with any of the following signs of systemic disease: Erythrocyte sedimentation rate > 30 mm/h, temperature > 37.8 °C, pulse rate > 90/min and hemoglobin < 10.5 g/dL (true-love and witts criteria)^[5]. Lichtiger created a scoring system for severe UC based on frequency of stools, nocturnal diarrhea, blood in stool, fecal incontinence, and abdominal pain^[6]. These criteria play a significant role in the decision to escalate therapy or proceed to colectomy in patients with severe disease. Rates of TAC within the first five years of disease range from 9%-35%, even with medical therapy^[7]. With a growing number of options available to both gastroenterologists and surgeons in the management of UC, treatment is becoming more individualized and variable. The following review provides a description of current medical and surgical management of acute severe UC.

STANDARD MEDICAL THERAPY

Patients presenting with signs of acute severe UC

require immediate admission to the hospital. They must have regular monitoring of vital signs and urine output as well as a comprehensive laboratory workup. Initial tests on admission should include a comprehensive metabolic panel, pre-albumin, albumin, complete blood count, and inflammatory markers [erythrocyte sedimentation rate and C-reactive protein (CRP)]^[5]. A tuberculin skin test should also be performed on that admission in preparation for possible treatment with immunosuppressant or biologic agents. Abdominal imaging should be obtained to evaluate for colonic dilation (greater than 5.5 cm) on plain X-ray or computed tomography scan, and the patient should be monitored for fever, leukocytosis and other signs of systemic sepsis that accompany toxic megacolon^[8,9].

Stool cultures and a clostridium difficile assay must be obtained to exclude infectious pseudomembranous colitis, and the frequency and consistency of bowel movements should be recorded.

Patients should take nothing by mouth and should be fluid resuscitated to a goal of 0.5 mL/kg per hour of urine output. The administration of intravenous fluids and the correction of electrolyte imbalances prevent dehydration and worsening of colonic dysmotility and dilatation^[10]. All patients who are not bleeding should be given thromboembolic prophylaxis due to the increased risk of thrombosis in the setting of systemic inflammation. In addition, the patient should undergo flexible sigmoidoscopy to confirm the diagnosis of acute severe UC and to obtain biopsies to rule out cytomegalovirus colitis^[11].

Patients with acute severe UC require constant reassessment, with antibiotic administration in the setting of infection, total parenteral nutrition in the setting of malnutrition, and escalation of therapy to medication non-responders. Kedia *et al.*^[12] proposed an algorithm for reassessing patient steroid response at days 1, 3 and 4-7 in which incomplete responders and non-responders either advance to rescue therapy or proceed to colectomy. In this algorithm, the Oxford criteria (> 8 stools/d or > 3 stools/d with a CRP > 45 mg/L) are used to determine the need for escalation of therapy^[13]. With careful attention to the patient's physical condition and severity of illness, the appropriate medical or surgical therapy can be selected to target the individual's ever-changing disease (Figure 1).

CORTICOSTEROIDS

Corticosteroids were introduced in the management of UC in the 1950's, though the first clinical trial proving their efficacy was not published until the 1970's^[5,14]. For the past 40 years, intravenous corticosteroids (methylprednisolone 60 mg/d or hydrocortisone 100 mg/8 h) for a 7-10 d course have been a cornerstone in the treatment of acute severe UC^[4,14]. A large review and meta-analysis reported the response to IV steroids to be 67% with short term colectomy rate of 29%^[4].

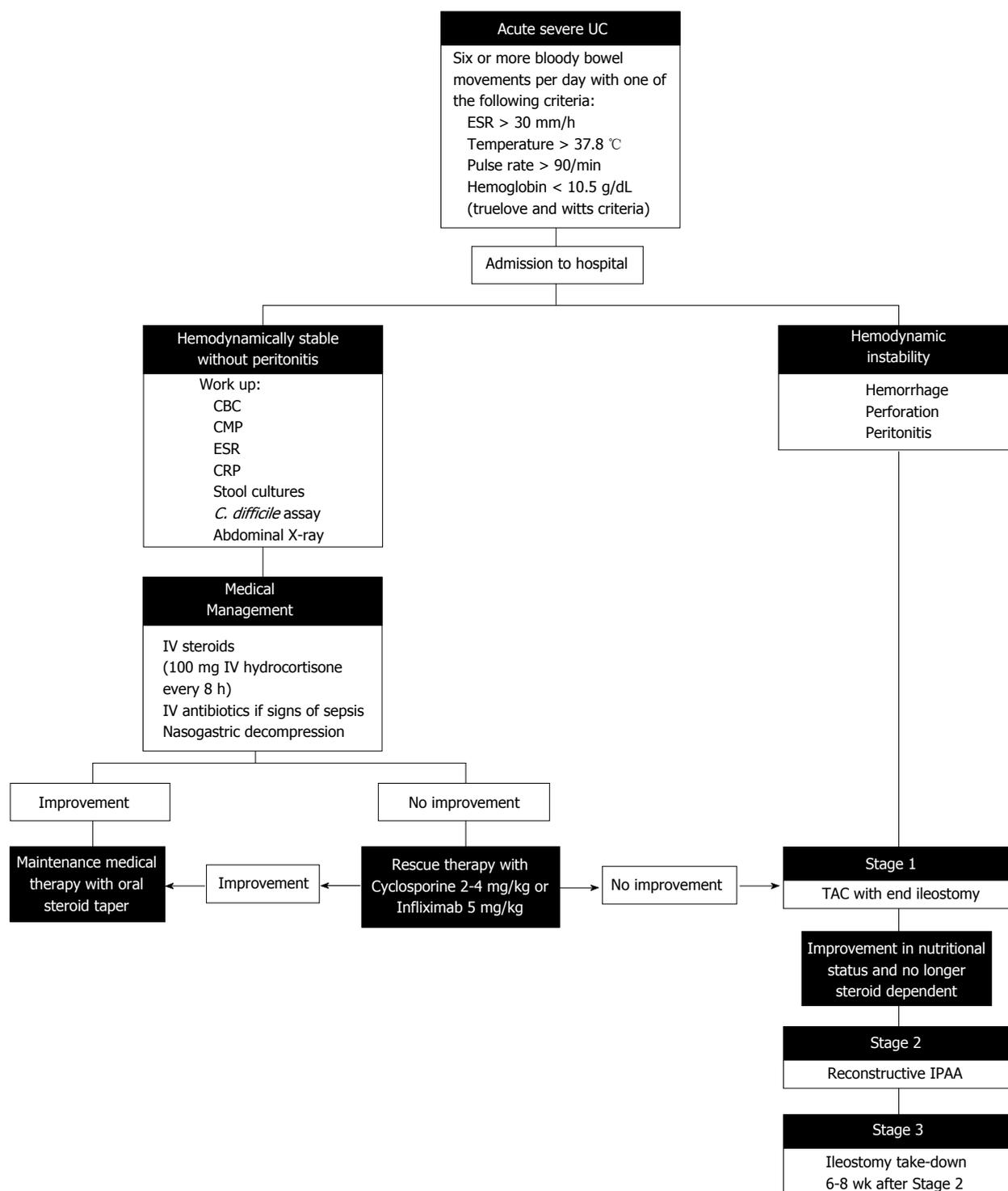


Figure 1 Algorithm for treatment of acute severe ulcerative colitis. UC: Ulcerative colitis; TAC: Total abdominal colectomy; IPAA: Ileal pouch-anal anastomosis; CBC: Complete blood count; CMP: Comprehensive metabolic panel; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

MEDICAL RESCUE THERAPY

Rescue therapies made their first appearance in the medical management of UC in the 1990's with the introduction of cyclosporine. Infliximab followed soon after as an alternative therapy with a different side-effect profile that could also serve as a salvage therapy in the setting of UC refractory to corticosteroids.

Cyclosporine (2-4 mg/kg) has been shown to induce

remission in 60%-80% of patients with acute severe colitis, but colectomy rates at four months remain close to 50% unless the patient is successfully bridged to maintenance therapy^[6,15,16]. The role of infliximab in the treatment of non-acute, moderate-to-severe UC has been reported in the Active Ulcerative Colitis Trials 1 and 2, with response rates between 61% and 69%^[17]. Infliximab (5 mg/kg) has also been shown to significantly decrease rate of colectomy at three months for patients with severe to

moderate attacks of UC^[18]. In an Italian trial by Kohn *et al.*^[19] there was an 85% response rate to infliximab with no colectomy in the 2 mo following hospital admission for acute severe UC and 67% at 23 mo. Multiple studies have compared infliximab and cyclosporine as rescue therapy for acute severe UC with no significant difference between the two therapies. Colectomy rates were similar at three and twelve months between patients receiving infliximab (31% and 41%) and cyclosporine (30% and 44%)^[20,21]. A recent systematic review and meta-analysis compared infliximab and cyclosporine as rescue therapy and found no significant difference in 3 or 12 mo colectomy rates among three randomized trials but reported significantly increased response to treatment and lower 12 mo colectomy rate among 12 non-randomized studies^[22].

While immunosuppressant and biologic agents have become established means of treating severe UC, there is conflicting evidence on the use of sequential therapy. Reports of the use of infliximab after failing steroids and cyclosporine have shown a 30% colectomy rate^[23]. A review of 10 studies in which rescue therapies were used sequentially for treatment of acute severe UC demonstrated colectomy rates of 28% at 3 mo and 42% at 12 mo with a 23% rate of adverse events—lower than previously reported in the literature^[24]. At this time, the selection of a rescue therapy agent, cyclosporine vs infliximab vs one agent following the other, is based primarily on physician comfort and experience, along with patient tolerance of side effects and susceptibility to infection.

IMMUNOMODULATORS

Although not currently the standard of care, vedolizumab, an integrin antibody, has been shown to induce steroid-free remission in approximately one third of UC patients who have failed anti-TNF therapy^[25]. Further investigation is required before recommendations can be made for its use in the treatment of acute severe UC.

Other agents such as thiopurines and methotrexate play a role in maintenance therapy and steroid dose reduction, but these drugs have shown no significant success as induction therapy to achieve remission in patients with active UC^[26,27].

ANTIBIOTICS

The role of antibiotics in the treatment of acute severe UC remains limited because even in severe UC there is no proven therapeutic benefit to oral or intravenous metronidazole, tobramycin, ciprofloxacin or vancomycin^[28-30]. Only in the setting of active infection or for pre-operative antibiotic prophylaxis do 2012 ECCO guidelines recommend that antibiotics be administered^[31].

SURGICAL THERAPY

Although tremendous advances have been made in the

medical treatment of UC, colectomy remains a cornerstone in the management of this disease. Overall, the rates of colectomy have not significantly changed since the addition of rescue therapies to the armamentarium of gastroenterologists. Predictors of the need for second-line treatment or colectomy are numerous, but several variables, including severity of disease, stool frequency, CRP, hypoalbuminemia (< 3 mg/dL), and radiographic evidence of colonic dilation (> 5.5 cm), all can be used in early identification of the need for escalation of therapy^[32-34]. A more recent scoring system also includes the need for blood transfusions or parenteral nutrition as predictors of need for colectomy^[35].

COLECTOMY AFTER MEDICAL RESCUE THERAPY

Due to the growing number of medical therapies for severe UC, patients are being referred for colectomy later after multiple attempts at medical salvage. These patients present in a poorer state of health, malnourished and anemic, and the delay is not without consequences.

Patients who undergo an operation after receiving high dose steroids or who are malnourished often have increased surgical complications^[36]. Post-operative complications include anastomotic leak, stricture, fistulae, and bowel obstruction. One study reported the rate of post-operative complications to be over three times higher, with the rate of sepsis being 13 times higher, in patients undergoing three-stage ileal pouch-anal anastomosis (IPAA) after treatment with infliximab^[37]. Similarly, significantly higher rates of major complications were found in patients undergoing longer duration of medical therapy (> 8 d) in a group of 80 patients with severe UC followed over the course of 7 years^[13].

The importance of continuous reassessment of the need for surgery is emphasized due to the mortality benefits of a well-timed or elective operation; mortality rates three years after elective colectomy (3.7%) are significantly lower than after admission without surgery (13.6%) or with emergent surgery (13.2%) in patients with acute severe UC^[38].

STAGED APPROACH

Surgical management of UC in the setting of failed medical therapy involves the performance of a TAC with an optional IPAA in two or three stages^[3]. In a three-stage approach, the initial operation involves a subtotal or TAC with creation of an end ileostomy. The stapled or hand-sewn rectosigmoid stump can be sutured as a mucous fistula to the distal aspect of the abdominal wall incision, may be closed and sutured to the subcutaneous tissue, or may be left unattached in the pelvis. The primary reason for creation of a mucous fistula or placement of the long rectal stump in the subcutaneous tissue is to avoid rectal stump breakdown and leakage with subsequent pelvic sepsis, especially in cases of severe

inflammation and thickening of tissue^[39]. The drawback to a mucous fistula lies in patient dissatisfaction that may occur with persistent discharge during the long-term recovery period^[40]. The manner in which the rectosigmoid is closed depends mainly upon patient anatomy and surgeon preference, but transanal rectal decompression is commonly performed following all techniques^[3]. TAC with end ileostomy as the first stage allows for immediate diversion of the fecal stream, avoids the dangers of a pelvic dissection or anastomosis in a critically ill patient, and allows for preservation of the rectum with the possible diagnosis of Crohn's colitis rather than UC.

The second stage of the procedure involves pouch formation with diverting ileostomy. Restorative proctocolectomy with IPAA is an elective operation performed in the absence of toxicity or severe malnutrition. Although proximal diversion does not prevent pelvic sepsis in the setting of IPAA, diverting ileostomy has been shown to lessen complications related to anastomotic leakage^[41,42]. The procedure can be technically challenging and involves identification of the rectal stump with full mobilization to the level of the levator ani muscles, proctectomy, and construction of a J-shaped pouch through a side-to-side anastomosis of the distal 40 cm of terminal ileum^[43]. Although several pouch designs have been promoted over the years, including the S-pouch and the W-pouch, the J-pouch has endured due to its relatively simple construction and equivalent or superior outcomes to other designs^[43,44]. The IPAA may be stapled or hand-sewn but fewer complications and better long-term quality of life have been reported in patients undergoing stapled anastomosis^[45].

The third stage of the procedure involves takedown of the diverting ileostomy and reestablishment of intestinal continuity. This final step should only be performed after water-soluble contrast enema has demonstrated patency and anastomotic integrity of the pouch.

In rare cases (5%), patients present with rectal sparing disease, and TAC with end ileostomy remains the first step to patient recovery^[46]. Only in these specific cases has ileorectal anastomosis as an alternative to pouch formation been described for reconstruction of the gastrointestinal tract^[47].

Although colectomy and pouch formation may be and are routinely performed as one procedure, this operation is reserved for UC patients who are healthy, well-nourished, off steroids and not experiencing an acute flare^[41]. Performing a three stage procedure allows for healthier, better nourished patients at the time of surgery^[48]. Some centers have attempted to abbreviate the hospital course of acute severe UC patients by performing a modified two-stage procedure (colectomy followed by IPAA and ileostomy takedown). Zittan *et al*^[49] demonstrated significantly lower rates of anastomotic leak (4.6% vs 15.7%) when comparing modified 2-stage IPAA to the traditional 2-stage procedure (colectomy with pouch formation followed by ileostomy takedown). Swenson *et al*^[50] demonstrated equivalent

patient outcomes with significantly lower hospital cost in patients with resolved severe colitis after colectomy who underwent a modified two-stage IPAA vs a three-stage procedure. The cost of medical therapy is not only affected by the operation performed but also by the timing of the procedure. In a comparison of patients with severe UC undergoing early colectomy with IPAA vs standard medical therapy, Park *et al*^[51] reported a cost analysis showing a \$90000 increase in cost to patients who received prolonged medical salvage therapy with very little improvement in quality of life.

ROLE OF LAPAROSCOPY

A laparoscopic approach to TAC in severe UC patients provides a reasonable alternative to the open approach and has been shown to be equally safe and feasible in comparison^[52]. While the laparoscopic approach has the advantage of reducing post-operative pain, time to stoma function, and overall hospital stay, it also leads to longer operative time and may be more technically demanding for the surgeon^[53,54].

LONG-TERM OUTCOMES OF IPAA

Although the ileal pouch does allow many patients to have a more normal life-style and defecation pattern, the procedure is not without enduring consequences. A recent study from the Cleveland Clinic published long-term outcomes of 74 patients who underwent IPAA and were followed over a 20-year period. Pouch-specific complications included pouchitis (45%), stricture (16%), fistula (30%), obstruction (20%), and change of diagnosis to Crohn's (28%). Long-term consequences of the procedure also included frequent stooling requiring anti-diarrheal medication (44%) and difficulty conceiving (25% and all women)^[44]. Pouch failure rates at 10 and 20 years have been reported to be 9% and 14%, although a 2016 study reported a failure rate of 2.4%, indicating that pouch outcomes may be improving^[44,55,56]. The three stage approach with proximal diversion may be associated with better outcomes as it reduces the impact that complications such as pelvic sepsis or anastomotic leak have on the ultimate quality of the pouch^[41].

While a substantial number of UC patients do elect to undergo IPAA after TAC, this procedure is not mandatory, and many choose to forgo the pouch completely. A Swedish cohort study of over 2000 patients who underwent colectomy for inflammatory bowel disease showed that less than half (43%) of the patients underwent reconstructive surgery over a ten year period^[57]. A 2015 review of UC patients with an end ileostomy or IPAA demonstrated equivalent improvement in quality of life at 1 year with the majority of the benefit related to the control of disease symptoms^[58].

CONCLUSION

The optimal treatment algorithm in the management

of severe UC remains controversial. The purpose of this review is to summarize the current medical and surgical options available in the treatment of acute, severe UC.

First line treatment for patients presenting with acute severe UC consists of intravenous steroids, but those who do not respond require escalation of therapy or emergent colectomy. The mortality of emergent colectomy has declined significantly in recent decades, but due to the morbidity of this procedure, second line agents such as cyclosporine and infliximab have been used as rescue therapy in an attempt to avoid emergent surgery. In this era of multiple medical modalities available in the treatment of acute severe UC, it is imperative that physicians consider the advantages and disadvantages of prolonged medical therapy in an attempt to avoid surgery. Colectomy remains a mainstay in the treatment of severe ulcerative colitis not responsive to corticosteroids and rescue therapy, and timely referral for surgery allows for improved post-operative outcomes with lower risk of sepsis and improved patient survival.

Options for reconstructive surgery include three-stage IPAA or a modified two-stage procedure. The three-stage procedure offers the advantage of a healthier, well-nourished patient, but the two-stage procedure offers fewer in-hospital days and decreased overall cost.

The numerous avenues of medical and surgical therapy have allowed for great advances in the treatment of patients with UC. In this era of options, it is important to maintain a global view, utilize rescue therapy when indicated, and then maintain an appropriate threshold for surgery. Colectomy remains a viable and often life-saving treatment and should not be viewed as the "therapy of last resort".

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Role of surgery for colorectal cancer in the elderly

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Abstract

The prevalence of subjects with colorectal cancer is expected to grow in the next future decades and surgery represents the most successful treatment modality for these patients. Anyway, currently elderly subjects undergo less elective surgical procedures than younger patients mainly due to the high rates of postoperative morbidity and mortality. Some authors suggest extensive surgery, including multistage procedures, as carried out in younger patients while others promote less aggressive surgery. In older patients, laparoscopic-assisted colectomy showed a number of advantages compared to conventional open surgery that include lower stress, higher rate of independency after surgery, quicker return to prior activities and a decrease in costs. The recent advances in chemotherapy and the introduction of new surgical procedures such as the endoluminal stenting, suggest the need for a revisitation of surgical practice patterns and the role of palliative surgery, mainly for patients with advanced disease. In this article, we discuss the current role of surgery for elderly patients with colorectal cancer.

Key words: Laparoscopy; Colorectal cancer; Elderly; Comorbidities; Colorectal surgery

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Core tip: Age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for colorectal cancer. Many studies underlined that age is not a predictor of post operative complications in these patients. Therapeutic or palliative surgery should not be avoided in the elderly based exclusively on age.

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INTRODUCTION

Colorectal cancer (CRC) represents the third most commonly diagnosed cancer in developed countries, with almost 694000 deaths estimated to have occurred in 2012^[1]. The prevalence of elderly subjects with CRC is expected to grow in the next future decades due to the increase of age in the general population^[2]. In fact, CRC is infrequently diagnosed before age of 40, with a highest risk around age of 70.75% of CRC are identified in patients aged 65 years or older^[3]. In both Europe and United States approximately 50% of CRC patients are older than 70 years of age and in this age group CRC is the second most common cause of cancer death^[4,5]. Thus, age could be considered as a major risk factor for the development of this cancer^[6].

Many studies showed that surgical approach represents the most successful treatment modality for patients with CRC. Over the past years it has been observed an improvement in the survival of subjects with this cancer mainly due to a reduction in operative mortality and a raising in the resection rate^[7]. However, there is significant evidence that elderly subjects undergo less elective surgical procedures than younger patients^[8] mainly due to the high rates of postoperative morbidity and mortality^[9].

IMPACT OF AGE ON CRC SURGERY

There is a lack of consensus on the impact of age on postoperative outcome after major colorectal surgery. In fact, comorbidities are higher in elderly subjects thus leading to difficult decisions whether these patients are suitable for extensive bowel resection or not. A review of the literature published in the *Lancet* in 2000 pointed out that elderly patients are less likely to have curative surgery than younger patients^[8].

In 2008, the International Society of Geriatric Oncology (SIOG) created a task force to develop guidelines for the treatment of elderly patients with CRC^[10]. The task force confirmed the paucity of clinical trial data in the elderly and pointed out that treatment for elderly CRC patients should be analogous to those of younger patients.

A registry-based study carried out by Damhuis *et al.*^[9] on 6457 patients with CRC, evaluated the influence of age and other variables on resection rates and operative risk. All subjects included in the study were enrolled from 1985 through 1992 in hospitals connected to the Rotterdam Cancer Registry. Data analysis showed that 87% of the patients underwent resection but resection

rates were lower for patients older than 89 years (67%) and for patients with rectal cancer (83%). Patients younger than 60 years had a postoperative mortality rate of 1% that constantly increased with age. Patients 80 years and older showed an operative risk of 10%. Multivariate analysis was conducted and pointed out that gender, age, cancer subsite and stage could be considered as independent prognostic factors. The authors concluded that chronological age alone should not be an exclusion criteria for performing surgery in elderly patients with CRC. Even in patients aged over 90 years, resections can be performed with acceptable risk.

Another study^[11] analysed the electronic records from the Rotterdam Cancer Registry for octogenarians and nonagenarians who underwent resection in the period 1987-2000. The results showed that for CRC, postoperative mortality rates increased from 8% in patients aged 80 to 84 years, to 13% in patients aged 85 to 89 years and to 20% in nonagenarians.

A systematic review of 28 independent studies and 34194 patients, carried out by the Colorectal Cancer Collaborative Group, analysed the results for different groups of patients aged 65-74 years, 75-84 years and 85+ years with those for patients aged < 65 years. Compared with younger subjects, elderly patients have an increased frequency of comorbid conditions, are more likely to present with later-stage disease and undergo emergency surgery^[8]. Moreover, many studies focused on the role of adjuvant chemotherapy, demonstrating that elderly are less likely to be recommended or to receive adjuvant treatment^[12].

COMORBIDITIES AND COMPLICATIONS

Traditionally, contraindications for major surgery in elderly patients include a poor functional status, associated comorbidities and impaired cognition^[13]. Anyway, in the last 30 years elderly patients with CRC took advantage of healthcare progress and a retrospective trend analysis showed a reduction of palliative procedures and a decline in operative mortality for these patients^[14].

Most elderly patients with CRC have significant comorbidities such as cardiovascular and pulmonary diseases. Such diseases increase the operative risk and the risk of postoperative morbidity and mortality^[15,16]. A study by Hermans *et al.*^[17] evaluated the impact of comorbidities on the outcome of colonic surgery in elderly patients with colon cancer.

Comorbid assessment tools provide helpful information on the impact of comorbidities at the initial diagnosis and prospective outcome of CRC patients due to their prognostic capacity on survival. According to the classification of Charlson *et al.*^[18], the evaluated comorbidities included previous malignancies, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, hypertension, diabetes, and others (rheumatoid arthritis, hyperthyroidism, hypothyroidism, and sclerodermia). Compared to younger

age, elderly subjects presented with more cardiovascular pathology and dementia and with more than one type of the previously described comorbidities. The authors concluded that the type and number of co-morbidities influence post-operative mortality and morbidity. Complications were seen in 24% of younger patients vs 50% of elderly patients. No difference was observed as regards major complications (e.g., anastomotic leakage, fascia dehiscence, or intra-abdominal abscesses). In the elderly group there was a high incidence of delirium, pneumonia, wound infections, and minor complications such as urinary tract infection, and electrolyte alterations. Other factors that may cause poor outcome of surgery in the elderly include delayed presentation and advanced stage of the disease^[19,20].

As regards preoperative factors that could influence the choice of treatment, Marventano *et al.*^[19] proposed a modified version of the Charlson comorbidity index (CCI) that was specifically developed for colorectal cancer patients. This version of CCI emphasized the importance of specific conditions to better predict the survival of the patients. Particularly, the inclusion of 6-mo weight loss $\geq 20\%$, smoking > 20 cigarettes/d, underweight condition, and cardiac arrhythmias to the other comorbid conditions tested in the CCI showed a better predictive value compared with the original CCI and other comorbidity indices (e.g., the Elixhauser method, the National Institute on Aging and National Cancer Institute comorbidity index, and the Adult Comorbidity Evaluation-27). Noteworthy, the Authors found that only moderate or severe renal disease and diagnosis of AIDS were independently associated with higher risk of death^[19].

An analysis of 31574 patients in the surveillance, epidemiology and end results-medicare database for patients diagnosed with colon cancer between 1992 and 2005 was conducted to describe patterns of surgery in patients aged > 80 years and examine outcomes with and without colectomy. The Authors demonstrated that 80% of the "oldest old" patients with colon cancer in the United States are undergoing surgical resection^[21]. In this study, 46% of subjects were diagnosed during an urgent or emergent hospital admission, with decreased 1-year overall survival (70% vs 86% for patients diagnosed during an elective admission). Older age, black race, more hospital admission, use of home oxygen, use of wheelchair, frailty and dementia were most predictive of nonoperative management. The 1-year overall survival rate for both operative and nonoperative patients was lower than the colon cancer-specific survival rate (operative patients: 78% vs 89%; nonoperative patients: 58% vs 78%)^[21].

A study by Kahn *et al.*^[22] showed that older age is not independently associated with complications after surgery for colorectal cancer. The Authors underlined the importance of clinical status and American Society of Anesthesiologists (ASA) class in patients' selection rather than age.

THERAPEUTIC OPTIONS FOR CRC IN THE ELDERLY

Different approaches to treat elderly subjects with CRC have been proposed over the past years. Some authors endorse extensive surgery, including multistage procedures, as carried out in younger patients^[23,24], while others promote less aggressive surgery^[25,26].

Most subjects with stage I or II CRC are treated by surgery, even if some patients with stage II could benefit from adjuvant therapy^[27,28]. Surgery followed by adjuvant chemotherapy is the standard treatment for stage III CRC. Subjects with metastases could benefit from chemotherapy alone or combined with targeted therapy. At this stage, surgery is indicated in selected patients. The treatment for stage IV CRC includes surgery and preoperative or postoperative, radiotherapy and/or chemotherapy.

Different factors could influence surgical outcomes in stage IV CRC, including the presence of liver metastases^[29,30] and cardiovascular disease^[31], the degree of peritoneal involvement and primary cancer resection^[32], the tumor differentiation, and age older than 75^[33].

There is still uncertainty about the effective benefit of surgery directed toward removal of the primary tumor for the management of asymptomatic patients with stage IV CRC and unresectable metastases. Palliative surgery is indicated for most patients with bowel obstruction or uncontrollable bleeding^[34].

Guidelines from the National Comprehensive Cancer Network recommend surgical treatment in stage IV CRC only in symptomatic patients at risk of obstruction, or with metastases suitable for potentially curative resection^[35].

A study by Temple *et al.*^[34] evaluated surgical practice patterns for patients over 65 years of age with stage IV CRC in a United States population-based cohort. They observed that 72% of patients received primary-cancer-directed surgery (CDS) with a 30-d postoperative mortality of 10%. CDS was less performed on patients with left-sided or rectal lesions, subjects older than 75 years, blacks, and those of lower socioeconomic status; but even among those older than age 75, the CDS rate was 69%. Chemotherapy was administered to 47% of patients that underwent CDS vs 31% of patients who did not. The resection of metastases was performed only on 3.9% of patients at any point from diagnosis to death^[34].

There is evidence that subjects with stage IV CRC could tolerate chemotherapy without requiring surgery to remove the primary tumor. In fact, a study by Tebbutt *et al.*^[36] showed that there were no differences in gastrointestinal complications (e.g., fistulas, peritonitis, obstruction) in patients who did not undergo CDS compared to those who had CDS^[36]. The recent advances in chemotherapy and the introduction of new surgical procedures (e.g., endoluminal stenting) suggest the need for a revisitation of surgical practice patterns and the role of palliative surgery for IV stage CRC patients.

Many studies underlined the importance of laparoscopic assisted colectomy (LAC) for the treatment of CRC. However the majority of them were conducted on patients younger than 65 years. In general, LAC showed a number of advantages compared to conventional open surgery that include lower stress, higher rate of independency after surgery, quicker return to prior activities and a decrease in costs^[37,38].

There are many issues related to the limited number of LAC carried out on elderly subjects requiring colectomy: First of all, the high number of comorbidities; second, the longer operative times; and third, the paucity of scientific literature assessing risks and benefits of this procedure in the elderly. A review of the literature carried out by Mutch^[37] identified 18 studies on LAC in the elderly. There is significant evidence that LAC could be performed in the elderly population safely and without significant increase in morbidity and mortality^[38].

A study by Vara-Thorbeck *et al.*^[39] represents the first report of LAC in older patients. The study was conducted on 18 patients that underwent LAC for CRC. Eleven subjects were older than 70 years. None of the cases were converted to open laparotomy, and the mortality was null. The results showed that LAC could be performed safely on both older and younger patients while maintaining the same principles of surgical technique as open colectomy. A number of more recent studies confirmed that laparoscopy-assisted colectomy in the elderly can be performed with no difference in morbidity or length of hospital stay compared with open surgery^[40-44]. Vignali *et al.*^[45], compared the outcomes of open colectomy vs LAC in a population of octogenarians. They observed that the patients undergoing LAC had a shorter hospital stay (LAC 9.8 d vs open 12.9 d), reduced morbidity (LAC 21% vs open 31%), and higher rate of independence at discharge (LAC 98% vs open 82%), thus confirming that the benefits of LAC are maintained with advancing age.

A study by Bardram *et al.*^[46] analyzed the outcomes of laparoscopy combined with a perioperative multimodal rehabilitation protocol in 50 patients of median age 81 years. After LAC, patients were treated with epidural local anaesthesia for 2 d, early mobilization and oral nutrition, with a significant improvement in recovery.

O'Connell *et al.*^[47] pointed out that in frail elderly with limited life expectancy, the benefits of cancer surgery are frequently unclear, and surgical resection of tumors is less performed as the patient ages.

A study by Finlayson *et al.*^[48] aimed to determine functional status and mortality rates after colon cancer surgery in older nursing home residents. They conclude that even when not curative, surgery for CRC may be an effective palliative procedure. Less invasive treatments, such as endoscopic treatment or embolization of bleeding tumors or the use of endoluminal stents for large bowel obstruction, may represent an alternative to surgery for individuals with limited life expectancy.

The international SIOG expert recommendations, according to the available evidence on CRC in the elderly, suggested that emergency surgery should be avoided

when possible; the use of colorectal stents should be taken into account to improve patient nutrition thus facilitating elective surgery 1-2 wk after the patient has presented as an emergency; the pathway of choice should be elective surgery with a prospective analysis of the perioperative variables and careful treatment; possible curative resection of liver metastases should be performed in healthy elderly subjects receiving a careful preoperative assessment and a high quality postoperative care^[10].

As regards rectal cancer, analysis of 991 treatments, in the 838 elderly rectal cancer patients from the Cote d'Or and Calvados tumor registries study^[49], showed 54% of patients to undergo curative resection, 7% to undergo palliative resection, 12% to undergo by-pass laparotomy, 27% to undergo no surgery, 17% to receive radiotherapy and 2% to receive chemotherapy. These data highlighted a low use of radiotherapy either combined with surgery or alone, while chemotherapy was almost never administered. Both surgery and radiotherapy are important for controlling local recurrence and therefore local failure rates. Recently the use of the surgical technique total mesorectal excision^[50] has contributed to a reduction in pelvic recurrences. A study by Kim *et al.*^[51] assessed the long-term oncological and functional outcomes of intersphincteric resection for T2 and T3 low rectal cancer. The authors observed a 5-year overall survival rates of 95.8% for T2 and of 94.7% for T3. The 5-year recurrence-free survival rates were 87.5% for T2 and 86.8% for T3 (Table 1). Radiotherapy has been shown to impact significantly on survival in resectable tumors^[52] and is critical for the management of patients with all stages of rectal tumors.

CONCLUSION

In general, there are age-related disparities in colon cancer treatment, with older patients being less likely to receive recommended therapy. According to the SIOG guidelines, elderly subjects should receive screening and earlier diagnosis; the management of CRC should be more aggressive and closer to that received by younger patients; the treatment should be the most intensive and appropriate according to the biological age and the presence of comorbidities^[10]. Many studies pointed out that age is not a predictor of post operative complications in patients with CRC^[53-56]. Age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for CRC. Thus, therapeutic or palliative surgery based solely on age should not be avoided in these patients. In the future, the surgical assessment of CRC in the elderly should take into account a multidisciplinary process before choosing the best possible therapy for each patient. There will be the need for services specialized in the care of at-risk older patients, rehabilitation and palliative care consultation. An appropriate management should also include the functional status, the grade of frailty, the life expectancy and also patient's requests.

Ref.	Year	No. of patients	Postoperative mortality	Resection rates	Comorbidities	Survival rate	Independent prognostic factors
Damhuis <i>et al</i> ⁽⁹⁾	1996	6457	1% for patients < 60 yr and steadily increased with age. The operative risk was 10% for patients > 80 yr	87% of the patients underwent resection. 67% for patients > 89 yr and 83% for patients with rectal cancer	-	-	Gender, age, subsite and stage
Damhuis <i>et al</i> ⁽¹⁰⁾	2005	2765	Increased from 8% for the age group 80-84 to 13% for those 85-89 to 20% in nonagenarian	-	-	-	-
Hermans <i>et al</i> ⁽⁷⁾	2010	207	In-hospital mortality was 16% in the elderly and 5% in the younger group ($P < 0.01$)	No differences between < 75 yr and > 75 yr: ileocecal resection (2% vs 4%); hemicolectomy right (42% vs 49%); transversum resection (1% vs 3%); hemicolectomy left (15% vs 8%); sigmoid resection (26% vs 22%); anterior resection (10% vs 9%); subtotal colectomy (3% vs 1%); double resection (1% vs 4%)	More co-morbidities > 75 yr, especially cardiovascular pathology ($P < 0.01$) and dementia ($P < 0.01$), more than one type of comorbidity according to the Charlson classification ($P < 0.05$)	5-yr survival rate in < 75 yr was 62% compared with 36% in the elderly ($P < 0.05$)	-
Neuman <i>et al</i> ⁽²¹⁾	2013	31574	30-d mortality rate of 10% after urgent/emergent admission	-	Hypertension, peripheral vascular disease, and chronic pulmonary disease were found to be associated with improved overall and cancer-specific survival	The 1-yr overall survival rate was lower than the colon cancer-specific survival rate (operative patients: 78% vs 89%, non-operative patients: 56% vs 76%)	Older age, black race, more hospital admissions, use of home oxygen, use of a wheelchair, being frail, and having dementia
Irvin ⁽²¹⁾	1988	306	The surgical mortality rates for patients > 70 yr were 6% overall, 4% after elective operations, and 16% after emergency surgery; the corresponding mortality rates for patients < 70 yr were 3%, 1%, and 20%	-	-	Crude actuarial 5-yr survival curves showed an increased death rate for patients > 70 yr after 18 mo and a significantly lower 5-yr survival ($P < 0.05$) but the age-corrected survival curves for the two groups were not significantly different	-
Temple <i>et al</i> ⁽³⁴⁾	2004	9011	The 30-d postoperative mortality was 10%. The 30-d surgical mortality was significantly greater in the no primary cancer-directed surgery (CDS) group among patients who underwent a surgical procedure, when compared with the primary CDS group (26% vs 9%, $P = 0.001$)	The rates of CDS declined with age: 76% of 65 to 69-yr-old patients received primary CDS, whereas the rate declined to 62% of patients age ≥ 85 yr	-	The overall median survival for the entire cohort was 7 mo. There were differences in survival between patients treated with CDS and no CDS exist (median, 10 mo vs 3 mo, respectively), but data are not reliably because of patient selection in the non-randomized setting	Left-sided or rectal lesions, age > 75 yr, blacks, marital status and lower socioeconomic status
Vallribera Valls <i>et al</i> ⁽⁴²⁾	2014	277: Laparoscopic group; 268: Open group	Open surgery group showed a higher mortality (6.7% vs 3.2%, $P = 0.034$). Mortality was significantly inferior in laparoscopy group in younger patients (< 75 yr, 0% vs 3%, $P = 0.038$)	-	Open surgery group showed a higher overall morbidity rate (37.3 vs 21.6%, $P = 0.001$), medical complications (16.4% vs 10.5%, $P = 0.033$), surgical complications (23.5% vs 15.5%, $P = 0.034$), the	-	-

Author	Year	Study Design	Population	Intervention	Control	Results	Conclusions
Vignali <i>et al</i> ^[45]	2005	61: Laparoscopic colectomy; 61: Open colectomy	Overall mortality rate was 2.4%. The morbidity rate was 21.5% in the laparoscopy group and 31.1% in the open group (P = 0.30)	Overall mortality rate was 2.4%. The morbidity rate was 21.5% in the laparoscopy group and 31.1% in the open group (P = 0.30)	-	Overall morbidity rate difference between open and laparoscopy approach disappeared in the oldest group (≥ 85 yrs old). Surgical site infections rate was inferior for patients < 75 yr old in laparoscopy group compared with open	-
Bouvier <i>et al</i> ^[46]	2005	1571 with colon cancer; 838 with rectal cancer	During the study period from 8.7% to 9.5% for colon and from 16.3% to 5.6% for rectum	69% in colon cancer; 54% in rectal cancer	-	Overall 3-yr survival rates were 45.2% for colon cancer and 46.2% for rectal cancer. Overall 5-yr survival rates were 40.9% and 37.3% respectively	Age, gender, period of diagnosis, treatment. A second multivariate analysis restricted to patients resected for cure and alive after the first month of follow-up showed that age between 85 and 89 was no longer a significant factor of survival
Heald <i>et al</i> ^[50]	1998	519 with rectal cancer	The operative mortality (30-d) was 3.3%	-	-	68% at 5 yr and 66% at 10 yr	-
Kim <i>et al</i> ^[51]	2016	62 with very low rectal cancer. Group I, n = 24, stage T2 Group II, n = 38, stage T3	No postoperative mortality in both groups	Temporary urinary retention (group I : 10 cases; Group II : 15 cases), postoperative paralytic ileus (group I : 2 cases; Group II : 3 cases), perineal abscess (group I : 1 case; Group II : 1 case), and anastomotic leakage (group I : 1 case; Group II : 1 case). Late complications, such as anastomotic stricture (group I : 6 cases; Group II : 10 cases), rectovaginal fistula (group I : 0 case; Group II : 1 case) after stoma closure	-	5-yr overall survival rates were 95.8% for group I and 94.7% for group II. The 5-yr recurrence-free survival rates were 87.5% for group I and 86.8% for group II	-
Schiffmann <i>et al</i> ^[54]	2008	517	30-d mortality was higher in the older age group (> 75 yr)	-	-	No differences in 30-d morbidity except in postoperative bleeding	-
Devon <i>et al</i> ^[55]	2009	898	The in-hospital mortality rate was 1% in the younger group (< 75 yr) compared with 4.2% in the older (> 75 yr) (P = 0.002)	-	-	The overall five-year survival was 68.7% and 57.3% in the younger and older groups, respectively, whereas colorectal cancer-specific five-year survival was not significantly different (74.0% vs 74.7%)	-
Paksoy <i>et al</i> ^[56]	1999	822	The postoperative (30 d) mortality was 3% in the younger group (< 65 yr) (20/565) and 7% in the older group (17/257) (difference not significant)	-	-	Five-year survival rates for older and younger patients were 33% and 45%, respectively (P < 0.05)	-

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Rubber band ligation of hemorrhoids: A guide for complications

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Abstract

Rubber band ligation is one of the most important, cost-effective and commonly used treatments for internal hemorrhoids. Different technical approaches were developed mainly to improve efficacy and safety. The technique can be employed using an endoscope with forward-

view or retroflexion or without an endoscope, using a suction elastic band ligator or a forceps ligator. Single or multiple ligations can be performed in a single session. Local anaesthetic after ligation can also be used to reduce the post-procedure pain. Mild bleeding, pain, vasovagal symptoms, slippage of bands, priapism, difficulty in urination, anal fissure, and chronic longitudinal ulcers are normally considered minor complications, more frequently encountered. Massive bleeding, thrombosed hemorrhoids, severe pain, urinary retention needing catheterization, pelvic sepsis and death are uncommon major complications. Mild pain after rubber band ligation is the most common complication with a high frequency in some studies. Secondary bleeding normally occurs 10 to 14 d after banding and patients taking anti-platelet and/or anti-coagulant medication have a higher risk, with some reports of massive life-threatening haemorrhage. Several infectious complications have also been reported including pelvic sepsis, Fournier's gangrene, liver abscesses, tetanus and bacterial endocarditis. To date, seven deaths due to these infectious complications were described. Early recognition and immediate treatment of complications are fundamental for a favourable prognosis.

Key words: Hemorrhoids; Rubber band ligation; Pain; Bleeding; Infection

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Core tip: Rubber band ligation of hemorrhoids is a very effective non-surgical treatment for internal hemorrhoids. Different techniques were developed mainly to improve efficacy and safety. This is an overall safe procedure, although severe complications can occur, such as infections. It is very important to know these possible complications to reduce their risk and to allow early recognition and successful treatment.

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GENERAL CONCEPTS OF HEMORRHOIDAL LIGATION

In the 1950s, Blaisdell^[1] described a new technique for the ligation of bleeding internal hemorrhoids which can be performed in the office without the need for hospitalization. This new concept was based on the fact that internal hemorrhoids are easily accessible, practically devoid of pain and thus, suitable for outpatient treatment. In addition, during this period, injection therapy was an alternative to surgery, but without any controlled destruction of hemorrhoidal tissue. The technique of office ligation of internal hemorrhoids was later modified and simplified using rubber bands by Barron^[2] in the 1960s. Since then, rubber band ligation (RBL) was established as one of the most important, cost-effective and commonly used treatments for first- to third-degree internal hemorrhoids, causing fibrosis, retraction, and fixation of the hemorrhoidal cushions^[3].

When compared to other non-surgical methods, like sclerotherapy and infrared coagulation, RBL has better long-term efficacy, requiring fewer sessions for treatment, although with a higher rate of post-treatment pain^[4,5]. Hemorrhoidectomy showed better response rates, but it was associated with more complications, time off work and pain than RBL^[4,6]. RBL should be considered as a first-line therapy for first- to third-degree internal hemorrhoids^[4] commonly indicated for bleeding and/or prolapsing. Surgical therapy can be considered in the presence of an important external component, thrombosis or recurrence after repeated banding^[6].

There are studies that evaluated the use of combined non-surgical therapies^[7-9]. A prospective randomized trial^[7] comparing the simultaneous application of sclerotherapy and RBL (sclerotherapy of the smaller non-prolapsing hemorrhoidal piles and RBL of the larger prolapsing piles), with sclerotherapy and RBL applied separately, showed that there was no significant difference between the combination and RBL alone groups.

RBL technique can be employed using an endoscope with forward-view or retroflexion or without an endoscope, using a suction elastic band ligator or a forceps ligator. Several patient positions can be used, without the need for bowel preparation or sedation^[3] and the ligations should be performed in the area above the dentate line that is devoid of sensory nerves.

The success rate of RBL ranges from 69% to 97%^[10]. A larger number of recurrences have been described with longer follow-up periods, but recurrences can be treated with repeat sessions and time to recurrence shortened with subsequent treatment courses^[10]. Recurrence rates are variable, with 6.6% to 18% of patients submitted to RBL requiring additional treatment sessions due to the recurrent symptoms^[10].

COMPLICATIONS OF RBL

There are several complications associated with this technique, which can be classified as minor or major (severe)^[11]. Mild bleeding, pain, vaso-vagal symptoms, slippage of bands, priapism, difficulty in urination, anal fissure, and chronic longitudinal ulcers are more common and normally considered minor complications. Massive bleeding, thrombosed hemorrhoids, severe pain, urinary retention needing catheterization, pelvic sepsis, fistula and death are major complications that have been less commonly reported.

Several studies described different rates of complications following RBL, ranging from 3%^[12] to 18.8%^[13]. The most common complications are pain and bleeding.

A review of 39 studies including 8060 patients submitted to RBL revealed post-banding complications in 14% of the patients, in the form of severe pain in 5.8%, haemorrhage in 1.7%, infection in 0.05%, anal fissure and fistula in 0.4%^[14].

In a prospective study by Bat *et al*^[11], including 512 patients submitted to RBL, 37 (7.2%) patients had complications. In this study RBL was performed using the Barron applicator, with a single ligation per session, with a total of one to seven ligations per person at four-week intervals. Minor complications were reported in 4.7% (thrombosed prolapsed hemorrhoids, slippage of bands, minor rectal bleeding, chronic longitudinal ulcer, priapism, difficulty in urination, and tender induration) and severe complications, requiring admission were described in 2.5% of the patients (massive bleeding, severe thrombosis of hemorrhoids, severe pain, perianal abscess, and fistula). Severe complications were more common in right anterior hemorrhoid RBL and in patients with previous hemorrhoidectomy. Most complications occurred following the first session.

Studies do not show any significant manometric change after RBL^[15-17], namely, in the maximum resting pressure and squeeze pressure.

Bleeding

Bleeding after RBL normally occurs after 10-14 d, probably due to the sloughing of the ligated hemorrhoids^[11,18,19].

Patients taking anti-platelet and/or anti-coagulant medication have a higher risk of secondary bleeding. There are cases of massive life-threatening haemorrhage following hemorrhoidal RBL in patients on acetylsalicylic acid (ASA)^[18,20,21] and clopidogrel^[19].

In a study by Bat *et al*^[11], including 512 patients submitted to RBL, five of the six patients who had massive bleeding, developed symptoms 10 d or more after the procedure. Three patients that were transfused were taking ASA regularly.

In a retrospective study^[10] including 805 patients who had undergone RBL aiming to evaluate the efficacy and safety of this procedure, higher bleeding rates were encountered with the use of ASA /nonsteroidal anti-inflammatory drugs (NSAIDs) and warfarin. Two (25%) of eight patients taking warfarin bled, whereas three

(7.5%) of 40 patients taking ASA or other NSAIDs bled.

Marshman *et al*^[22] conducted a study, including 241 patients undergoing RBL over a five-year period and focused on complications. Three (1.2%) patients required hospitalization for complications, of these patients, two on oral anticoagulants were admitted for significant bleeding.

In a retrospective study^[23], including 364 patients submitted to RBL while on antithrombotic therapy, holding antithrombotic medication 7-10 d following the procedure, appeared to equalize the risk of bleeding to that of patients not taking antithrombotic medications. There were 23 bleeding complications, and patients on clopidogrel experienced 50% of the significant bleeding episodes and 18% of the insignificant bleeding episodes, having a higher risk for bleeding complications, but due to the small sample size, this difference did not reach statistical significance. These authors defend that not stopping the drug before the procedure reduces the risk of ischemic events and allows ligation in the first consultation. Also, the greatest risk for bleeding typically occurs from 5 to 10 d after ligation.

It is routinely recommended that patients should stop this medication for at least 1 wk prior to, and 2 wk post RBL^[18]. The risk of the hemorrhoidal bleeding against the risk of thrombotic events must be balanced.

Concerning liver cirrhosis few data are published. In a prospective study including 500 patients submitted to RBL of symptomatic internal hemorrhoids, this procedure proved to be safe in 16 patients with coagulation disorders due to liver cirrhosis^[13].

Pain

Pain is one of the most common complications of RBL. Some studies reported mild anal pain in at least 25%-50% of patients, for the first 48 h after banding^[24,25], sometimes associated with nausea, shaking, light headedness, and urinary retention^[25].

In a prospective study^[26] specifically evaluating pain and patient satisfaction following RBL of hemorrhoids, pain was the most common symptom occurring in almost 90% of patients, with the pain scores higher 4 h following the procedure. At 1 wk, 75% of patients reported themselves as being pain-free; however, 7% were still experiencing moderate-to-severe pain. A total of 65% required oral analgesia during the week following RBL, most frequently on the day of the procedure. Vaso-vagal symptoms (dizziness or fainting) occurred in 30%, more commonly at the time of the procedure and in the evening of that day. Patients requiring oral analgesia and those experiencing bleeding or vaso-vagal symptoms were significantly less likely to be satisfied with RBL.

To minimize complications, before application, the tissue should be tested and if the patient complains of discomfort following the ligation, the band should be removed immediately and reapplied^[27].

Infectious complications

Septic complications have been described after hemo-

rrhoid treatments, namely, after injection sclerotherapy, RBL, cryotherapy, hemorrhoidectomy and stapled hemorrhoidopexy^[28,29].

Several infectious complications have been reported following RBL including pelvic sepsis, Fournier's gangrene, liver abscesses, tetanus and bacterial endocarditis. Deaths due to these infectious complications were also reported.

One of hypotheses is related to the transmural necrosis or slough following banding that facilitates the development of deep infection by migration of the bowel bacterial flora, which can spread to adjacent tissues^[30-32]. Transient bacteraemias have been described following digital rectal examination, protoscopy, colonoscopy, injection sclerotherapy and hemorrhoidectomy^[33-37].

One of the most serious complications is pelvic sepsis, with several reports in the literature^[14,30,31,38-41]. Suspicion should arise in patients with pain, fever, edema and urinary retention^[28-31], normally 3-10 d following banding. To our knowledge, only one case that developed septic complications was human immunodeficiency virus (HIV) positive^[40].

A case of Fournier's gangrene in an elderly patient with diabetes following RBL was described. The patient recovered after surgical debridement and antibiotherapy^[42].

Liver abscesses associated with the treatment of hemorrhoids were first described related to hemorrhoidectomy^[43,44] and sclerotherapy^[45]. To our knowledge, there are six case reports of liver abscesses due to RBL of hemorrhoids^[20,46-50]. Most cases were male (5/6 patients), more frequently due to *Klebsiella* (4/6 patients) and multiple abscesses (5/6 patients) were normally present. All patients recovered and only in one case a right hepatectomy was necessary (Table 1).

Tetanus due to RBL was described in two patients^[51,52], both of whom survived.

There is a only a case report of patient with a ventricular septal defect that developed endocarditis leading to septic pulmonary and renal emboli following single-quadrant banding of hemorrhoids^[53]. The patient recovered after cardiac surgery.

The literature shows that all seven deaths linked to RBL were due to septic complications^[32,38,54,55]. Most cases were male (six patients) and no predisposing factors have been established. Time until symptom onset was between 3 to 10 d after banding, and the most common initial symptoms were pain and urinary retention (Table 2).

Early recognition and immediate treatment of infectious complications are fundamental. There are several authors recommending enemas, application of povidone-iodine solution and oral antibiotics before the procedure to reduce the risk, but studies supporting these recommendations are lacking.

SPECIAL SITUATIONS

There are certain conditions that have been considered a contraindication for RBL of hemorrhoids due to a higher risk of complications, namely, HIV and Crohn's disease.

In 1989, there was a case report of a 45-year-old

Table 1 Case reports of liver abscesses due to rubber band ligation of hemorrhoids

Age (yr)	Sex	Bacteria	Comorbidities	No.	Treatment	Outcome	Ref.
58	Male	Klebsiella aerogenes	Diabetes	Multiple	Antibiotics, drainage	Resolution	[20]
58	Male	Klebsiella pneumoniae	Previous pulmonary tuberculosis	Multiple	Antibiotics, drainage, right hepatectomy	Resolution	[46]
40	Male	Citrobacter freundii		Single	Antibiotics, drainage	Resolution	[47]
64	Male	Fusobacterium necrophorum	Asthma	Multiple	Antibiotics, drainage	Resolution	[48]
49	Male	Klebsiella pneumoniae	Diabetes, hypertension, dyslipidaemia, stroke, previously treated pulmonary tuberculosis	Multiple	Antibiotics	Resolution	[49]
61	Female	Klebsiella pneumoniae	Peptic ulcer, dyslipidemia	Multiple	Antibiotics, drainage	Resolution	[50]

Table 2 Deaths related to rubber band ligation

Age (yr)	Sex	Comorbidities	Time until symptom onset (d)	Symptoms	Bacteria	Ref.
38	Male	None	4	Pain, urinary retention	None	[32]
54	Male	None	10	Vomiting, urinary retention, fever	None	[32]
34	Male	None		Pain, urinary retention, fever	<i>Enterobacteriaceae</i> (abdomen fluid) <i>Escherichia coli</i> (retroperitoneum and blood)	[32]
37	Male	None	5	Pain, urinary retention	<i>Escherichia coli</i> (urine and rectal cultures)	[32]
73	Male	Not described	3	Pain, fever, urinary retention,		[38]
27	Male	Schizophrenia	4	Fever, pain, difficulty passing urine	<i>Clostridia perfringens</i> , <i>Clostridia sporogenes</i> , <i>Bacteroids</i> (pelvic muscles), <i>Escherichia coli</i> (rectal cultures)	[54]
68	Female	None	7	Anal pain, difficulty passing urine, vomiting	<i>Enterococcus</i> (perianal fluid)	[55]

HIV positive male patient who developed a supralelevator abscess after RBL^[40]. The authors concluded that this procedure is potentially dangerous in HIV patients and it should be abandoned. Although this complication was also described in HIV negative patients following RBL^[38] and, to our knowledge, this is the only infectious complication described in an HIV positive patient. In a retrospective review^[56] of asymptomatic HIV positive patients that were submitted to RBL of symptomatic hemorrhoids, this technique proved to be safe and effective. It was performed in 11 HIV positive patients and no complications were reported. Median CD4 cell count was 450 (range, 200-1000) cells/ μ L and there was a median of two (range, 1-4) bands per patient.

In a retrospective study^[57], including 42 patients with ulcerative colitis and 20 with Crohn's disease, treated both surgically and conservatively for hemorrhoids over a 41 year period, patients with ulcerative colitis had a low complication rate (4 complications after 58 courses of treatment) and Crohn's disease had a high complication rate (11 complications after 26 courses of treatment). No reference was made to RBL treatment in this study. Thus, concerning Crohn's disease and RBL very few data are published. D'Ugo *et al*^[58] published a 9-year retrospective study of 45 Crohn's disease patients treated for hemorrhoids either medically or surgically. In this series RBL was considered a surgical treatment, and in total two patients submitted to it reported no complications.

DIFFERENT TECHNICAL APPROACHES

Suction vs forceps ligation

A prospective randomized clinical trial including 100

patients with second- and third-degree hemorrhoids compared suction and forceps ligation concerning pain after the procedure, intra-procedure bleeding and other complications. The forceps group had higher pain scores immediately after ligation and at 24 h post-banding, needed higher amount of analgesia and had higher intra-procedure bleeding^[59]. Authors hypothesized that this is due to poorer visualization and forceps-induced physical trauma of the friable hemorrhoids.

Single vs multiple ligations

Initially, single ligation per session was recommended due to the belief that a higher complication rate is associated with multiple banding, namely, pain and tenesmus after the procedure^[2].

A retrospective study^[60] comparing patients with multiple banding in a single session ($n = 155$) and single banding ($n = 22$) showed that patients with multiple hemorrhoidal banding did experience more discomfort and pain (29% vs 4.5%), but that this was well tolerated and manageable with oral analgesia of limited duration. Vasovagal reactions, limited bleeding, urinary symptoms, and local swelling and oedema were also more common. There were no cases of massive bleeding or sepsis.

Randomized controlled trials comparing single and triple band ligation^[27,61] showed that triple RBL is an equally safe and effective procedure for managing internal hemorrhoid disease. Fewer treatment sessions are required for triple RBL, so this strategy is more cost-effective^[61]. Furthermore, there is a risk of possible bleeding from untreated hemorrhoids after an initial RBL for other hemorrhoids^[2].

Endoscopic vs non-endoscopic ligation

The endoscopic hemorrhoidal ligation was initially described in 1998, in the forward-view^[62] and then in retroflexion^[63,64]. Some authors favoured the retroflexed position due to easy assessment and treatment^[63].

Endoscopic ligation proved to be an effective and safe technique for treating internal hemorrhoids. In a study by Berkelhammer *et al*^[63], retroflexed endoscopic band ligation of second- and third-degree bleeding internal hemorrhoids, with a mean of three bands (range 1-6) placed in a single session, showed an excellent result in 80% of patients with second-degree hemorrhoids (better than third-degree hemorrhoids with an excellent result in 54%). Major, nonfatal complications were detected in 4% (severe pain, delayed haemorrhage requiring transfusion, urinary retention, and severe thrombosis of external hemorrhoids) of patients. In a study by Fukuda *et al*^[64], retroflexed endoscopic multiple band ligation was performed on patients with symptomatic first- to fourth-degree internal hemorrhoids, with a mean of 8 bands (range 4-14) placed per treatment session. The long-term response was excellent for 89% of the patients, without any major complications in the 82 patients included (severe pain, late-onset haemorrhage requiring transfusion, or severe thrombosis of external hemorrhoids).

Endoscopic ligation has some advantages over rigid instruments that are more difficult to manoeuvre and have limited visualization, allowing for more band placement and photographic documentation of the procedure^[62,63]. There are randomized studies comparing ligation with flexible videoendoscopes (retrograde or antegrade) and the conventional technique with rigid proctoscopes^[65,66]. These trials showed that the long-term efficacy and safety were similar, but with videoendoscopes fewer treatment sessions were needed and a higher proportion of patients treated with a single session^[65].

Local anaesthetic vs no-local anaesthetic in hemorrhoidal ligation

The use of local anaesthesia after hemorrhoidal banding in order to reduce post-procedural pain was studied. In 2015, a meta-analysis^[24] including four randomized controlled trials (387 patients in total), comparing pain and other associated symptoms in patients who received a local injection after hemorrhoidal banding and patients who did not, showed that the post-procedure pain score was significantly lower in the group of patients with local anaesthetic injection. These studies included different anaesthetic treatment protocols. Hooker *et al*^[25] randomized patients to receive a local injection of 0.5 mL of 0.5% bupivacaine with 1:200000 epinephrine, an injection of normal saline, or no injection, immediately superior to each band. In patients receiving bupivacaine within 30 min post-banding, there was a significant reduction in pain, nausea and shaking, which may be useful in the immediate period. However, bupivacaine injection did not reduce pain at 6 h or more post-banding, and did not have other benefits. In a study by

Law *et al*^[67] patients received 1-2 mL of 2% lignocaine injected into the banded hemorrhoidal segment, but no post-ligation pain reduction was reported. Kwok *et al*^[68] randomized patients to an anesthetic injection of 1 mL of 0.5% bupivacaine without adrenaline in the submucosa proximally to the rubber band site and showed that this reduced discomfort compared with no local anaesthetic by the time patients left the clinic (30 min after the procedure). Benefit beyond this period was not obtained. Authors hypothesized that local anaesthetic injection deep to the banded tissue, until a bleb large enough to encompass the "base" of the hemorrhoid was raised, would be more effective than injection into the devitalized banded tissue.

Bupivacaine effect lasts for 4 to 6 h^[25], so this could help in the short-term period following banding, but no study has thus far showed that this can be helpful beyond this period.

CONCLUSION

RBL of hemorrhoids is a very effective and safe procedure, with severe complications being uncommon. Before applying the bands, it is very important to know the patient's medical history, namely, comorbidities and medication. After RBL, patient education is mandatory, including analgesia, softening of the stools, warm sitz baths and information concerning early and late complications. If complications occur, early recognition and immediate treatment are fundamental for a successful outcome.

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Minimally invasive management of anastomotic leaks in colorectal surgery

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Abstract

Anastomotic leakage is an unfortunate complication of colo-

rectal surgery. This distressing situation can cause severe morbidity and significantly affects the patient's quality of life. Additional interventions may cause further morbidity and mortality. Parenteral nutrition and temporary diverting ostomy are the standard treatments of anastomotic leaks. However, technological developments in minimally invasive treatment modalities for anastomotic dehiscence have caused them to be used widely. These modalities include laparoscopic repair, endoscopic self-expandable metallic stents, endoscopic clips, over the scope clips, endoanal repair and endoanal sponges. The review aimed to provide an overview of the current knowledge on the minimally invasive management of anastomotic leaks.

Key words: Minimally invasive surgery; Anastomotic leak; Colorectal surgery

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Core tip: Anastomotic leakage is the most feared complication of colorectal surgery, leading to significant patient morbidity and mortality. Its incidence is 3%-6%, even in experienced hands. Despite the high prevalence of this condition, there is no consensus on the proper management of anastomotic leaks. In this review, we summarize and discuss the current knowledge on minimally invasive treatment strategies for anastomotic leakage after colorectal surgery.

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INTRODUCTION

Anastomotic leak (AL) following colorectal surgery is a feared complication with an incidence of 3%-6%, even

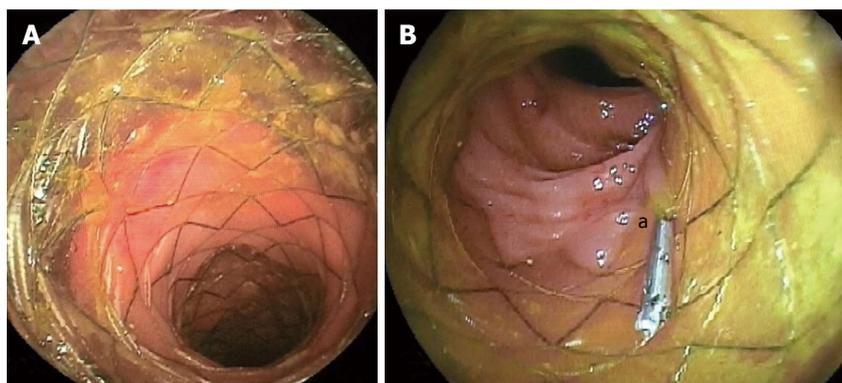


Figure 1 Self-expanding metal stent for anastomosis leakage. A: Endoscopic image after deployment of the stent; B: Stent with clip (a) at the proximal end.

in experienced hands^[1]. ALs can cause severe morbidity, cost, and affect the patient's quality of life. Moreover, major additional interventions may lead to further morbidity and mortality (with of 10%-20%)^[2]. Currently, technological developments in minimally invasive treatment modalities for ALs have caused them to be used widely. These modalities include laparoscopic repair, endoscopic self-expandable metallic stents (SEMS), endoscopic clips, over the scope clips (OTSCs), endoanal repair and endoanal sponges.

In this review, we summarize and discuss the current knowledge on minimally invasive treatment strategies for ALs after colorectal surgery.

LAPAROSCOPIC REPAIR AND MANAGEMENT

In the last two decades, there have been significant developments in the field of minimally invasive surgical procedures, including laparoscopy. Despite these advances in laparoscopic instrumentation and techniques, the laparoscopic management of AL after colorectal surgery is still under debate.

A retrospective study by Cucurullo *et al*^[3] reported that AL was the most common finding (57.1%) at laparoscopic re-intervention. In this study, 91.7% of cases were managed by anastomotic repair, peritoneal lavage and temporary diverting ostomy. Only 8.3% of ALs required a Hartmann's procedure because of gross fecal contamination. The conversion rate to open surgery was 5.6%, because of extensive colonic ischemia and generalized peritonitis. Lee *et al*^[4] also reported an 8.2% conversion rate, and all ALs were treated with ileostomy/colostomy, with or without anastomotic repair. They compared the results of open and laparoscopic management, and observed significantly shorter hospital stay, lower 30-d postoperative morbidity and complication, and improved stoma closure rate in the laparoscopic group. In other studies by Wind *et al*^[5] and Vennix *et al*^[6], the morbidity rate, hospital stay, intensive care unit admission, and incisional hernia rate were reduced in the laparoscopic re-intervention group. Furthermore, re-laparoscopy can be used as a diagnostic tool if clinical

concerns exist, despite an adjunctive diagnostic imaging with reported diagnostic accuracy between 93% and 100%^[7].

Laparoscopic re-intervention is a safe, feasible and effective technique, and can also be considered as a diagnostic option as the first therapeutic approach for evaluating suspected postoperative complications. Today, many studies encourage the use of laparoscopy for the treatment of complications following minimally invasive colorectal surgery in skilled hands.

ENDOSCOPIC SEMS, AND OTHER STENTS

The use of colonic stents has significantly evolved over the last decades as an alternative method of converting emergency surgery for obstructing colorectal cancers to safer definitive elective surgery or as palliative treatment for inoperable malignant colorectal strictures, with high success rates^[8]. Moreover, the application of colonic stents has gained increasing attention in recent years for postoperative complications following colorectal surgery, including ALs, fistulas and perforations (Figure 1). In particular, smaller ALs that are not associated with severe sepsis might benefit from colonic stenting after laparoscopic peritoneal lavage and drainage, and fashioning of stoma^[9]. By contrast, some authors considered that endoscopic stenting could be utilized in patients with or without a stoma, in combination with percutaneous drainage of infected intraabdominal collections^[10].

Several types of intestinal stent are available, such as a SEMS (uncovered, partially or fully covered), a self-expanding plastic stent, and a biodegradable stent. Colonic stent-related complications include stent migration, anorectal pain, incontinence, perforation, rectal bleeding and stent obstruction^[9,11]. The stent can only be placed across an end-to-end anastomosis, and the distal end of the stent must be no less than 5 cm proximal to the anal verge^[10-12]. Stents placed very distally in the rectum may cause increased rectal pain, tenesmus or fecal incontinence^[11-13].

The risk of stent migration is high in the lower gastrointestinal tract because of the increased intestinal motility, and has been reported in 25% to 40% of

patients^[14-16]. This rate is lower in uncovered or partially covered stents than in biodegradable and fully covered stents^[9,10,12]. Migration has been also described when large-diameter stents have been used^[11,14]. However, the use of a partially covered SEMs prevents migration and allows for tissue in-growth; however, its removal is technically difficult^[11,12]. Clips or endoscopic suturing are alternative methods to anchor the stent in place and to reduce migration risk^[14] (Figure 1B). Optimal timing of stent removal is controversial. If possible, stents should be removed after adequate healing of the dehiscence is confirmed endoscopically and following resolution of clinical signs and symptoms^[16].

A recent study found that SEMs application was successful in 86% of 22 patients with ALs following colorectal surgery^[13]. In that study, fully covered SEMs were used in 19 patients and uncovered SEMs in three patients. Stent migration occurred in only one of the 22 patients (4.5%); this patient was in the covered stent group and stent migrated 6 mo after placement. Most of the patients complained of incontinence after placement of the stent, which regressed spontaneously after an average of 14 wk.

Recent advances and innovations in stent technology have led to the development expandable polydioxanone biodegradable stents as an effective alternative treatment of AL following colorectal surgery. The biodegradable stent does not to be removed, which can decrease mucosal hyperplastic reactions and adverse events associated with stent removal, compared with metal stents^[9,10,12,14].

Based on limited data, stent placement appears to be an alternative therapeutic option for selected patients with AL after colorectal surgery when performed by skilled endoscopists. Migration and cost are the major limitations of these stents.

ENDOSCOPIC CLIPS

Application of clips to approximate the edges of the leaking anastomosis is one of the endoscopic management techniques. Standard endoclips, which are used to control small perforations and bleeding, may be used to close an AL; however, the low closure of force of these clips limit their use for more scarred, fibrotic and irradiated tissues.

The first clip was manufactured by the Olympus Corporation (Japan) in 1995. Thereafter, a disposable pre-loaded version of this clip, known as Quickclips[®] (Olympus Ltd., Tokyo, Japan), has gained popularity. Thereafter, OTSC (Ovesco Endoscopy, endoscopy, Tubingen, Germany) were introduced; and in 2011, Cook Medical from United States produced the Instinct[™] Endoscopic Hemoclip.

The OTSC is the most preferred clips to control AL. This clip is made of super-elastic nitinol, which is a biocompatible and magnetic resonance imaging-safe material, and has the benefit of a larger clip area with increased compression. Firstly, Kirschniak *et al*^[17] published their successful results using OTSC in 11 patients with bleeding or iatrogenic perforations. Application of OTSCs for leaks has since become popular. Weiland *et al*^[18] reported a general success rate of 84.6%. Arezzo *et al*^[19] used OTSCs

for colorectal surgery on 14 patients with leaks no larger than 15 mm (maximum diameter), and without luminal stenosis and abscess. Their success rate was also 86%. Occasionally, the first attempt fails, but repeated attempts will be successful in order to close the dehiscence of AL^[20].

Favorable results with OTSCs are obtained in the absence of fibrotic tissue. Closure of chronic leaks and fistulas seems to be a considerable challenge and may decrease the success rate^[21]. Contrastingly, OTSCs have significant cost benefits compared with ileostomy, and achieve full-thickness wall closure. Moreover, they require a shorter hospital stay and avoid temporary ileostomy^[19]. OTSCs can close defects up to 30 mm^[22]. Application of multiple clips may be possible for larger defects; however, there is limited experience of it^[23,24].

ENDOSCOPIC VACUUM-ASSISTED CLOSURE

Negative pressure wound therapy or vacuum-assisted closure is now a well-established treatment modality for chronic and difficult to heal wounds. Recently, this minimally invasive method has been proposed as an effective approach to manage ALs after colorectal surgery, with success rates ranging from 56.6% to 100%^[25-29]. In the original technique, after the presence of the abscess cavity is confirmed by diagnostic colonoscopy, the enteric and purulent contents are aspirated and then irrigated. Finally, an open pored, polyurethane sponge with an attached evacuation tube connected to a drainage system is inserted *via* an introducer sleeve that is fitted over an endoscope and placed through the dehiscence and into the pelvic cavity^[10,12,16,25].

The endo-sponge continuously removes secretions, improves microcirculation, and therefore induces granulation formation in the defect. It also aids closure of the pelvic cavity by the application of negative pressure of 125 mmHg^[26] (Figure 2). One disadvantage of this method is the requirement to change the sponge every 2-4 d until the abscess cavity has regressed^[25,28,29]. However, this treatment is more effective at shrinking cavities, especially when used within 6 wk after the AL^[10,30]. It should be noted that generalized peritonitis is not an indication for endo-sponge therapy^[12,25,29]; and the overall complication rates are around 20%, mainly comprising anastomosis stenosis, recidivate abscess and fistula^[26].

In 2008, a large series of endoscopic vacuum-assisted closure therapy cases was reported by Weidenhagen *et al*^[25]. In that study, definitive closure of the cavity was achieved in 28 of the 29 patients (96.6%) over a mean treatment period of 34 d (range 4-79 d). In a recent review, Strangio *et al*^[26] found that complete healing of the cavity was achieved in near 95% of cases overall, following a median of 30 d of treatment and the performance of a median of 11 sessions. The authors emphasized that endo-sponge applications might be safely performed in patients with or without a diverting ileostomy. Weidenhagen *et al*^[25] reported that four patients were treated without the construction of a divert-

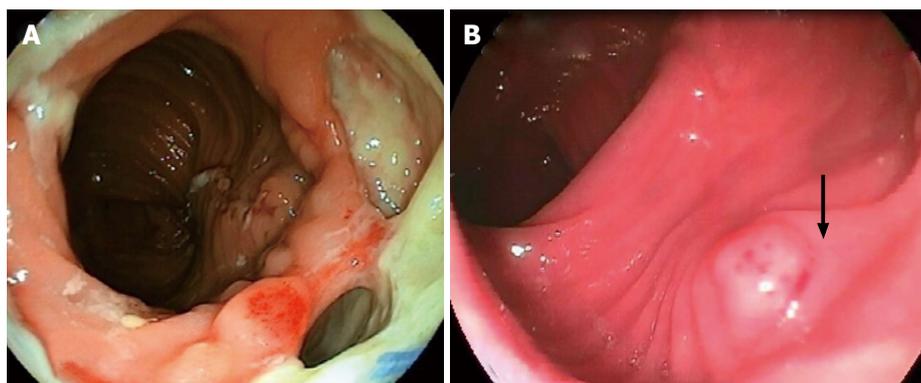


Figure 2 Endoscopic appearance of anastomotic leakage. A: Anastomotic leak with a cavity before endoscopic vacuum-assisted closure therapy; B: The same cavity covered with granulation tissue (black arrow) three weeks after vacuum therapy was initiated.

Table 1 Recent successful studies managed minimally invasively after acute or chronic anastomotic leak										
Ref.	Year	Cases	Procedure	Gender (F/M)	Age (yr)	Previous diagnose or treatment	Success n (%)	Failure or complications n (%)	Follow-up	
Lamazza <i>et al</i> ^[13]	2015	22	SEMS	11/11	68	Anterior resection (all) Neoadjuvant (21)	19 (86.4)	Failure: 3 (13.6) Stent migration: 1 (4.5)	18-42 mo	
Arezzo <i>et al</i> ^[19]	2012	14	OTSC	8/6	68.5	Anterior resection (12) Colostomy closure (1) Right hemicolectomy (1)	12 (85.7)	1 patient needed further surgery	4 mo	
Sulz <i>et al</i> ^[20]	2014	6	OTSC	1/5	66.5	Colorectal resection	5 (83.3)	Failure: 1 (Succeeded with 2 nd OTSC)	N/A	
Weidenhagen <i>et al</i> ^[25]	2008	29	VAC	5/24	66.7	Rectal cancer (22) Rectosigmoidal cancer (3) Large rectal adenoma (2) Diverticulitis (1) Endometrial cancer infiltration (1)	28 (96.6)	1 (Hartmann's procedure)	VAC duration: 34.4 ± 19.4 d	
Blumetti <i>et al</i> ^[31]	2011	5	Transanal repair	N/A	52	Coloanal anastomosis (4) Colorectal anastomosis (1)	4 (80)	Failure: 1 (20)	Time to repair: 8-15 mo	

F/M: Female/male; SEMS: Self-expandable metallic stent; OTSC: Over the scope clip; N/A: Data not available; VAC: Vacuum-assisted closure.

ing stoma. Similarly, Glitsch *et al*^[28] reported successful endoscopic transanal vacuum-assisted rectal drainage for AL after rectal resection in 16 of 17 patients (94.1%). They also found that the closure time was directly dependent on the cavity size, distance from anastomosis to the anal verge and the patient's age. Patients with anastomoses that were 6 cm or less from the anal verge, who were elderly (aged over 62 years), and had a cavity measuring 5 cm × 6 cm or more had considerably longer healing times.

Endoscopic vacuum-assisted closure therapy seems a safe and useful therapeutic option for the local and minimally invasive management of AL after colorectal surgery, with high success rates. However, further prospective clinical studies with randomized data and larger numbers of patients are needed to clarify the beneficial effects of endo-sponge therapy in patients with anastomotic insufficiency.

TRANSANAL REPAIR

Transanal repair is another preferred method for treatment of delayed ALs. Candidates for this method should have a documented persistent sinus or cavity diagnosed

by contrast enema, without any evidence of recurrence and co-morbidity. Transanal repair uses a primary repair or repair with flap, especially for sinus formation of AL. The flap should be prepared with skin or mucosa, although there is limited supporting data concerning this in the literature. Endorectal flap advancement is well described in ileorectal anastomotic sinuses. Blumetti *et al*^[31] published their two-center study in 2012 and reported six transanal repairs for five patients with an 80% success rate.

In 2015, Brunner *et al*^[32] reported two consecutive patients managed by transanal primary repair and irrigation of the abdominal cavity for AL after single incision laparoscopic sigmoid resection for stage II/III diverticulitis. They mentioned no residual leaks, no anastomotic strictures and normal rectal functions.

A summary of some recent successful studies managed minimally invasively after anastomotic leakage and the outcomes in SEMS, OTSC, vacuum-assisted closure and transanal repair is shown in Table 1.

CONCLUSION

Anastomotic leaks continue to be critical and life-threat-

ening events, with considerable morbidity and mortality. Patients with ALs are often critically ill, and non-operative management strategies should be the preferred first-line approach. Currently, minimally invasive treatment options are a promising alternative to surgical treatment, with satisfactory outcomes for the management of ALs. Nevertheless, there is a need for further, large, high quality, randomized, controlled trials on the long-term outcome, function and clinical efficacy of these different techniques.

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Basic Study

Fibrinogen-thrombin collagen patch reinforcement of high-risk colonic anastomoses in rats

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Conflict-of-interest statement: There is no conflict of interest in performing this study by either of the authors; material was donated by the Department of General and Digestive Surgery of Riotinto Hospital and Virgen del Rocío Hospital.

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Abstract

AIM

To evaluate the effectiveness of human fibrinogen-thrombin collagen patch (TachoSil®) in the reinforcement of high-risk colon anastomoses.

METHODS

A quasi-experimental study was conducted in Wistar rats ($n = 56$) that all underwent high-risk anastomoses (anastomosis with only two sutures) after colectomies. The rats were divided into two randomized groups: Control group (24 rats) and treatment group (24 rats). In the treatment group, high-risk anastomosis was reinforced with TachoSil® (a piece of TachoSil® was applied over this high-risk anastomosis, covering the gap). Leak incidence, overall survival, intra-abdominal adhesions, and histologic healing of anastomoses were analyzed. Survivors were divided into two subgroups and euthanized at 15 and 30 d after intervention in order to analyze the adhesions and histologic changes.

RESULTS

Overall survival was 71.4% and 57.14% in the TachoSil® group and control group, respectively ($P = 0.29$); four rats died from other causes and six rats in the treatment group and 10 in the control group experienced colonic leakage ($P > 0.05$). The intra-abdominal adhesion score was similar in both groups, with no differences between subgroups. We found non-significant differences in the healing process according to the histologic score used in both groups ($P = 0.066$).

CONCLUSION

In our study, the use of TachoSil® was associated with a non-statistically significant reduction in the rate of leakage in high-risk anastomoses. TachoSil® has been shown to be a safe product because it does not affect the histologic healing process or increase intra-abdominal adhesions.

Key words: Colon; Rats; Anastomosis; Leak; TachoSil®; Surgery

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Core tip: Anastomotic leakage is one of the most important complications in gastrointestinal surgery. We have performed a pioneering risk anastomosis procedure, carried out with a high risk of leakage, to test the use of thrombin and fibrinogen patch for the reinforcement and prevention of potential leakage. We obtained a significant reduction in the mortality rate without adding comorbidity. Patch application is simple and does not exceed operating time, and its use can be extremely helpful in emergency surgery or special situations that provide a high possibility of anastomosis dehiscence.

García C, García Ruiz S, Docobo Durantez F, Morales-Conde S, Padillo Ruiz J. Fibrinogen-thrombin collagen patch reinforcement of high-risk colonic anastomoses in rats. *World J Gastrointest Surg* 2016; 8(9): 627-633 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/627.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.627>

INTRODUCTION

Anastomotic leakage is a severe post-operative complication that can threaten a patient's life. It has a mean incidence in the published literature of 4%-8%, and its mortality can reach up to 22%^[1,2]. Several methods have been used to attempt to reduce anastomotic leakage associated with colonic surgery, with diverse results. As some authors have reported, staplers are the only method that maintains the incidence of anastomotic leakage under 10%^[3]. Other authors have used glues and tissue sealants to reinforce the suture. Cyanoacrylates and fibrin glues are most often used, with varying results in the literature; some studies state that the use of cyanoacrylates and fibrin sealants in this kind of surgery is both efficient and advantageous^[4,5], while others have failed to demonstrate such benefits^[6]. Few studies have analyzed other materials, such as TachoSil®, a human fibrinogen and thrombin patch. TachoSil® contains human fibrinogen, human thrombin, and the following excipients: Equine collagen, human albumin, riboflavin (E101), sodium chloride, sodium citrate (E331), and L-arginine-hydrochloride. TachoSil® is indicated in adults as a supportive treatment in surgery for the improvement of hemostasis, the promotion of tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient. Experimental studies have tried to assess if this product can improve the results of colonic anastomoses, with diverse results^[7-10]. An important aspect of this topic is the definition of high-risk anastomoses. Tebala *et al.*^[5] defined this kind of anastomoses as including emergency surgery, ischemic or inflammatory tissues, esophagus or extraperitoneal rectus, and immunosuppression.

We hypothesized that colonic anastomosis carried out under poor conditions can be improved with the use of TachoSil® by decreasing anastomotic leakage and its complications.

MATERIALS AND METHODS

Study design

A prospective, comparative, semi-experimental study in animals was conducted to analyze the effects of the application of a human fibrinogen-thrombin patch (TachoSil®) over high-risk anastomosis sites. The hypothesis was that this product would decrease the incidence and severity of colonic leakage. We compared the results with a control group in which there was only high-risk anastomosis. The study was carried out under the conditions established by the Helsinki statement,

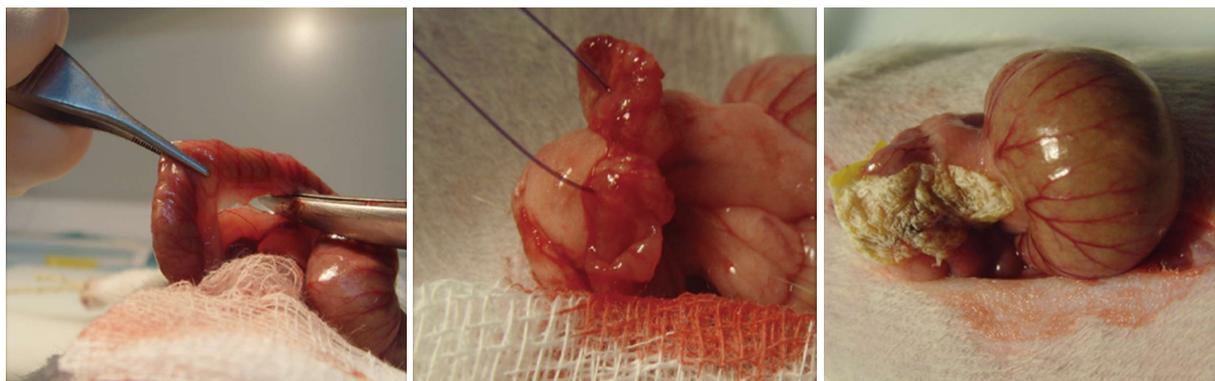


Figure 1 Surgical technique.

Table 1 Adhesive score

Adhesive score
0: No adhesions
1: Extremely soft adhesions
2: Stronger adhesions, but dissectible with dull dissection
3: Stronger adhesions only dissectible with sharpen tools
4: Stenosis

which regulates the terms and conditions for animal experiments. There was no competing interest for any of the authors. The authors did not receive any grant or sponsorship for this study. Materials were donated by the Department of Surgery of the University Hospital of Virgen del Rocío and Riotinto Hospital.

Animals

This study was performed on 56 white Wistar rats of both sexes weighing between 250 g and 350 g. Animals were divided into two groups (control group and treatment group), each consisting of 28 individuals. High-risk anastomosis was performed in all rats. A piece of fibrinogen-thrombin sealant was added that covered the entire anastomosis site in the treatment group.

Technical procedure

Anesthesia was induced with intraperitoneal ketamine (20 mg/kg), after which a laparotomy was performed. We then performed a partial colectomy of 2-3 cm just after the cecum, which was closed with an anastomosis with only two stitches of 4-0 monocryl in the mesenteric and anti-mesenteric borders of the colon. In addition, a 2 cm × 2 cm piece of TachoSil® was applied over the anastomosis, with light compression using small, wet gauze in the treatment group. Each piece was lightly wetted with 0.9% saline. The gauze was gently removed and the anastomosis site checked after 5 min to ensure the TachoSil® was in the proper location. The laparotomy was closed with 3-0 vicryl suture in a simple continuous suture for the muscle plane and 3-0 silk in a simple interrupted suture for the skin (Figure 1).

The early deceased animals underwent necropsy in order to establish the cause of death. The survivors

were euthanized at 15 and 30 d post-operatively after a randomized process. During necropsy, the formation of intra-abdominal adhesions was quantified with a numeric scale (Table 1) to compare both groups at 15 and 30 d post-operatively. In all animals, colonic anastomosis was retrieved to analyze the histopathologic healing process according to the Biert scheme (Table 2), which analyzed nine parameters. The histologic analysis, using hematoxylin and eosin staining, was performed by a pathologist blinded for the two groups.

Statistical analysis

The program used for statistical analysis was SPSS v16 for Windows, and the statistical review was performed by a biomedical statistician. Numerical results were analyzed using means and standard deviations. The Kaplan-Meier method was used to assess survival. Leakage incidence was analyzed with the χ^2 test for dichotomous variables. The intra-abdominal adhesion score was compared between groups with the Mann-Whitney test, as the variable was qualitative. The histopathologic healing process was analyzed with the Student's *t*-test, with sub-analysis performed with the Mann-Whitney test when necessary. A *P* value < 0.05 was considered significant.

RESULTS

Survival and leakage incidence

The number of events, defined as death as a consequence of colonic leakage, was 10 (35.7%) in the control group and 6 (21.4%) in the TachoSil® group. All deaths happened before the fourth post-operative day. Four animals in both groups died due to other causes, namely hemorrhage, post-anesthesia and bowel obstruction, with no relation to the experimental study. The mean survival per group was 19.5 ± 2.6 (control) and 23.7 ± 2.2 d (TachoSil®). With these results, the overall survival was 57.14% and 71.4% in the control and TachoSil® groups, respectively (*P* = 0.29) (Figure 2), with no significant differences between the groups.

Intra-abdominal adhesions

The results are shown in Table 3. We performed com-

Table 2 Histopathologic Biert' scheme

Parameters	Score			
	0	1	2	3
Necrosis	No	Small patches	Large patches	Massive
PMNs	Normal	Slightly increased	Strong infiltration	Massive infiltration
Lymphocytes	Normal	Slightly increased	Strong infiltration	Massive infiltration
Macrophages	Normal	Slightly increased	Strong infiltration	Massive infiltration
Edema	No	Slight	Strong	Massive
Epithelium	Glandular normal	Cubic normal	Cubic incomplete	Absent
Submucosa-muscular	Good bridges	Mild bridges	Few bridges	Bridges absent
Angiogenesis	Extensive	Strong	Slight	Absent
Fibrosis	Extensive	Strong	Slight	Absent

PMNs: Polymorphonuclear cells.

Table 3 Intra-abdominal adhesion score in survivorings animals

	Mann-Whitney mean ranges	P value
Survivors (15 d vs 30 d)	25.11 vs 11.12	0.0012
Control (15 d vs 30 d)	10.53 vs 5.5	0.017
TachoSil (15 d vs 30 d)	14.75 vs 6.25	0.001
Control vs TachoSil (15 d)	9.5 vs 10.45	0.685
Control vs TachoSil (30 d)	9.71 vs 8.50	0.584

Table 4 Most relevant parameters in histopathologic analysis (mean ± SD)

	Control	TachoSil	P value
PMNs	0.21 ± 0.42	0.78 ± 0.64	0.010
Macrophages	0.50 ± 0.65	0.89 ± 0.47	0.026
Edema	0.43 ± 0.64	0.94 ± 0.63	0.017
Epithelium regeneration	0.64 ± 0.92	1.11 ± 0.58	0.031

PMNs: Polymorphonuclear cells.

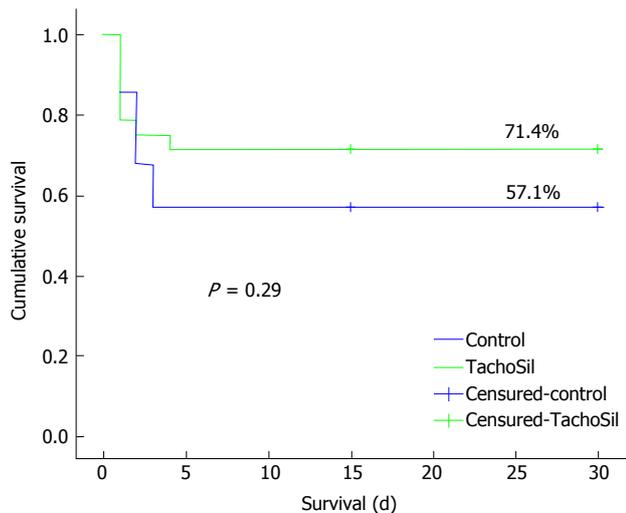


Figure 2 Survival in both groups.

parisons according to both the time (15 d vs 30 d) and group [control (16 rats) vs TachoSil® (20 rats)]. Distribution of animals sacrificed: control-15 d = 9 rats, control-30 d = 7 rats; TachoSil-7 d = 10 rats, TachoSil-15 d = 10 rats. The adhesion score was significantly different when comparing all groups according to the time, showing a much better score in animals euthanized at day 30. However, no differences were found at day 15 or day 30 when comparing groups.

Histopathologic healing process

Healing of the anastomoses was analyzed following the Biert scheme. The global results are shown in Figures 3 and 4.

Only four parameters (Table 4) showed significant

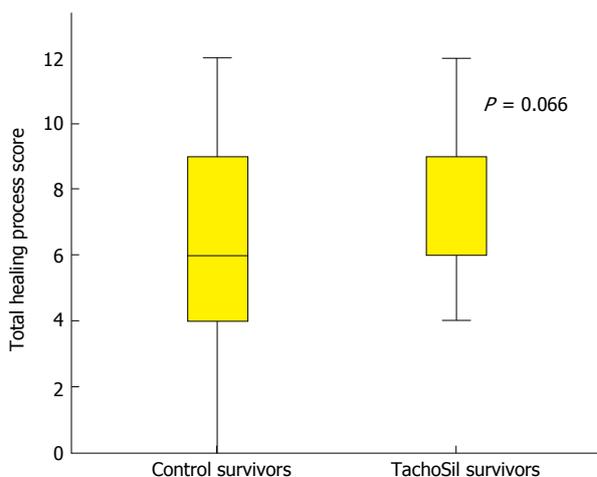


Figure 3 Healing of the anastomoses in both groups.

differences between the control and TachoSil® groups with the Student's *t*-test, and were always worse in the TachoSil® group polymorphonuclear cells 0.21 ± 0.42 vs 0.78 ± 0.64, *P* = 0.01; macrophages 0.50 ± 0.65 vs 0.89 ± 0.47, *P* = 0.026; oedema 0.43 ± 0.64 vs 0.94 ± 0.63, *P* = 0.017; and epithelium regeneration 0.64 ± 0.92 vs 1.11 ± 0.58, *P* = 0.031. The rest of parameters were similar between groups.

When we applied the total score for this analysis, defined as the sum of all values of each parameter, we found nearly significant differences between groups. Among all survivors, the control group had a mean total healing score of 6.21 ± 3.21, whereas the TachoSil® group had a mean of 8 ± 2.05 (*P* = 0.066) (Figure 3).

Sub-analysis of this total healing process score accord-

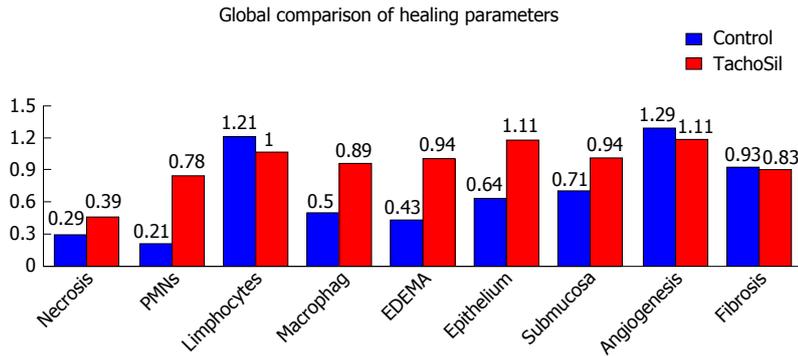


Figure 4 Global comparison of healing parameters. PMNs: Polymorphonuclear cells.

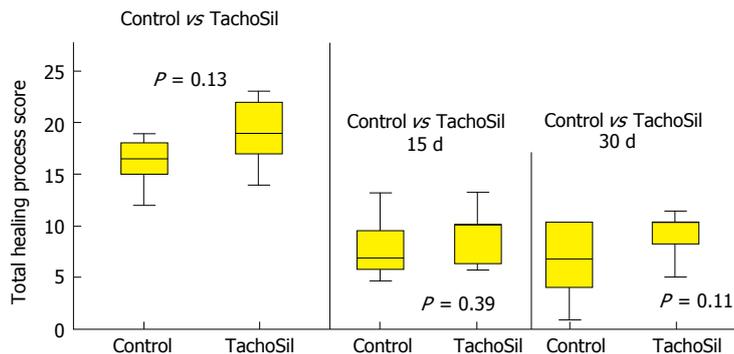


Figure 5 Healing process scores at 15 d and 30 d, and global analysis in surviving animals.

ing to the post-operative day (15 and 30 d) did not show statistically significant differences, but we did see a trend towards a worsened healing process in the TachoSil® group, especially at the end of the period. On days 15 and 30, the results were 7.5 vs 9.5 ($P = 0.39$) and 6.17 vs 9.9 ($P = 0.112$) in the control group vs the TachoSil® group, respectively (mean ranges) (Figure 5). There were no differences when the analysis was performed between groups (global analysis) (7.15 vs 10.75; $P = 0.13$).

DISCUSSION

Colonic anastomosis failure can be a life threatening complication following colonic surgery. Over time, great efforts have been made to improve the results of this procedure and define the risk factors for anastomosis failure^[1,2,11]. Systemic factors (such as diabetes and steroid use) and local factors (such as radiotherapy and tension or hemorrhage in the suture) can lead to a poor result in the healing process of the colon^[12-14]. The period in which a leak occurs is usually between days 5 and 6 post-operation. Before this period, the strength of anastomosis is mainly held by the suture, but after day 5 or 6 the healing process of the colonic wall, especially with regards to the collagen formation, is most important, as the suture material loses efficacy at that time. A variety of products^[6,15-19] have been used to reinforce intestinal anastomoses (e.g., cyanoacrylate, fibrin sealants, amniotic, collagen and dura mater membranes, and mechanical staplers), all with different results. The application of a

fibrinogen and thrombin patch over colonic anastomoses is a relatively new idea^[7]. Some authors^[19,20] used the classical cecal puncture model to define high-risk anastomosis, thereby providing the sepsis model^[20-24]. To date, there has not been any consensus regarding the definition of high-risk anastomosis and, to our knowledge, there have been few studies that have examined the application of TachoSil® over colonic anastomoses^[7-10,20-24], with only one carried out using a high-risk anastomosis^[10]. Although these studies showed the method to be safe and feasible, some results have been controversial; Ozel *et al*^[7] showed that this product increased the inflammatory reaction and led to a worsened healing process with less mechanical strength. In contrast, Stumpf *et al*^[9] found that it led to a better histopathologic healing process as a consequence of the decrease in suture material in the anastomotic line and that a suture-free anastomosis is reliable. Norden-toft *et al*^[8,22] studied this product applied over normal small-bowel anastomoses and found no differences in the mechanical strength, degree of stenosis, or healing process, with the incidence of anastomotic leakage also being similar between groups. In our study, we noted an evident reduction of anastomotic leakage incidences (31.7% vs 21.4% in control and TachoSil® groups, respectively), but these differences were not significant ($P = 0.29$). Even when a potentially injurious agent such as 5-fluorouracil is used, it has been verified that applying anastomosis TachoSil® confers greater resistance by acting as a protective agent^[24]. In a study using mice, Pantelis *et al*^[10] achieved a statistically significant difference in

the lethality and leakage rates in the group that received TachoSil[®], as well as finding that its use did not increase the formation of intra-abdominal adhesions. They did not find any differences between groups. In studies that analyzed the use of TachoSil[®] in bowel anastomoses, Nordentoft *et al*^[8] reported no differences between groups. In contrast, Ozel *et al*^[7] noted that TachoSil[®] increased the formation of peri-anastomotic adhesions. Regarding the histopathologic healing process, we found neither advantages nor disadvantages when TachoSil[®] was applied. However, when we analyzed this process with both individual and global scores, some individuals were statistically different with regards to group (control or treatment), but when the global score was compared, no differences were observed. Some authors, such as Ozel, affirmed that if TachoSil[®] is used, the neutrophilic granulocyte count can increase, and this carries a worsened prognosis for healing as a result of excessive metalloproteinases. These results were also observed by van der Ham *et al*^[21]. In contrast, Pantelis observed that if TachoSil[®] is applied in high-risk anastomosis, an improvement in the healing process can be observed. In our study, the healing process is exacerbated and inflammatory parameters were increased when TachoSil[®] was used, compared to the control group. However this does not affect the creation of useful anastomosis, only higher growth of tissue in the area where it is applied, accompanied by obvious signs of inflammation. This has not affected the result of the study and the rate of leakage has decreased, therefore we believe that a stronger healing process is useful in reinforcing the consistency of anastomosis.

We think that, despite the worsened healing in some individual parameters in the TachoSil[®] group, the improvement in leak incidence can be explained by the sealant effect of the collagen patch (*i.e.*, the mechanical sealant achieved by this sponge, which is a well-established effect of this product)^[7,8,23].

In conclusion, our study showed that the application of TachoSil[®] led to a non-statistically significant decrease in both mortality and anastomotic leakage rates. Furthermore, the use of this product did not affect the histopathologic healing process or increase the formation of adhesions, and so it can be regarded as a very safe product. We focused on the importance of the mechanical effect of TachoSil[®] in sealing the anastomosis gap. The use of TachoSil[®] is not justified in routine colonic surgery due to the low colonic anastomotic leakage rates in those procedures. Although we demonstrated that TachoSil[®] does not decrease the complication rate in high-risk anastomoses, based on the controversial data existing in the literature, we recommend that clinical studies should be performed to clarify this topic, as it may have potentially important effects in surgery.

anastomosis in rats. The hypothesis to be tested is decreasing anastomotic leaks using this product. The triple-blind comparative results confirm a decrease in leakage anastomotic.

Research frontiers

The main frontier of the study is the reduction of anastomosis leakage in anastomosis with risk factors.

Innovations and breakthroughs

Decreasing the rate of leaks in anastomosis using an absorbable sheet on the anastomosis when the procedure was performed in high-risk conditions.

Applications

The results can be applied in digestive surgery (*i.e.*, intestinal and colorectal anastomosis), especially in emergency surgeries and patients with high comorbidities.

Peer-review

This manuscript showed the potential application of TachoSil[®] in colonic sutures after surgery. The study was straight-forward and rational. The application apparently has some merits.

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COMMENTS

Background

This is an experimental study to test the absorbable product TachoSil[®] in risk

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Retrospective Study

Total pancreatectomy: Short- and long-term outcomes at a high-volume pancreas center

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient gave informed consent for institutional data collection and sharing.

Conflict-of-interest statement: Dr. Zakaria, Dr. Stauffer, Dr. Raimondo, Dr. Woodward, Dr. Wallace and Dr. Asbun report no biomedical financial interests or potential conflict of interest.

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Abstract

AIM

To identify the current indications and outcomes of total pancreatectomy at a high-volume center.

METHODS

A single institutional retrospective study of patients undergoing total pancreatectomy from 1995 to 2014 was performed.

RESULTS

One hundred and three patients underwent total

pancreatectomy for indications including: Pancreatic ductal adenocarcinoma ($n = 42$, 40.8%), intraductal papillary mucinous neoplasms ($n = 40$, 38.8%), chronic pancreatitis ($n = 8$, 7.8%), pancreatic neuroendocrine tumors ($n = 7$, 6.8%), and miscellaneous ($n = 6$, 5.8%). The mean age was 66.2 years, and 59 (57.3%) were female. Twenty-four patients (23.3%) underwent a laparoscopic total pancreatectomy. Splenic preservation and portal vein resection and reconstruction were performed in 24 (23.3%) and 18 patients (17.5%), respectively. The 90 d major complications, readmission, and mortality rates were 32%, 17.5%, and 6.8% respectively. The 1-, 3-, 5-, and 7-year survival for patients with benign indications were 84%, 82%, 79.5%, and 75.9%, and for malignant indications were 64%, 40.4%, 34.7% and 30.9%, respectively.

CONCLUSION

Total pancreatectomy, including laparoscopic total pancreatectomy, appears to be an appropriate option for selected patients when treated at a high-volume pancreatic center and through a multispecialty approach.

Key words: Intraductal papillary mucinous neoplasms; Laparoscopic total pancreatectomy; Pancreatic ductal adenocarcinoma; Laparoscopy; Pancreas cyst; Pancreas cancer

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Core tip: Treatment by total pancreatectomy for diseases of the pancreas has been gained acceptance and used more frequently by pancreatic surgeons. This review highlights a large volume single institutional experience with this operation demonstrating acceptable short-term and long-term outcomes.

Zakaria HM, Stauffer JA, Raimondo M, Woodward TA, Wallace MB, Asbun HJ. Total pancreatectomy: Short- and long-term outcomes at a high-volume pancreas center. *World J Gastrointest Surg* 2016; 8(9): 634-642 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/634.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.634>

INTRODUCTION

In selected patients, total pancreatectomy (TP) has been established as a potential option in the treatment of pancreatic ductal adenocarcinoma (PDAC), invasive or diffuse intraductal papillary mucinous neoplasms (IPMN), multiple pancreatic neuroendocrine tumors (PNET)^[1-4]. TP is still also one of the treatment modalities in chronic pancreatitis with severe pain, pancreatic fistula or hemorrhage after pancreaticoduodenectomy (PD)^[3,5-7]. Improvement in postoperative management, including better pancreatic enzyme formula, long-acting insulin, and autologous islet cell transplantation, has made TP

a viable choice in the treatment of different pancreatic diseases^[8,9].

Although TP is performed at an increasing rate at major pancreatic centers, there is still debate regarding its indications and outcomes^[2-4]. This study aimed to analyze the indications and short- and long-term outcomes of TP in the spectrum of pancreatic resections in our high-volume center.

MATERIALS AND METHODS

We conducted a retrospective study of 103 patients who underwent TP between March 1995 and December 2014 at Mayo Clinic in Jacksonville, Florida using data collected from an institutional review board-approved prospective database.

The preoperative data, including demographic data and clinical picture, operative details, and postoperative data were collected and analyzed.

Operative strategy

The American Society of Anesthesiologists classification^[10] and Eastern Cooperative Oncology Group performance status^[11] were used for evaluation of the preoperative risk. All patients were optimized medically prior to surgery.

TP was performed either open or laparoscopic. It was done as pylorus-preserving, standard, or completion TP (of previous distal pancreatectomy or PD). The operation was done with and without splenectomy.

In cases with partial resection in pancreatic tumors, the specimen margin was analyzed by frozen section. The procedure was converted to TP if the margins showed carcinoma *in situ* or invasive carcinoma. TP was not performed for frozen section findings of moderate dysplasia or adenomatous changes at the margin. International consensus guidelines for the management of patients diagnosed with IPMN was used throughout the study time period, as appropriate. Guidelines from 2006^[12] were followed up until these were updated in 2012^[13].

The International Study Group of Pancreatic Surgery (ISGPS) classification of venous resection was used as follows^[14]: Type I: Partial venous resection with direct closure (venorrhaphy); Type II: Partial venous excision with closure by patch graft; Type III: Excision with primary end to end venous anastomosis; Type IV: Venous resection with interposition venous graft.

Histopathological data on pancreatic tumor staging were collected according to the tumor, node and metastases staging system. IPMN pathology was defined as per World Health Organization criteria into 4 categories based upon the degree of dysplasia: Adenoma, border line (low-moderate dysplasia), carcinoma *in situ* (CIS) high-grade dysplasia), or invasive carcinoma^[2]. PDAC without IPMN was considered to be de novo, but PDAC associated with IPMN was considered to be arisen from these IPMN.

Postoperative complications occurring in the first 90 d

Table 1 Demographics for 103 patients undergoing total pancreatectomy with subgroup analysis

Variable	Overall (n = 103)	PDAC (n = 42)	IPMN (n = 40)	LTP (n = 24)
Age, yr ¹	70.2 (32-84.5)	70.3 (33.3-84.5)	71.3 (42.9-81.1)	70.3 (37.3-84.5)
Body mass index ¹	25.1 (17.7-42.1)	24.2 (17.7-39.8)	25.8 (18.5-42.1)	26.7 (17.7-36.3)
Male	44 (42.7%)	18 (42.9%)	19 (47.5%)	13 (54.2%)
Hypertension	70 (68%)	29 (69%)	31 (77.5%)	14 (58.3%)
Diabetes	46 (44.7%)	19 (45.2%)	16 (40%)	13 (54.2%)
Cardiac disease	31 (30.1%)	8 (19%)	14 (35%)	7 (29.2%)
Pulmonary disease	19 (18.4%)	7 (16.7%)	7 (17.5%)	5 (20.8%)
ASA				
II	24 (23.3%)	11 (26.2%)	9 (22.5%)	2 (8.3%)
III	72 (69.9%)	26 (61.9%)	29 (72.5%)	22 (91.7%)
IV	7 (6.8%)	5 (11.9%)	2 (5%)	0
Type of resection				
Standard	35 (34%)	17 (40.5%)	10 (25%)	5 (20.8%)
Pylorus preserving	56 (54.4%)	20 (47.6%)	27 (67.5%)	16 (66.7%)
Completion	12 (11.6%)	5 (11.9%)	3 (7.5%)	3 (12.5%)

¹Values are median (range), values in parenthesis are percentages unless otherwise indicated. ASA: American Society of Anesthesiologists score; IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy; PDAC: Pancreatic ductal adenocarcinoma.

after surgery were graded from (0 to 5) according to the Clavien system^[15]. Grade I and II complications were considered minor and Grade III, IV and V were considered major complications. International consensus guidelines were used to evaluate specific complications^[16,17]. Major glycemic events included complications or readmissions related to severe hyperglycemia or hypoglycemia. Cardiac complications, pulmonary complications, renal insufficiency, or hepatic insufficiency were defined as temporary organ system dysfunction requiring supportive care over the usual standard postoperative measures.

The follow-up period (1-18 years) was from date of surgery. Any death during the hospital stay or within the first 90 d after surgery was defined as perioperative mortality. Readmissions to any facility were recorded for 90 d after surgery.

After analysis of results and outcomes from our previous publication in 2009^[4], patients undergoing consideration for total pancreatectomy were sent for preoperative evaluation and counseling by a nutrition and endocrine team for the anticipated exocrine and endocrine insufficiency caused by surgical intervention. Postoperatively, patients were seen and followed in the hospital setting by the inpatient nutrition and endocrine team for ongoing education and management regarding the subsequent pancreatic insufficiency. Insulin and enzyme replacement were determined according to individual patient needs. In addition, percutaneous jejunostomy feeding tube placement became a standard procedure during TP after 2009, and many patients were started on enteral tube feeds in the hospital setting and continued on after discharge to aid in avoiding readmissions for malnutrition.

Postoperatively, patients were treated on the medical-surgical floor and intensive care use was not routine unless indicated. Perioperative use of parenteral nutrition and blood product transfusion was also limited unless indicated. Based on final pathology, adjuvant

treatments including chemotherapy or radiotherapy were recommended to patients undergoing TP for periampullary adenocarcinoma.

Statistical analysis

Data were collected and analyzed by a biomedical statistician using SPSS version 21.0 (SPSS Inc., Chicago, IL, United States). A Kaplan-Meier curve was used for the analysis of survival.

RESULTS

From March 1995 to December 2014, 983 pancreatic resections were performed for benign and malignant pancreatic diseases; TP was performed in 103 patients (10.5%). The demographic and preoperative clinicopathological data are listed in Table 1. Subgroup analysis for those undergoing TP for PDAC and IPMN is shown. Indications for TP (rather than partial pancreatectomy) was multifocal disease (55 patients, 53.4%), positive margins (23 patients, 22.3%), elective completion TP for recurrence of the primary pathology (5 patients, 4.9%), or other (20 patients, 19.4%). There were no cases with emergent TP as treatment for postoperative pancreatic fistula (POPF) or hemorrhage from patients undergoing partial pancreatectomy in this study. POPF was treated with interventional radiological procedures, and in this study, all completion TP was performed in an elective fashion for pancreatic pathology.

Overall, 79 patients (76.7%) underwent an open TP. Laparoscopic TP (LTP) was attempted in 31 patients (30.1%), and conversion to open occurred in 7 patients (22.6%) due to adhesions from chronic pancreatitis in 5 patients, bleeding in 1 patient, and portal vein involvement by the tumor in 1 patient. Of the 24 patients who did not require conversion from LTP, a hand-assisted approach was used for 2 patients, and subgroup analysis is given in the tables. LTP was introduced in November

Table 2 Operative variables for 103 patients undergoing total pancreatectomy with subgroup analysis

Variable	Overall (n = 103)	PDAC (n = 42)	IPMN (n = 40)	LTP (n = 24)
Operative time (min) ¹	426 (165-930)	390 (165-636)	435 (240-930)	534 (234-770)
Estimated blood loss (mL) ¹	500 (50-18000)	500 (50-7800)	525 (50-18000)	200 (50-600)
Intraoperative pRBC transfusion (unit) ¹	1 (0%-40%)	2 (0%-30%)	1 (0%-40%)	0 (0%-2%)
Vein resection	18 (17.5%)	13 (40%)	4 (10%)	1 (4.2%)

¹Values are median (range), values in parenthesis are percentages unless otherwise indicated. IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy; PDAC: Pancreatic ductal adenocarcinoma; pRBC: Intraoperative packed red blood cell.

2008, and a total of 52 patients (50.5%) had TP after this date. Of these, 28 (53.8%) underwent open surgery and 24 (46.2%) underwent LTP. Spleen-preserving TP was done in 29 patients (28.2%), four of whom underwent spleen-preserving LTP.

Operative variables are found in Table 2. LTP was found to have longer operative times, but less blood loss. Vein resection was performed in 18 patients (17.5%). The resections were conducted according to the ISGPS classification of vein resection, which included type I (lateral venorrhaphy) in 4 patients (22.22%), type II (patch graft) in 2 (11.11%; 1 from gonadal vein and 1 from bovine graft), type III (primary anastomosis) in 6 (33.33%), and type IV (interposition venous graft) in 6 (33.33%; 4 by 14 mm polytetrafluoroethylene synthetic graft, 1 from gonadal vein, and 1 from splenic vein). One patient of LTP had venous resection and laparoscopic lateral venorrhaphy.

Table 3 gives the 90-d complications and postoperative outcomes, including length of stay and readmission rate, for those undergoing TP overall and by subgroup. Major postoperative complications were found in 33 (32%) patients, and reoperation was done for 7 patients (6.8%) due to abdominal collections (4 patients), post-pancreatectomy hemorrhage (2 patients), and intestinal fistula not responding to conservative or radiological interventions (1 patient).

Pathological indications for TP are listed in Table 4. PDAC and IPMN were the most common indications for surgery. Sixty-two patients (60.2%) were found to have IPMN upon final pathology. Forty patients (38.8%) had this as the only pathologic process, while IPMN was associated with other pancreatic pathology in 22 patients (21.4%).

Twenty of 42 patients with PDAC (47.6%), had tumor recurrence; 10 (50%) had distant metastasis (mainly to the liver and lung), 3 (15%) local recurrence, and 7 (35%) had both distant and local recurrence. The mean time of recurrence was 9.5 mo (range: 2.5-27 mo).

Overall, the 90-d perioperative mortality was 7 patients (6.8%). The 1-, 3-, 5-, and 7-year total survival rate for all 103 patients were 73.7%, 61.3%, 57.5%, and 53.8%, respectively (Figure 1A). The 1-, 3-, 5-, and 7-year survival for patients without malignant tumors (50 patients) were 84%, 82%, 79.5%, and 75.9%, respectively, while in patients with malignant findings (53 patients) the survival rates were 64%, 40.4%, 34.7%,

and 30.9%, respectively. The 1-, 3-, 5-, and 7-year survival rates in patients who had PDAC (42 patients) were 59.5%, 29.2%, 21.9%, and 18.3%, respectively (Figure 1B).

The 1-, 3-, 5-, and 7-year survival rates in patients with non-invasive IPMN (44 patients) were 84.1%, 76.9%, 73.8%, and 70.1%, respectively, while in patients with invasive IPMN (18 patients) the survival rates were 77.8%, 44.8%, 37.3%, and 29.8%, respectively.

DISCUSSION

Enthusiasm for TP has varied with time. This major operation should be assessed carefully for operative risk and postoperative outcomes after the loss of the exocrine and endocrine functions of the pancreas^[1,3].

Murphy *et al*^[5] reported that there was an increase in the rate of TP in the United States between 1998 and 2006. In about a 20-year span, 50.5% of the TP on this series were performed during the last 6 years of the study. In this publication, there was increased utilization of elective TP, especially after early diagnosis of multifocal pancreatic pathologies like IPMN and multiple PNET, and the role of TP in the management of chronic pancreatitis was limited only to patients with refractory pain not responding to medical treatment.

On the other hand, there was significant decline in the use of emergency TP as in POPF and hemorrhage. This was mainly due to better use of radiologic drainage and arterial embolization which became available and preferable to relaparotomy^[6]. In our study, we had only 1 patient who underwent an emergency TP for abdominal trauma.

The recommendations of the international consensus guidelines in the management of IPMN depended on its site in the main duct or side branches and its clinical and morphological picture in preoperative imaging study. TP should be performed in patients with positive multiple surgical margins for invasive IPMN or high-grade dysplasia on frozen section^[13]. In our study, the existence of main duct IPMN as the primary pathology accounted for 38.8% of all TP performed, and IPMN associated with other tumors accounted for 21.4%, but elsewhere IPMN has been reported to encompass 22% of all TP performed^[3].

Dallemagne *et al*^[18] demonstrated the feasibility

Table 3 Postoperative outcomes and complications (90 d) for 103 patients undergoing total pancreatectomy

Variable	Overall (n = 103)	PDAC (n = 42)	IPMN (n = 40)	LTP (n = 24)
Cardiac	10 (9.7%)	5 (11.9%)	3 (7.5%)	1 (4.2%)
Pulmonary	15 (14.6%)	7 (16.7%)	6 (15%)	5 (20.8%)
Renal insufficiency	8 (7.8%)	3 (7.1%)	6 (15%)	4 (16.7%)
Hepatic insufficiency	3 (2.4%)	1 (2.4%)	3 (7.5%)	2 (8.3%)
Major glycemic event	6 (5.8%)	3 (7.1%)	2 (5%)	1 (4.2%)
Post-pancreatectomy hemorrhage	5 (4.9%)	0 (0.0%)	4 (10%)	4 (16.7%)
A	2 (1.9%)	0	2 (5%)	2 (8.3%)
B	1 (0.8%)	0	0	1 (4.2%)
C	2 (1.9%)	0	2 (5%)	1 (4.2%)
Delayed gastric emptying	14 (13.6%)	5 (11.9%)	5 (12.5%)	2 (8.3%)
A	4 (4.9%)	2 (4.8%)	2 (5%)	0
B	5 (4.9%)	2 (4.8%)	1 (2.5%)	1 (4.2%)
C	5 (4.9%)	1 (2.4%)	2 (5%)	1 (4.2%)
Wound infection	11 (10.7%)	5 (11.9%)	2 (5%)	2 (8.3%)
Intra-abdominal abscess	14 (13.6%)	2 (4.8%)	8 (20%)	4 (16.7%)
Biliary fistula	2 (1.9%)	0	1 (2.5%)	0
Mesenteric/portal vein thrombosis	5 (4.9%)	2 (4.8%)	2 (5%)	1 (4.2%)
Reoperation	7 (6.8%)	2 (4.8%)	2 (5%)	2 (8.3%)
Patients intensive care stay	64 (62.1%)	24 (57.1%)	30 (75%)	10 (41.7%)
Median intensive care stay, d ¹ (range)	2 (1-59)	2 (1-12)	2 (1-59)	2 (1-33)
Overall morbidity	66 (64.1%)	27 (64.3%)	25 (62.5%)	10 (41.7%)
Major (III-V)	33 (32%)	13 (31%)	13 (32.5%)	5 (20.8%)
IIIa	14 (13.6%)	5 (11.9%)	6 (15%)	0
IIIb	3 (2.9%)	2 (4.8%)	0	0
IVa	4 (4.9%)	1 (2.4%)	2 (5%)	2 (8.3%)
IVb	5 (4.9%)	2 (4.8%)	1 (2.5%)	2 (8.3%)
V	7 (6.8%)	3 (7.1%)	4 (10%)	1 (4.2%)
Length of stay, d ¹ (range)	9 (3%-71%)	9 (3%-71%)	10 (4%-67%)	8 (4%-52%)
Readmission	26 (25.2%)	12 (28.6%)	8 (20%)	3 (12.5%)

¹Values are median (range), values in parenthesis are percentages unless otherwise indicated. IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy; PDAC: Pancreatic ductal adenocarcinoma.

and advantage of TP with the laparoscopic approach. They reported two cases of TP with pylorus and splenic preservation with good postoperative outcomes. Blood loss, intensive care unit length of stay, and overall hospital length of stay were shorter^[19-21]. Asbun and Stauffer also reported 11 patients with LTP^[19].

Zeh *et al.*^[22] and Buchs *et al.*^[23] reported that robotic assistance LTP can offer more advantages. Giulianotti documented five cases with laparoscopic robotic surgery, with spleen-preserving technique in two of them (Kimura technique)^[24]. Also, Boggi *et al.*^[25] showed the feasibility of robot-assisted LTP in a series of 11 patients without conversion to open surgery.

Choi *et al.*^[26] and Ferrone *et al.*^[27] reported four patients with laparoscopic-assisted pylorus and spleen-preserving TP with segmental excision of the splenic artery and vein (Warshaw's procedure), but with a small midline opening for completion of the anastomosis.

In our study, 24 patients underwent full LTP, 16 underwent pylorus-preserving LTP, and 5 underwent spleen-preserving LTP. Patients with LTP had a higher negative margins rate and significantly more lymph nodes removed than in open surgery.

There are still high postoperative complications after TP. In our study, 32% of patients had a major complication after TP. This matches with other series that had complication rates of 32%-54%^[4,28]. However,

the complications after partial resection and TP were not significantly different in one study done on 124 patients with TP^[29].

The postoperative outcomes related to exocrine and endocrine pancreatic functions may affect the enthusiasm for TP. Postoperative diabetes may be difficult to control, with reported mortality from hypoglycemia^[30,31]. In our study, no such deaths were reported. The improvements in insulin, well-trained nurses, and exposure to a diabetic care team prior to the procedure led to dramatically improved diabetic outcomes post-TP^[30,32]. Since 2008, at our institution, we have implemented a preoperative TP pathway in which patients receive glucose management, enzyme replacement, and nutritional education prior to the operation. The indications and management decisions are done through discussion at a multidisciplinary Pancreas Board that is held on a weekly basis.

Wu *et al.*^[33] reported that islet autotransplantation (IAT) is a safe modality for patients who had chronic pancreatitis and underwent TP, and a significant number of patients can achieve insulin independence for a long time after receiving enough islet equivalent per kg body weight. None of our patients who underwent TP for chronic pancreatitis were candidates for TP and IAT as all had concerns for neoplasia. Any candidate for TP and IAT are sent to those referral centers. Hence, there is a possible bias towards a small number of patients

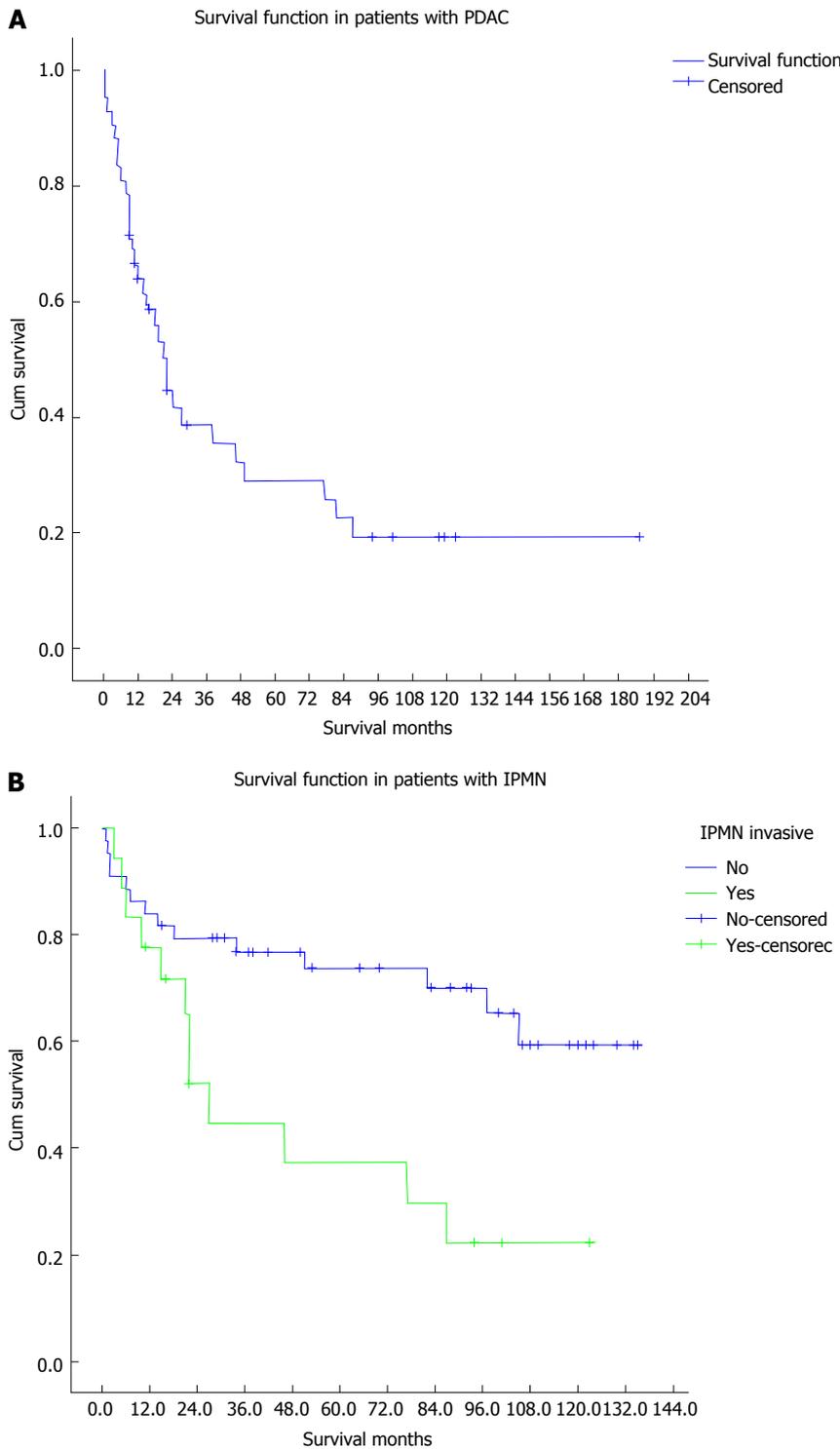


Figure 1 Kaplan Meier curve for survival. A: Survival in patients with pancreatic ductal adenocarcinoma; B: Survival in patients with intraductal papillary mucinous neoplasms. PDAC: Pancreatic ductal adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasms.

undergoing TP for chronic pancreatitis at our institution.

The development of enzyme replacement formulations and the use of the duodenum-preserving TP have improved morbidity from exocrine insufficiency. However, in one study, the pylorus-preserving TP was not associated with significantly different nutritional status than the standard TP^[34].

Intraoperative frozen section analysis of the resection

margins during partial pancreatectomies is important to emphasize R0 resection. There was a significantly better survival in patients undergoing completion TP after positive margins during PD than patients undergoing R1 resection in a study done on 33 patients with PDAC^[35]. In our study, 21.4% of the patients who underwent distal pancreatectomies and pancreaticoduodenectomies also had positive resection margins in the pathological study

Table 4 Pathologic findings for 103 patients undergoing total pancreatectomy

Variable	Overall (n = 103)	LTP (n = 24)
Malignant	n = 53	n = 12
Pancreatic ductal adenocarcinoma	42 (40.8%)	5 (20.8%)
<i>De novo</i>	23 (22.3%)	3 (12.5%)
Arising from IPMN	19 (18.5%)	2 (8.3%)
Neuroendocrine	7 (6.8%)	6 (25%)
Cholangiocarcinoma with IPMN	1 (0.97%)	0
Ampullary adenocarcinoma with IPMN	1 (0.97%)	1 (4.2%)
Renal cell carcinoma	1 (0.97%)	0
Sarcoma	1 (0.97%)	0
Tumor size, cm ¹	3.5 ± 2.4 (0.5%-14%)	3.2 ± 2.5 (1.3%-10%)
Margin negative (R0)	41 (77.4%)	11 (91.7%)
Number of lymph nodes harvested ¹	23 ± 14 (1%-61%)	28 ± 11 (11%-41%)
Non malignant	n = 50	n = 12
IPMN	40 (38.8%)	11 (45.8%)
Chronic pancreatitis	8 (7.8%)	1 (4.2%)
Ampullary adenoma with IPMN	1 (0.97%)	0
Trauma	1 (0.97%)	0

¹Values are mean (range), values in parenthesis are percentages unless otherwise indicated. IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy.

and required TP in the same operative sitting.

Survival of patients undergoing TP varied according to the underlying disease process. Patients with benign disease had a high survival rate whereas those with invasive IPMN or other malignant tumors had poor survival as shown in our study. Some institutions reported high operative mortality rates to be greater than 20% and associated with high morbidity, and this led these centers to stand against the role of TP^[36-38]. However, recent institution series have reported lower perioperative mortality rates to be 3%-6.1%^[4,5,32], which was near to our 90-d perioperative mortality rate of 6.8%. The improved results in recent years are likely due to improvements in perioperative support, education, and possibly, enhanced surgical technique.

In a recent study, Johnston *et al.*^[7] reported that the first month perioperative mortality after TP was 5.5%. The median survival was 15 ms, and the 1-, 3-, and 5-year overall survival rates were 60%, 22% and 13%, respectively. In multivariate analysis, the factors that affected survival were age, positive lymph nodes, positive surgical margin, tumor grade, tumor size, and adjuvant chemotherapy.

Baiocchi *et al.*^[2] and Salvia *et al.*^[39] reported that IPMN was resectable in 90%-100% of the patients. The survival rates for CIS, invasive carcinoma, and presence of nodal metastasis were 80%-90%, 50%-70% and 40%-50%, respectively.

The role of emergency TP is declining in favor of alternative interventional radiological strategies for the management of POPF and hemorrhage. Venous reconstruction in appropriately selected patients with PDAC and locally advanced tumor can be done safely

without negatively affecting recurrence or survival when compared to patients without vein involvement by the tumor. LTP appears to be a feasible and safe procedure when performed by experienced hands at a high-volume center. The significant metabolic derangements after TP may not become immediately apparent in the post-operative inpatient recovery phase, and may lead to a high rate of readmissions later on, so strict follow-up protocol should be available for these patients. A multidisciplinary approach with all-encompassing peri-operative education that includes diabetic and nutritional counseling appears to be essential in the successful management of these patients.

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COMMENTS

Background

In selected patients, total pancreatectomy (TP) has been established as a potential option in the treatment of pancreatic ductal adenocarcinoma, invasive or diffuse intraductal papillary mucinous neoplasms, multiple pancreatic neuroendocrine tumors.

Research frontiers

A single institutional retrospective study of patients undergoing total pancreatectomy from 1995 to 2014 was performed.

Innovations and breakthroughs

TP is performed at an increasing rate at major pancreatic centers, there is still debate regarding its indications and outcomes. This study aimed to analyze the indications and short- and long-term outcomes of TP in the spectrum of pancreatic resections in this high-volume center.

Applications

Total pancreatectomy, including laparoscopic total pancreatectomy, appears to be an appropriate option for selected patients when treated at a high-volume pancreatic center and through a multispecialty approach.

Terminology

The authors conducted a retrospective study of 103 patients who underwent TP between March 1995 and December 2014 at Mayo Clinic in Jacksonville, Florida using data collected from an institutional review board-approved prospective database.

Peer-review

The staff and surgeons are very experienced, presenting excellent post-operative outcome and long-term survival.

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Retrospective Study

Short-term and middle-term evaluation of laparoscopic hepatectomies compared with open hepatectomies: A propensity score matching analysis

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract**AIM**

To compare short-term results between laparoscopic hepatectomy and open hepatectomy using a propensity score matching.

METHODS

A patient in the laparoscopic liver resection (LLR) group

was randomly matched with another patient in the open liver resection (OLR) group using a 1:1 allocated ratio with the nearest estimated propensity score. Patients of the LLR group without matches were excluded. Matching criteria included age, gender, body mass index, American Society of Anesthesiologists score, potential comorbidities, hepatopathies, size and number of nodules, preoperative chemotherapy, minor or major liver resections. Intraoperative and postoperative data were compared in both groups.

RESULTS

From January 2012 to January 2015, a total of 241 hepatectomies were consecutively performed, of which 169 in the OLR group (70.1%) and 72 in the LLR group (29.9%). The conversion rate was 9.7% ($n = 7$). The mortality rate was 4.2% in the OLR group and 0% in the LLR group. Prior to and after propensity score matching, there was a statistically significant difference favorable to the LLR group regarding shorter operative times (185 min vs 247.5 min; $P = 0.002$), less blood loss (100 mL vs 300 mL; $P = 0.002$), a shorter hospital stay (7 d vs 9 d; $P = 0.004$), and a significantly lower rate of medical complications (4.3% vs 26.4%; $P < 0.001$).

CONCLUSION

Laparoscopic liver resections seem to yield better short-term and mid-term results as compared to open hepatectomies and could well be considered a privileged approach and become the gold standard in carefully selected patients.

Key words: Laparoscopic hepatectomy; Morbidity and mortality; Hepatocellular carcinoma; Liver resection; Colorectal metastases; Open hepatectomy; Propensity score matching

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Core tip: This is a retrospective study to compare short-term results between laparoscopic hepatectomy and open hepatectomy using a propensity score matching. Each patient in the laparoscopic liver resection group was randomly matched with another patient in the open liver resection group using a 1:1 allocated ratio with the nearest estimated propensity score. Prior to and after propensity score matching, results were in favour of laparoscopic liver resection. Laparoscopic liver resections seem to yield better short-term and mid-term results as compared to open approach and could well be considered a privileged approach and become the gold standard in carefully selected patients.

Untereiner X, Cagnet A, Memeo R, De Blasi V, Tzedakis S, Piardi T, Severac F, Mutter D, Kianmanesh R, Marescaux J, Sommacale D, Pessaux P. Short-term and middle-term evaluation of laparoscopic hepatectomies compared with open hepatectomies: A propensity score matching analysis. *World J Gastrointest Surg*

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INTRODUCTION

Since the development of laparoscopic cholecystectomy in 1987, the laparoscopic approach extended to several abdominal procedures. However, it took a very long time for laparoscopic liver surgery to expand.

The first non-anatomical liver resection was described by Reich *et al*^[1] in 1991 and the first anatomical hepatectomy was described by Azagra *et al*^[2] in 1996. Historically, laparoscopy was used to evaluate hepatic lesions before an open hepatectomy^[3,4] or to evaluate the carcinomatosis or peritoneal spread before the surgery and to treat cystic lesions by means of fenestrations^[5,6]. Surgical techniques were progressively developed to propose resections of benign^[2], then malignant lesions (hepatocellular carcinomas and hepatic metastases)^[7,8].

The main reasons accountable for this lack of enthusiasm for laparoscopic hepatectomies, in addition to the technical complexity of interventions, were the lack of appropriate instrumentation, the risk of gas embolism, the risks of uncontrolled bleeding, the fear of not being able to follow oncological principles with a subsequent risk of tumoral dissemination. However, some surgical teams decided to look into the possibilities of laparoscopic hepatic resections.

Indications for laparoscopic hepatectomies were defined during the first international consensus conference held in Louisville, United States^[9] in 2008 and revised in Morioka^[10] in 2014. This approach was used for patients selected with the following criteria: Location and size of lesions, liver function, and the experience of the surgical team. Although it was demonstrated that the laparoscopic approach elicits several advantages in the short- and mid-term (less postoperative pain, quicker restoration of bowel habits, less respiratory and parietal morbidity, improved quality of life, and reduced hospital stay)^[11,12], laparoscopic liver surgery remains currently limited to simple and peripheral resections, and few extensive and complex resections were reported^[13].

In the literature, such series include few patients and most monocentric series are retrospective ones with potential selection biases.

The objective of our study was to evaluate the short-term and mid-term results of laparoscopic hepatectomies as compared to open hepatectomies using a propensity score matching in order to rule out selection biases.

MATERIALS AND METHODS

From January 2012 to January 2015, data of all patients who consecutively underwent hepatectomy in two University hospital settings were collected prospectively.

All patients who required liver surgery whatever the pathology (metastasis, hepatocellular carcinoma, adenoma, neuroendocrine tumor, cholangiocarcinoma, *etc.*) were included. The laparoscopic approach did not modify the operative indications established for open surgery. Indications for laparoscopic hepatectomies were determined according to the latest recommendations^[9,10]. Exclusion criteria for the laparoscopic approach included the following: A poorly defined lesion or a lesion proximal to main vessels, decompensated cirrhosis or severe heart or respiratory failure^[14]. The following variables were analyzed: Type of liver resections (segmentectomies, bisegmentectomies, wedge resections, *etc.*), use of radiofrequency, number of resected segments, operative time, number of clampings, duration and type of clamping, rate of conversion, blood loss, number of transfusions, length of hospital stay, rate of R0 resection margins. All postoperative complications were indexed, namely respiratory (atelectasis, pneumopathy), cardiovascular (cardiac rhythm disorders, ischemia, cardiac decompression, hypertension), renal (acute renal failure, pyelonephritis, cystitis), parietal infections, deep collections, bleeding, biliary fistulas, liver failure, ascites. Liver segmentation was defined according to the Couinaud classification^[15]. Liver resections were defined according to the Brisbane classification in 2000^[16], using the following definitions: Hepatectomy was defined as major when 3 or more segments were removed. Other hepatectomies, which were limited, were performed on 2 segments or less (standard segmentectomy, bisegmentectomy or subsegmentectomy). Postoperative mortality and morbidity was defined as death or complications which occurred in the first 90 postoperative days and were graded according to the Clavien-Dindo classification^[17,18].

Complications were indexed as medical complications, including respiratory complications (atelectasis, pneumopathy), cardiovascular complications (including cardiac rhythm disorders, ischemia, cardiac decompression, hypertension), renal complications (acute renal failure, pyelonephritis, cystitis liver failure, ascites, and as surgical complications including parietal infections, deep collections, biliary fistulas, bleeding, eviscerations, parietal collections and acute digestive ischemia).

Preoperative evaluation

A complete patient evaluation included computed tomography-scan and/or magnetic resonance imaging acquired in 3 phases with a volumetric rendering. Patient personal files were discussed in a multidisciplinary meeting. Resectability was defined by the absence of extrahepatic invasion, the absence of ascites, and a normal liver function. All hepatic resections were performed by expert surgeons skilled in both laparoscopic and open hepatobiliary surgery.

Propensity score matching

All demographic and preoperative data of patients operated on using the open liver resection (OLR) group or the laparoscopic liver resection (LLR) group were compared using a univariate analysis in order to evaluate

the comparability of both groups. A propensity score matching was calculated to take into account and limit selection biases as well as confusion between the two groups. This method allows comparing the effects of the two types of intervention (open vs laparoscopy) taking into account the variables which influence the choice of the procedure type. The propensity score was assessed using logistic regression including the following variables: Age, gender, co-morbidity, American Society of Anesthesiologists (ASA) score, the use of neoadjuvant therapy, body mass index, total number of nodules, and type of resection. The choice of such variables was based on the results of the univariate analysis and/or the known influence of specific factors on the selection of the intervention type. A 1:1 balance ratio was used for propensity score matching, based on the nearest matching PS method^[19-21]. After the matching process, both groups were compared regarding their initial characteristics in order to re-evaluate the comparability of both groups. Finally, matched groups could be compared regarding the different variables of interest in the study.

Statistical analysis

Asymmetrical quantitative variables were presented as medians combined with the first and third quartiles after their distribution had been evaluated. Qualitative variables were presented as numbers and percentages. Comparison of the quantitative variables was performed using a Mann-Whitney test. Comparison of qualitative variables was performed using Pearson's χ^2 test or Fisher's exact test depending on numbers. A *P* value < 0.05 was considered as significant. Analyses were performed using the 3.2.0 version R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population and short-term results prior to matching

Between January 2012 and January 2015, a total of 241 consecutive hepatectomies were performed, including 169 hepatectomies using laparotomy (70.1%) and 72 laparoscopic ones (29.9%), including 8 which were performed by means of the da VinciTM robotic surgical system (*da Vinci Si*TM System; Intuitive Surgical, Inc., Sunnyvale, CA, United States).

As for patient characteristics, both groups were comparable, except for gender ratio (*P* = 0.042), the existence of a co-morbidity (67.5% of patients in the OLR group and 54.2% of patients in the LLR group, *P* = 0.0499), the existence of a hepatopathy including hepatic steatosis and cirrhotic livers (13% in the OLR group vs 36.1% in the LLR group, *P* < 0.001), and preoperative chemotherapy (59.8% in the OLR group vs 36.1% in the LLR group, *P* < 0.001) (Table 1). In addition, there were statistically more lesions in the OLR group as compared to the LLR group 3.0 (1.0-5.0) vs 1.0 (1.0-2.0); *P* < 0.001) and more major hepatectomies in the OLR group as compared to the LLR group (40.8% vs 12.5%, *P* <

Table 1 Demographic data and preoperative variables before and after propensity score matching *n* (%)

	OLR (<i>n</i> = 169)	LLR (<i>n</i> = 72)	<i>P</i> value	OLR (<i>n</i> = 72)	LLR (<i>n</i> = 72)	<i>P</i> value
Gender (M:F)	106:63	35:37	0.042	37:35	35:37	0.739
Age (yr), median (IQR)	65 (58-71)	61 (49-71)	0.091	62 (52-67)	61 (49-71)	0.794
BMI (kg/m ²), median (IQR)						
< 30	141 (83.74)	58 (80.6)	0.590	58 (80.6)	59 (81.9)	0.831
> 30	28 (16.6)	14 (19.4)		14 (19.4)	13 (18.1)	
Co-morbidities	114 (67.5)	39 (54.2)	0.0499	43 (59.7)	39 (54.2)	0.501
Dyslipidemia	53 (31.4)	16 (22.2)	0.151	20 (27.8)	16 (22.2)	0.441
Diabetes	27 (16.0)	12 (16.7)	0.894	10 (13.9)	12 (16.7)	0.643
Hypertension	60 (35.5)	28 (38.9)	0.617	24 (33.3)	28 (38.9)	0.488
Deep venous thrombosis/pulmonary embolism	20 (11.8)	6 (8.3)	0.423	6 (8.3)	6 (8.3)	1
Arteriopathy	8 (4.7)	3 (4.2)	1	1 (1.4)	3 (4.2)	0.620
Renal failure	7 (4.1)	1 (1.4)	0.442	1 (1.4)	1 (1.4)	1
Hepatopathy	22 (13.0)	26 (36.1)	< 0.001	14 (19.4)	26 (36.1)	0.026
Cirrhosis	18 (10.7)	21 (29.2)	0.002	10 (13.9)	21 (29.2)	0.067
Steatosis	11 (6.5)	4 (5.6)		3 (4.2)	4 (5.6)	
Sains	140 (82.8)	47 (65.3)		59 (81.9)	47 (65.3)	
Cardiopathy	35 (20.7)	9 (12.5)	0.131	10 (13.9)	9 (12.5)	0.806
Arrhythmia-atrial fibrillation	9 (5.3)	3 (4.2)	1	2 (2.8)	3 (4.2)	1
COPD	13 (7.7)	11 (15.3)	0.072	2 (2.8)	11 (15.3)	0.02
ASA score (I / II / III) (<i>n</i>)	36/82/51	26/28/18	0.055	21/34/17	26/28/18	0.565
ASA1 + 2	118 (69.8)	54 (75.0)	0.416	55 (76.4)	54 (75.0)	1
ASA3 + 4	51 (30.2)	18 (25.0)	0.416	17 (23.6)	18 (25.0)	1
Preoperative chemotherapy	101 (59.8)	26 (36.1)	< 0.001	30 (41.7)	26 (36.1)	0.494
Number of nodules, median (IQR)	3.0 (1.0-5.0)	1.0 (1.0-1.0)	< 0.001	1.5 (1.0-2.0)	1.0 (1.0-1.0)	< 0.001
Nodule max. size (mm), mean (IQR)	30.0 (20.0-45.0)	26.5 (20.0-44.3)	0.352	26.5 (20.0-44.3)	30.0 (20.0-55.3)	0.138
Resection type						
Major resection	69 (40.8)	9 (12.5)	< 0.001	15 (20.8)	9 (12.5)	0.180
Minor resection	100 (59.2)	63 (87.5)		57 (79.2)	63 (87.5)	
Benign lesions						
Adenoma	3 (1.8)	9 (12.5)	0.001	3 (4.2)	9 (12.5)	0.129
Nodular hyperplasia	2 (1.2)	3 (4.2)	0.159	2 (2.8)	3 (4.2)	1
Hydatid cysts	5 (3.0)	2 (2.8)	1	3 (4.2)	2 (2.8)	1
Angioma	1 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Other pathologies (Caroli disease, sclerosing cholangitis, traumatic, etc.)	2 (1.2)	2 (2.8)	0.585	2 (2.8)	2 (2.8)	1
Malignant tumors						
Hepatocellular carcinoma	25 (14.8)	24 (33.3)	0.001	11 (15.3)	24 (33.3)	0.012
Colorectal metastases	101 (59.8)	18 (25.0)	< 0.001	38 (52.8)	18 (25.0)	< 0.001
Cholangiocarcinoma	11 (6.5)	5 (6.9)	1	4 (5.6)	5 (6.9)	1
Gallbladder cancer	1 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Klatskin tumor	2 (1.2)	1 (1.4)	1	2 (2.8)	1 (1.4)	1
Neuroendocrine tumors	7 (4.1)	1 (1.4)	0.442	5 (6.9)	1 (1.4)	0.209
Other types of metastasis	25 (14.8)	24 (33.3)	0.001	11 (15.3)	24 (33.3)	0.012
Preoperative blood test, median (IQR)						
Albumin (g/dL)	40.0 (38.0-43.0)	41.0 (39.0-44.0)	0.293	40.5 (38.0-44.0)	41.0 (39.0-44.3)	0.465

OLR: Open liver resection; LLR: Laparoscopic liver resection; ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease.

0.001). There was a significant difference concerning pathologies with 9 adenoma resections in the LLR group (12.8%), vs 3 in the OLR group (1.8%) (*P* = 0.001), 24 hepatocarcinomas in the LLR group (33.3%) vs 25 in the OLR group (14.8%), (*P* = 0.001), and 101 colorectal metastasis resections in the OLR group (59.8%) vs 18 in the LLR group (25%), *P* < 0.001 (Table 1).

Details of the procedures performed are outlined in Table 2. It can be observed that fewer segments were resected in the LLR group (median of 1 vs 2; *P* < 0.001) and that there were more segmentectomies performed in the LLR group (40.3% vs 7.1%; *P* < 0.001), fewer bisegmentectomies (13.9% vs 27.2%, *P* = 0.025), fewer right hepatectomies (4.2% vs 15.4%,

P = 0.014) and fewer associations with destruction by radiofrequency (12.5% vs 32%, *P* = 0.002) as compared to the OLR group. There was a statistically significant difference in favor of LLR concerning operative time, blood loss, and length of hospital stay. In addition, there were significantly fewer medical complications in the LLR group (4.2% vs 2.8%, *P* < 0.001), taking all types into account (Table 2).

The conversion rate was 9.7% (*n* = 7), the reason for that being the presence of several pedicular adenopathies, which required an extensive dissection in one patient, and there were difficulties of access in 6 other patients. The mortality rate was 4.2% in the OLR group and 0% in the LLR group. The reason for death

Table 2 Operative and postoperative data before and after propensity score matching *n* (%)

	OLR (<i>n</i> = 169)	LLR (<i>n</i> = 72)	<i>P</i> value	OLR (<i>n</i> = 72)	LLR (<i>n</i> = 72)	<i>P</i> value
Resection type						
Bisegmentectomy	46 (27.2)	10 (13.9)	0.025	30 (41.7)	10 (13.9)	< 0.001
Segmentectomy	12 (7.1)	29 (40.3)	< 0.001	8 (11.1)	29 (40.3)	< 0.001
Wedge resection	49 (29.0)	24 (33.3)	0.502	20 (27.8)	24 (33.3)	0.469
Left hepatectomy	23 (13.6)	5 (6.9)	0.188	8 (11.1)	5 (6.9)	0.383
Right hepatectomy	26 (15.4)	3 (4.2)	0.014	6 (8.3)	3 (4.2)	0.494
Enlarged right hepatectomy	15 (8.9)	1 (1.4)	0.044	2 (2.8)	1 (1.4)	1
Combined resection and radiofrequency	54 (32.0)	9 (12.5)	0.002	13 (18.1)	9 (12.5)	0.354
Number of resected segments, median (IQR)	2.0 (0.0-4.0)	1.0 (0.0-1.3)	< 0.001	2.0 (0.0-2.0)	1.0 (0.0-1.3)	0.004
Operation length (min), median (IQR)	250 (190-330)	185 (150-254)	< 0.001	247.5 (187.5-332.5)	185.0 (150.0-253.8)	0.002
Pedicular clamping	110 (65.1)	40 (55.6)	0.162	43 (59.7)	40 (55.6)	0.613
Intermittent	96 (56.8)	34 (47.2)	0.354	36 (50.0)	34 (47.2)	0.739
Permanent	14 (8.3)	6 (8.3)		7 (9.7)	6 (8.3)	0.771
No clamping	59 (34.9)	32 (44.4)		29 (40.3)	32 (44.4)	0.613
Clamping duration (min), median (IQR)	22.0 (0.0-38.0)	15.0 (0.0-35.0)	0.174	25.0 (0.0-36.5)	15.0 (0.0-35.0)	0.411
Blood loss (mL), median (IQR)	300 (30-500)	100 (30-356)	0.003	300.0 (30.0-562.5)	100.0 (30.0-356.3)	0.002
Transfusion (<i>n</i>), median (IQR)	41 (24.3)	12 (16.7)	0.193	16 (22.2)	12 (16.7)	0.400
Length of hospital stay (d), median (IQR)	10.0 (7.0-14.0)	7.0 (5.8-10.0)	< 0.001	9.0 (7.0-12.0)	7.0 (5.8-10.0)	0.004
R0 resection margin	139 (82.3)	63 (87.5)	0.311	62 (86.1)	63 (87.5)	0.806
Conversion rate	NA	7 (9.7)	0.065	NA	7 (9.7)	0.326
Postoperative complications \geq 1						
Respiratory	30 (17.8)	6 (8.3)	0.060	18 (25.0)	6 (8.3)	0.007
Atelectasis	21 (12.4)	4 (5.6)	0.109	11 (15.3)	4 (5.6)	0.056
Pneumopathy	10 (5.9)	2 (2.8)	0.518	7 (9.7)	2 (2.8)	0.166
Renal	7 (4.1)	0 (0.0)	0.107	5 (6.9)	0 (0.0)	0.058
Acute renal failure	6 (3.6)	0 (0.0)	0.183	5 (6.9)	0 (0.0)	0.058
Cystitis/pyelonephritis	1 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Cardiovascular	7 (4.1)	4 (5.6)	0.737	2 (2.8)	4 (5.6)	0.681
Wall infection	8 (4.7)	2 (2.8)	0.728	6 (8.3)	2 (2.8)	0.275
Deep collection	19 (11.2)	6 (8.3)	0.498	8 (11.1)	6 (8.3)	0.574
Hemorrhage	3 (1.8)	0 (0.0)	0.556	2 (2.8)	0 (0.0)	0.497
Liver failure	7 (4.1)	1 (1.4)	0.442	4 (5.6)	1 (1.4)	0.366
Ascites	5 (3.0)	2 (2.8)	1	5 (6.9)	2 (2.8)	0.441
Biliary fistula	10 (5.9)	2 (2.8)	0.518	1 (1.4)	2 (2.8)	1
Medical complications	47 (27.8)	3 (4.3)	< 0.001	19 (26.4)	3 (4.3)	< 0.001
Surgical complications	7 (4.1)	2 (2.8)	0.729	4 (5.6)	2 (2.8)	0.681
I - II	47 (27.8)	21 (29.2)	0.690	21 (29.2)	21 (29.2)	0.447
III-IV	33 (19.5)	12 (16.7)		13 (18.1)	12 (16.7)	
V	4 (2.4)	0 (0.0)		3 (4.2)	0 (0.0)	
Postoperative mortality 30 d	2 (1.2)	0 (0.0)	1	2 (1.2)	0 (0.0)	0.080
Postoperative mortality 60 d	3 (1.8)	0 (0.0)	0.556	0 (0.0)	0 (0.0)	1
Postoperative mortality 90 d	5 (3.0)	0 (0.0)	0.326	0 (0.0)	0 (0.0)	1

OLR: Open liver resection; LLR: Laparoscopic liver resection.

was the occurrence of multivisceral failure after a right hepatectomy in 3 ASA 3 patients including 2 who were treated for a cholangiocarcinoma and one for liver metastases of a colorectal cancer which received 3 cycles of neoadjuvant FOLFOX therapy.

Population and short-term results after matching and PS

After using the propensity score, all 72 patients of the LLR group were matched to 72 patients of the OLR group. Both groups were comparable as far as patient characteristics were concerned, except for liver diseases which were more important in the LLR group (36.1% vs 19.4%, $P = 0.026$), the type of segment resected ($P < 0.05$), and

the pathology, with more hepatocellular carcinomas in the LLR group (33.3% vs 15.3%, $P = 0.012$) and fewer colorectal metastases (25% vs 52.8% in the OLR group, $P < 0.001$), (Table 1). More bisegmentectomies were performed in the OLR group (41.7% vs 13.9%, $P < 0.001$) but more segmentectomies in the LLR group (40.3% vs 11.1%, $P < 0.001$).

There was still a significant difference in terms of operative time ($P = 0.002$), a shorter hospital stay ($P = 0.004$) in the LLR group, less blood loss ($P = 0.002$), and fewer medical complications (4.3% vs 26.4%, $P < 0.001$) in the LLR group. Other values from both groups were comparable (Table 2).

DISCUSSION

The objective of this study was to compare short-term results of hepatectomies performed using a laparoscopic and an open approach, using the propensity score in order to reduce the selection bias. After matching, it has more open resection for liver metastases of a colorectal cancer than the laparoscopic approach. Indeed in colorectal cancer, metastases are often multiple and difficult to be able to remove by laparoscopic approach. Among the population, there was a selection of indications with more limited and minor resections in the laparoscopic group with fewer resected lesions. After a matching and a propensity score were applied to the essential factors which influence morbi-mortality, a significant decrease in blood loss could be observed, as well as the length of hospital stay, operative time, and postoperative medical complications in the laparoscopic group.

Despite an increase in the number of centers which use laparoscopic hepatobiliary surgery, the use of this approach is not very widespread (5% to 30% of liver resections)^[22-27]. Only a few centers report a strong activity representing 50% to 80%^[28-30] of liver resections. Over a period of 3 years, we report 72 laparoscopic hepatectomies, out of 241 hepatectomies in total, which means that 29.9% of hepatectomies were performed laparoscopically. Our indications for laparoscopic hepatectomy are the same as for open surgery. Most often, we would decide to choose a laparoscopic approach due to the location and the size of the tumor^[9,10]. As shown in our series, laparoscopic is most often used for anterolateral resections (segments 2 to 6). Wedge resections, segmentectomies, and left lobectomies remain the best laparoscopic indications^[22,30,31]. Major hepatectomies, especially right hepatectomies, were mainly performed using an open approach due to technical difficulties^[32-36]. Resection of lesions located in segments VII, VIII, I va and I is still not properly documented due to exposure difficulties and proximity with the inferior vena cava and suprahepatic veins. Superior posterior segments can be approached using transdiaphragmatic ports^[37,38], or using a transthoracic route^[39]. In addition, laparoscopic resection is not recommended for lesions greater than 5 cm in diameter, due to manipulation difficulties with a risk of tumoral rupture and of obtaining insufficient resection margins^[22,26,29]. The hepatic pedicle is systematically controlled at the beginning of the intervention in order to perform a pedicular clamping if required (55.6% of cases in our series). We report 6 permanent clampings but this corresponds to very superficial resections. In most cases, we privileged intermittent clamping, as this allows for a better liver tolerance, especially in cirrhotic patients^[40-42], as well as a better short- and long-term prognosis^[43]. We used intermittent clamping using a laparoscopic approach systematically. Additionally, laparoscopic clamping, which is associated with pneumoperitoneum pressure, allows to decrease bleeding and almost completely eliminates the use of continuous aspiration, which is not feasible.

Average clamping time was 15 min with the LLR vs 22 min with the OLR ($P = 0.174$). Intermittent clamping was 20 min with reperfusion phases of 10 min in all patients, except for cirrhotic patients, in which clamping would not exceed 15 min.

In addition, we do not report any gas embolism in our series, a rare occurrence which has, however, previously been described in laparoscopic surgery^[22,27,28]. It has been demonstrated that in order to decrease this risk, the use of carbon dioxide (a highly soluble gas) should be privileged, as well as low insufflations pressures^[44]. We did not use Argon although it allows for a good hemostasis, because it increases the risk of gas embolism in liver surgery^[45].

After PS, our study clearly demonstrated the benefits of the laparoscopic approach. There was a decrease in intraoperative bleeding (100 mL vs 300 mL, $P = 0.002$), a reduction in the length of hospital stay^[11] with a median of 7 d vs 9 d ($P = 0.004$) and even a shorter operative time (185 min vs 247.5 min, $P = 0.002$). The same goes for postoperative outcomes which appear to be simpler with fewer medical complications, especially respiratory ones (4.3% vs 26.4%, $P < 0.001$), also described in the series by Fuks *et al.*^[46]. As for surgical complications, laparoscopy does not provide any real benefits. Some authors have reported similar results^[47-49], like Cannon *et al.*^[50] (23% vs 50%, $P = 0.004$), Simillis in his meta-analysis^[51]. In the laparoscopic group, no deaths have been recorded; the same goes for unusual complications, and less than 20% of patients were transfused during hospitalization.

The conversion rate described in the literature ranges from 5% to 15%^[22-24,30]. The 2 main reasons for conversion are: Firstly, a technical problem due to a difficult exposure, a risk of tumoral rupture dissemination for fragile lesions or a doubt concerning the sufficient resection margin. The second reason is uncontrolled bleeding. In our series, we report a conversion rate of 9.7%, the main reason for it being exposure difficulties, which make resection difficult.

The results were obtained in our series as well as in series published by surgeons with experience in liver surgery and laparoscopic surgery, and consequently these results can only be extrapolated with caution in all centers.

In conclusion, the development of liver surgery using a laparoscopic approach has been a gradual process, and some liver resections currently seem feasible and safe in patients selected in centers in which surgeons have experience in both hepatic surgery and laparoscopic surgery. This study compared the complications mainly for minor resections after matching; although bicentric study with small groups, the laparoscopic liver resections seem to produce the same results as the open approach in the short- and middle-term. It could be considered as an alternative to open surgery and become the gold standard for carefully selected patients. However, complementary studies seem necessary, especially for long-term oncological results and for major hepa-

tectomies, in order for the laparoscopic approach to become a widely used alternative to hepatectomies using laparotomy.

COMMENTS

Background

Laparoscopic surgery is a consolidate technique who is diffusing rapidly also in some subspeciality who initially were contraindicated.

Research frontiers

The aim of this paper is to evaluate the impact of short and mid-term results of laparoscopy in liver surgery.

Innovations and breakthroughs

Minimally invasive approach represents the standard of care for most digestive cancer and it has to be confirmed for liver malignancies.

Applications

The extended indication for liver malignancies are even more frequent and need to be confirmed by short, middle and long term results.

Terminology

Minimally invasive and laparoscopic approach, liver resection, and better postoperative outcome are the main subjects of the paper.

Peer-review

This article has some important information to promote introduction of laparoscopy in the hepatobiliary and pancreatic field.

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Retrospective Study

Barium appendicitis: A single institution review in Japan

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Abstract**AIM**

To review clinical experience with barium appendicitis at a single institution.

METHODS

A retrospective review of patients admitted with a diagnosis of acute appendicitis, from January 1, 2013 to December 31, 2015 was performed. Age, gender, computed tomography (CT) scan findings if available, past history of barium studies, pathology, and the presence of perforation or the development of complications were reviewed. If the CT scan revealed high density material in the appendix, the maximum CT scan radiodensity of the material is measured in Hounsfield units (HU). Barium appendicitis is defined as: (1) patients diagnosed with acute appendicitis; (2) the patient has a history of a prior barium study; and (3) the CT scan shows high density material in the appendix. Patients who meet all three criteria are considered to have barium appendicitis.

RESULTS

In total, 396 patients were admitted with the diagnosis of acute appendicitis in the study period. Of these, 12 patients (3.0%) met the definition of barium appendicitis. Of these 12 patients, the median CT scan radiodensity of material in the appendix was 10000.8 HU, ranging from 3066 to 23423 HU (\pm 6288.2). In contrast, the median CT scan radiodensity of fecaliths in the appendix, excluding patients with barium appendicitis, was 393.1 HU, ranging from 98 to 2151 HU (\pm 382.0). The CT scan radiodensity of material in the appendices of patients with barium appendicitis was

significantly higher than in patients with nonbarium fecaliths ($P < 0.01$).

CONCLUSION

Barium appendicitis is not rare in Japan. Measurement of the CT scan radiodensity of material in the appendix may differentiate barium appendicitis from routine appendicitis.

Key words: Acute appendicitis; Barium appendicitis; Barium sulfate; Upper gastrointestinal imaging; Gastric cancer screening

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Core tip: This is a retrospective study to review clinical experience with barium appendicitis at a single institution in Japan. In the three years of study period, 12 patients (3.0%) were diagnosed as barium appendicitis among 396 patients with acute appendicitis. The computed tomography (CT) scan radiodensity of material in the appendices of patients with barium appendicitis was significantly higher than in patients with nonbarium fecaliths. Barium appendicitis is not rare in Japan. Measurement of the CT scan radiodensity of material in the appendix may differentiate barium appendicitis from routine appendicitis.

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INTRODUCTION

Acute appendicitis is one of the most common surgical problems encountered in clinical surgical practice. While the exact etiology of acute appendicitis remains unclear, an obstruction of the appendiceal lumen can result in the development of acute appendicitis^[1]. In Japan, upper gastrointestinal imaging using barium sulfate is widely used in mass screening programs for gastric cancer^[2]. Barium sulfate is not harmful to the intestinal mucosa and complications after a barium study are considered to be very rare^[2-4]. Acute appendicitis caused by residual barium is also thought to be a very rare complication after a barium study^[3-5]. General surgeons in Japan often encounter patients with acute appendicitis who have residual barium felt to be the responsible etiologic agent.

We performed a retrospective review of patients admitted with a diagnosis of acute appendicitis, and specifically reviewed those with acute appendicitis suspected to be caused by residual barium.

MATERIALS AND METHODS

Tokyo Bay Urayasu Ichikawa Medical Center is a secondary referral hospital in Chiba prefecture, Japan, providing acute surgical care. A retrospective analysis was conducted of patients seen from January 1, 2013 to December 31, 2015. Patients for review were identified based on their medical records including patients admitted with the diagnosis of acute appendicitis. Age, gender, computed tomography (CT) scan findings if available, past history of barium studies, pathology, and the presence of perforation or the development of complications were reviewed. If the CT scan revealed high density material in the appendix, the maximum CT scan radiodensity of the material is measured in Hounsfield units (HU).

Barium appendicitis is defined as: (1) patients diagnosed with acute appendicitis; (2) the patients have a history of a prior barium study; and (3) the CT scan shows high density material in the appendix. Patients who meet all three criteria are considered to have barium appendicitis.

Data were analyzed with Fisher's exact test and the Mann-Whitney *U* test. A *P*-value less than 0.05 is considered statistically significant.

RESULTS

From January 1, 2013 to December 31, 2015, 396 patients were admitted with the diagnosis of acute appendicitis, including 210 males and 186 females. The median age is 37 years, ranging from 5 to 86 years. Of these, 12 patients (3.0%) met the definition of barium appendicitis (Table 1, Figure 1), including ten males and two females, with a median age of 48 years, ranging from 37 to 62 years. Of these 12 patients, the median CT scan radiodensity of material in the appendix was 10000.8 HU, ranging from 3066 to 23423 HU (± 6288.2). According to these data, the CT scan radiodensity of residual barium is generally higher than 3000 HU. If we apply this value as a cutoff, we can identify seven more patients with suspected barium appendicitis based on CT scan radiodensity alone. According to the medical records, these seven patients had no definite history of a preceding barium study, excluding one patient who specifically denied having a barium study. The median CT scan radiodensity of fecaliths in the appendix, excluding patients with barium appendicitis, was 393.1 HU, ranging from 98 to 2151 HU (± 382.0). The CT scan radiodensity of material in patients with barium appendicitis was significantly higher than patients with non-barium fecaliths ($P < 0.01$).

Ten of 12 patients with barium appendicitis underwent laparoscopic appendectomy urgently. One patient underwent interval laparoscopic appendectomy after initially successful non-operative management. In one patient, there was obvious perforation with abscess formation and non-operative management was initially undertaken. Following this, the patient refused interval appendectomy. The interval from barium study to the diagnosis of appendicitis was variable, ranging from 2 d to 10 mo.

The pathological results in patients with barium appen-

Table 1 Patient characteristics

Age	Gender	Maximum CT density (HU)	Perforation	Appendix pathology	Interval between barium study and diagnosis	Treatment
52	M	10243	+	Phlegmonous	8 mo	Laparoscopic appendectomy
37	M	23423	-	Gangrenous	2 d	Laparoscopic appendectomy
45	M	6620	-	Gangrenous	1 mo	Laparoscopic appendectomy
49	M	15286	-	Phlegmonous	16 d	Laparoscopic appendectomy
44	M	3066	-	Gangrenous	1 mo	Laparoscopic appendectomy
62	M	18286	+	Gangrenous	Not documented	Laparoscopic appendectomy
45	M	8192	+	Chronic appendicitis	3 mo	Primary non-operative management followed by interval appendectomy
46	M	11514	-	Phlegmonous	10 mo	Laparoscopic appendectomy
60	F	3178	-	Gangrenous	Not documented	Laparoscopic appendectomy
44	M	8727	-	Gangrenous	3 mo	Laparoscopic appendectomy
45	M	7806	-	Gangrenous	5 mo	Laparoscopic appendectomy
41	F	3669	+	N/A	1 mo	Non-operative management without interval appendectomy

M: Male; F: Female; CT: Computed tomography; HU: Hounsfield units; N/A: Not analyzed.



Figure 1 Abdominal computed tomography scans with axial and coronal views. A and B: High density material is seen inside the swollen appendix (arrows); C and D: High density material is seen inside the swollen appendix and in the peritoneal cavity with a fluid collection (arrow heads). This strongly suggests a perforated appendicitis with residual barium.

ditis are available for 11 patients. Seven patients had gangrenous appendicitis and three had phlegmonous appendicitis. One patient, who underwent interval appendectomy, had chronic inflammation of the appendix. The rate of gangrenous appendicitis is 58.3% in patients with barium appendicitis and 56.4% in patients without barium appendicitis. The rate of gangrenous appendicitis is almost the same in patients with typical (unassociated with barium) appendicitis compared to patients with barium appendicitis. Four out of 12 patients had a perforation (33.3%), confirmed by intraoperative or imaging findings. The perforation rate in patients with

barium appendicitis was higher than in patients without barium appendicitis (18.8% in this study), which is not statistically significant ($P = 0.25$). Interestingly, although the rate of gangrenous appendicitis is almost the same in patients with barium appendicitis and typical appendicitis the perforation rate was higher in patients with barium appendicitis.

DISCUSSION

Barium appendicitis is a rare complication after barium examinations and was first described by Gubler *et al*^[6]

in 1954. Although retained barium in the appendix after barium studies is very common^[7], especially after colon studies, more than 90% of patients evacuate the barium within 72 h^[3,4,7]. The true pathophysiology of barium appendicitis remains unclear. The true incidence of barium appendicitis is also unknown because only a few case reports or small case series have been reported to date^[3-7]. The time interval between the barium study and the diagnosis of barium appendicitis in several previous studies ranges from four hours to four years^[5,8]. In the present study, the range is 10 d to 10 mo. The wide range of values suggests that retained barium in the appendix alone does not result in appendicitis. There would appear to be other factors that contribute to the development of acute appendicitis.

Acute appendicitis is one of the most common surgical emergencies encountered by general surgeons. Obstruction of the appendiceal lumen, often due to a fecalith, lymphoid hyperplasia, or rarely a cecal or appendiceal tumor, is generally thought to be the cause of acute appendicitis in many patients^[1,9]. Fecaliths are a cause of obstruction of the appendiceal lumen, although they are not always found at surgery. Fecaliths are composed of inspissated stool, mucus with trapped calcium phosphate and inorganic salts, which finally obstructs the appendiceal lumen^[10,11]. In this study, fecaliths were identified in 34% of patients with acute appendicitis based on imaging findings. It is unknown if the high density material in the appendix in patients with barium appendicitis is composed of only barium or if it is combined with other material such as that found in a fecalith. However, luminal obstruction of the appendix by residual barium resulted in the development of acute appendicitis. As mentioned, an additional cause of barium appendicitis may be a pre-existing fecalith in the appendix. Fecaliths not only cause appendicitis, but also are considered to be associated with appendiceal perforation^[11,12]. In this study, the perforation rate in patients with barium appendicitis was higher than in patients without barium appendicitis. Although it is not statistically significant, this suggests that residual barium may be a risk factor for appendiceal perforation, similar to a fecalith. The fact that typical appendicitis has the same rate of gangrenous inflammation in this study also supports this hypothesis.

In this study, the CT scan radiodensity of material in the appendix in patients with barium appendicitis is significantly higher than that of fecaliths in patients with typical appendicitis. These data suggest that the CT scan radiodensity of material in the appendix may differentiate barium from normal fecaliths. We acknowledge that in general, not all patients undergo CT scans to establish the diagnosis of acute appendicitis. However, during the study period, about 3% of patients presented with acute appendicitis believed to be caused by residual barium. Since acute appendicitis is one of the most common surgical emergencies, and the fact that in Japan, barium is widely used in studies screening for gastric cancer^[2], we believe that the diagnosis and recognition of barium

appendicitis as a complication of barium studies is worthwhile, especially in Japan.

According to data reporting the complications after gastric cancer screening in Japan, the total complication rate after barium studies is reported to be less than 0.04%^[13]. The most common reported complication after barium studies was aspiration, followed by allergic reaction and bowel obstruction. There have also been severe complications reported such as intestinal perforation due to residual barium^[13]. Interestingly, there were no reports of barium appendicitis^[13], although barium appendicitis occurred in 3% of patients with acute appendicitis in this study. There is an approximate 7% lifetime risk of developing appendicitis^[1,9], thus, a 3% incidence in patients with acute appendicitis is a significant number. Since acute appendicitis is often treated with appendectomy no matter what the etiology, the true incidence of barium appendicitis is likely underestimated.

Several limitations are acknowledged in this study. First, this is a single institution retrospective analysis. Second, there is no confirmation of what the high density material in the resected appendices actually was. Pathological confirmation may support the results of this study, if it is specifically checked in a prospective study.

In conclusion, barium appendicitis is not rare in Japan. Measurement of the CT scan radiodensity of material in the appendix may differentiate barium appendicitis from routine appendicitis. Since barium is widely used in Japan for gastric cancer screening, determination of the true incidence of barium appendicitis is important.

This material was presented in part at the 116th annual congress of the Japan Surgical Society (April 15th 2016, Osaka, Japan).

COMMENTS

Background

Barium appendicitis is a rare complication of gastrointestinal imaging using barium sulfate. The true incidence of barium appendicitis is unknown. However, general surgeons in Japan often encounter patients with acute appendicitis where the etiology appears to be a barolith in the appendix. The authors review their clinical experience with barium appendicitis at a single institution in Japan.

Research frontiers

The exact incidence of barium appendicitis is unknown. This study reviews their experience with appendicitis and the incidence of barium appendicitis among all patients who presented with acute appendicitis.

Innovations and breakthroughs

Barium appendicitis is thought to be a rare complication of gastrointestinal imaging. However, this study shows that barium appendicitis represents about 3% of all patients with acute appendicitis.

Applications

Measurement of the computed tomography (CT) scan radiodensity of high density material in the appendix may help to differentiate barium appendicitis from typical appendicitis. This may also help elucidate the true incidence of barium appendicitis in future studies.

Terminology

HU: Hounsfield units.

Peer-review

Barium appendicitis is a rare clinical condition. Barolith can occur due to post-examination retained barium in appendix lumen and it can cause appendicitis. CT definings in this manuscript is well-thought evidence and helps diagnose.

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Eosinophilic ascites: A diagnostic and therapeutic challenge

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Abstract

Eosinophilic gastroenteritis (EGE) is a rare condition characterized by eosinophilic infiltration of the gastrointestinal tract. Depending on the dominant layer of infiltration it is classified into three types namely, mucosal, muscularis and subserosal. The most uncommon variant is the subserosal type characterized by primarily subserosal disease, eosinophilic ascites and peripheral hypereosinophilia. The clinical features are non-specific with history of atopic predisposition and allergy. Endoscopic biopsy is frequently non-diagnostic due to an uninvolved gastrointestinal mucosa rendering its diagnosis a challenge. The mainstay of diagnosis is peripheral hypereosinophilia and eosinophil-rich ascitic fluid on diagnostic paracentesis. Oral steroid therapy is usually the first line of treatment with dramatic response. Due to a propensity for relapse, steroid-sparing therapy should be considered for relapses of EGE. We report a case of subserosal EGE with diagnostic clinical features and treatment response and review the current strategy in the management of eosinophilic ascites.

Key words: Gastrointestinal; Atopy; Eosinophilic ascites; Endoscopic biopsy; Eosinophilia

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Core tip: Eosinophilic gastroenteritis (EGE) is a rare condition and the diagnosis of subserosal EGE is challenging due to its nonspecific symptoms and signs and frequently non-diagnostic biopsy on gastrointestinal endoscopy. This review describes a patient with typical findings of peripheral hypereosinophilia and eosinophilic

ascites and outlines the current strategy in the diagnosis and treatment of subserosal EGE.

Agrawal S, Vohra S, Rawat S, Kashyap V. Eosinophilic ascites: A diagnostic and therapeutic challenge. *World J Gastrointest Surg* 2016; 8(9): 656-659 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/656.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.656>

INTRODUCTION

Eosinophilic gastroenteritis (EGE) is a rare and potentially fatal condition with clinico-pathologic characteristics of peripheral hypereosinophilia and eosinophilic infiltration of the gastrointestinal tract. It is classified into three pathologic types depending on the dominant gastrointestinal layer of eosinophilic infiltration^[1]. The subserosal type characterized by primarily subserosal disease and eosinophilic ascites is the rarest presentation of EGE^[2,3]. Biopsy of the mucosal layer obtained during upper gastrointestinal endoscopy frequently fails to diagnose subserosal EGE. The diagnosis of subserosal EGE is challenging because of its rarity, nonspecific clinical presentation and non-diagnostic endoscopy. This study presents the typical clinico-pathologic and radiologic findings in subserosal EGE and reviews the current diagnostic and therapeutic strategy in patients with abdominal pain, ascites and peripheral hypereosinophilia.

CASE REPORT

A 35-year-old female presented to the clinic with complaints of abdominal distension and an episode of self-limiting diarrhea three weeks ago. She admitted to the recent use of green tea and increased consumption of nuts in her diet. Past medical history was remarkable for recurrent allergic bronchitis. On examination there was no evidence of pallor, icterus or peripheral edema and abdominal examination revealed moderate distention with a doughy consistency. Abdominal ultrasonography demonstrated moderate ascites with no signs of portal hypertension, liver or renal disease. Contrast-enhanced abdominal computed tomography confirmed the presence of free peritoneal fluid, diffuse circumferential thickening of small bowel loops, distal stomach and esophagus (Figure 1). Laboratory examination revealed peripheral eosinophilic leukocytosis with 52% eosinophils (total leukocyte count 22900 cells/mm³) and no immature myeloid precursors. The C-reactive protein, erythrocyte sedimentation rate and IgE levels were within normal limits. Tumor marker CA-125 was normal. Skin prick test results for food allergens and stool examination for bacteria, ova and parasites were negative. Diagnostic paracentesis was moderately cellular with 100% eosinophils, negative for malignant cells and sterile (Figure 2). Upper endoscopy and colonoscopy demonstrated mild erythema of the gastric antrum with an unremarkable

esophagus, duodenum, colon and terminal ileum. Histology revealed a mild inflammatory infiltrate in the lamina propria of the gastric antrum and duodenum comprising of lymphocytes, plasma cells and scattered eosinophils (Figure 3). Echocardiographic findings were normal. Bone marrow aspiration and biopsy showed hypercellularity with a marked increase in mature eosinophils without blasts. The findings confirmed a diagnosis of subserosal EGE.

The patient was treated with oral prednisone 25 mg daily with rapid symptomatic improvement and normalization of the hypereosinophilia within a week of initiation of steroid therapy. Four months after the weaning of steroids, follow-up abdominal computed tomography demonstrated complete resolution of the peritoneal fluid and bowel wall thickening. Two years after completion of therapy, the patient remains asymptomatic and free of ascites or hypereosinophilia.

DISCUSSION

EGE is a rare disease with an estimated prevalence of 28/100000 in United States^[4]. Klein *et al*^[1] classified EGE into three types based on the dominant layer of eosinophilic infiltration (1) predominant mucosal disease characterized by iron deficiency anemia, protein-losing enteropathy and malabsorption; (2) predominant muscle layer disease characterized by localized or diffuse thickening of the bowel wall with features of pyloric narrowing and obstructive symptoms; and (3) predominant subserosal disease characterized by eosinophil-rich ascites^[1-5]. Mucosal EGE is the most common type (70%) followed by muscularis (20%) and subserosal (10%)^[6,7]. EGE may also present with obstructive jaundice due to biliary tract involvement or extraintestinal manifestations such as eosinophilic cystitis, eosinophilic splenitis and hepatitis^[7-9].

Talley *et al*^[10] have defined three diagnostic criteria for EGE (1) presence of gastrointestinal symptoms; (2) biopsies of the gastrointestinal tract showing eosinophilic infiltration or characteristic radiologic findings with peripheral eosinophilia or eosinophil-rich ascites with; and (3) no evidence of parasitic or extraintestinal disease. Characteristic findings of EGE on abdominal computed tomography include thickening of bowel wall or fold, layering of the bowel wall, luminal narrowing without obstruction, intra- or extra-luminal granuloma, mesenteric lymphadenopathy with peripheral rim-like enhancement or necrosis and ascites^[11]. The etiology of EGE is unclear however, an atopic predisposition is noted in patients with EGE with a history of allergy reported in 50% patients with EGE^[10]. A genetic predisposition is suspected as 16% of patients with EGE have a family member with a similar condition^[9]. The majority of the patients diagnosed with EGE are 20-50 years of age with no reported gender predisposition^[3].

The differential diagnosis of eosinophilic ascites includes parasitic infection (*Strongyloides stercoralis*, *Toxocara canis*), abdominal tuberculosis, rupture of hydatid cyst, chronic pancreatitis, vasculitis (Churg-Strauss

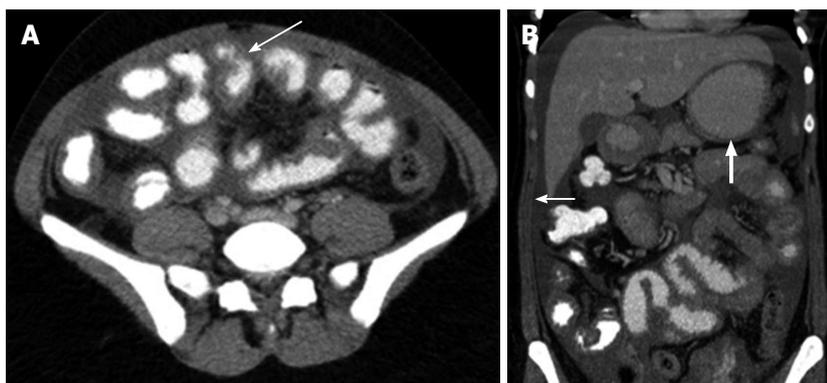


Figure 1 Findings on contrast-enhanced abdominal computed tomography. A: Sagittal section demonstrates thickened loops of small bowel (arrow); B: Coronal image demonstrates free peritoneal fluid (arrow), thickened loops of small bowel and circumferential mural thickening of the distal stomach (heavy arrow).

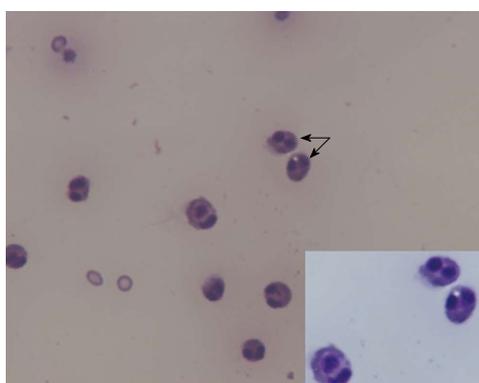


Figure 2 Diagnostic paracentesis demonstrates ascitic fluid rich in eosinophils (arrow), magnification 10 ×. Inset, eosinophils in ascitic fluid, May Grunwald Giemsa, magnification 100 ×.

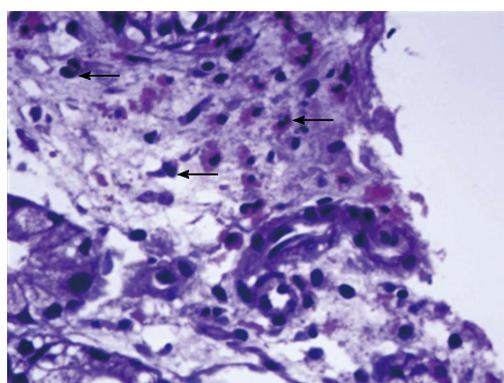


Figure 3 Endoscopic biopsy of gastric mucosa demonstrates scattered eosinophils (arrows) in the lamina propria. Hematoxylin and eosin, magnification 40 ×.

syndrome), hypereosinophilic syndrome, malignancy and Crohn’s disease^[12]. The diagnosis of subserosal EGE remains challenging because of its rarity and non-specific clinical features. The most common clinical features include abdominal pain (90.4%), nausea and vomiting (57.1%), diarrhea (52.3%) and abdominal distension (38.1%)^[13]. It should be considered in the diagnostic evaluation of patients with abdominal pain, ascites and peripheral hypereosinophilia and a high index of suspicion should be maintained by the physician^[3]. The mainstay of diagnosis of subserosal EGE is confirmation of eosinophil-rich ascitic fluid on diagnostic paracentesis and peripheral hypereosinophilia.

The overall prognosis of EGE is good with an excellent response to oral steroids comprising the first line of therapy^[2]. Prednisone 20-40 mg daily in divided doses is highly effective with symptomatic remission in 80% patients within a week and normalization of eosinophil counts within two weeks of initiation of therapy^[13]. Other medical therapy includes antihistaminic drugs, sodium cromoglycate, montelukast and ketotifen^[2,12,14,15]. Ketotifen an antihistaminic drug and mast cell stabilizer has been used to successfully treat eosinophilic ascites as the sole therapeutic intervention. Casella *et al*^[15] recommend ketotifen as the first-line approach to eosinophilic ascites because it is a relatively inexpensive and safe drug. Sur-

gical intervention is rare and reserved for patients with obstructive complications^[2,3]. The clinical course may be characterized by periods of remission and relapses usually when the steroid therapy is discontinued in up to 50% patients^[14]. Steroid-sparing therapy with antihistamines, mast cell inhibitors, leukotriene receptor antagonists, anti-interleukin drugs including ketotifen is useful in the treatment of relapses to avoid the side-effects of steroids^[12,15]. In rare cases of failure to respond to steroid therapy, total parenteral nutrition or immunosuppressive agents including oral azathioprine or cyclophosphamide may be added to the steroid regimen in patients with diffuse mucosal disease^[5].

COMMENTS

Case characteristics

A 35-year-old female presented with abdominal distension and diarrhea and was diagnosed with subserosal eosinophilic gastroenteritis (EGE). She responded to oral steroid therapy with complete resolution of the ascites and normalization of peripheral hypereosinophilia.

Clinical diagnosis

Subserosal EGE.

Differential diagnosis

Ovarian cancer, abdominal tuberculosis, vasculitis, parasitic infection, congestive

heart failure.

Laboratory diagnosis

Peripheral hypereosinophilia and eosinophil-rich fluid on diagnostic paracentesis.

Imaging diagnosis

Abdominal computed tomography demonstrated moderate ascites with diffuse wall thickening of the small bowel.

Pathological diagnosis

Mucosal biopsy of the stomach and duodenum on upper endoscopy was non-diagnostic.

Treatment

Oral steroid therapy.

Experiences and lessons

A high index of suspicion of subserosal EGE in patients with abdominal pain, ascites and peripheral hypereosinophilia. Oral steroids adequate for initial therapy and ketotifen may be considered for relapse of EGE.

Peer-review

The manuscript deals with a case report and a review on an important condition and is well written.

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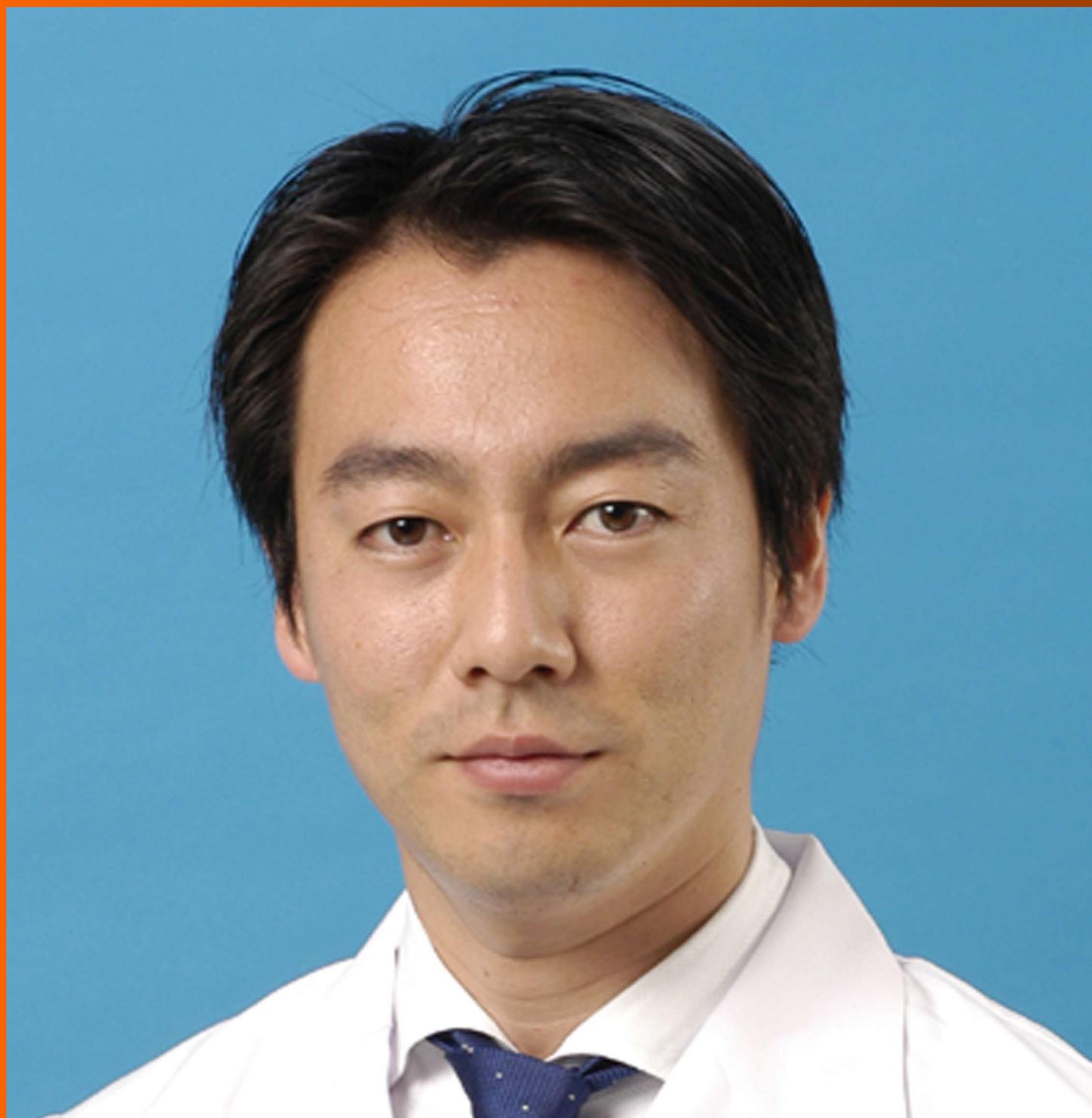
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Goblet cell carcinoids of the appendix: Tumor biology, mutations and management strategies

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Abstract

Malignant neoplasms of the appendix are rare and represent less than 1% of gastrointestinal cancers. Goblet cell carcinoids (GCC) tumors are a distinctive group of heterogeneous appendiceal neoplasm that exhibit unique clinical and pathologic features. This review focuses on

the current diagnostic procedures, pathogenesis, possible signaling mechanisms and treatment options for GCC. Perspectives for future research are discussed. The tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Previous findings of Notch signaling as a tumor suppressor in Neuroendocrine tumors may have a similar role in this tumor too. Loss of Notch signaling may be the driver mutation with other successive downstream mutations likely favors them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. A multi-disciplinary approach is suggested for optimal outcomes. Surgery remains the main treatment modality. Simple appendectomy may be sufficient in early stages while right hemicolectomy is recommended for advanced tumors. Cytoreductive surgery with heated intraperitoneal chemotherapy may improve survival in a select few with metastatic peritoneal disease. These tumors have an unpredictable behavior even in early stages and local recurrence and delayed metastases may be seen. Lifelong surveillance is warranted.

Key words: Goblet cell carcinoid of the appendix; Notch-1 signaling; Immunomarkers; Math-1 signaling; Intestinal stem cells; Disease management

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Core tip: Goblet cell carcinoids tumors are a distinctive group of heterogeneous appendiceal neoplasm that exhibit unique clinical and pathologic features. The pathogenesis is unclear however the tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Loss of Notch signaling may be the driver mutation with other successive downstream mutations likely favors them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. Surgery remains the main treatment modality. We discuss the clinical implications of this cancer focusing on the tumor biology, mutations,

signaling mechanisms and management.

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INTRODUCTION

Malignant neoplasms of the appendix are rare and represent less than 1% of gastrointestinal cancers. Studies evaluating data for appendiceal malignancies from seer database between 1973-2001 showed the age-adjusted incidence of cancer of appendix was 0.12 cases per 1 million people per year^[1,2]. They are further classified into colonic type adenocarcinoma, mucinous tumors, signet ring cell tumors, carcinoids [neuroendocrine tumors (NETs)] and goblet cell carcinoids (GCC). Overall five-year survival is highest for appendiceal carcinoid (83%) and lowest for signet ring cancers (18%)^[1,2]. This review focuses on GCC of the appendix. The current diagnostic procedures, pathogenesis, signaling mechanisms and possible mutations are presented. Treatment options for this neoplasm are defined and summarized, although evidence-based data are lacking. Surgery remains the treatment mainstay.

GCC tumors are a distinctive group of heterogeneous appendiceal neoplasm that exhibit unique clinical and pathologic features. These hybrid tumors have both glandular and neuroendocrine morphology and are designated with various terminologies: Adenocarcinoids, crypt cell carcinoma, mixed carcinoid-adenocarcinoma and amphicrine tumors. These various terminologies do not reflect consistent morphology, biologic behavior or accepted criteria for the diagnosis. GCC was first described by Gagné *et al*^[3] in 1969, Subbuswamy *et al*^[4] subsequently coined the term GCC in 1974. Warner *et al*^[5] in 1979 suggested a probable origin from crypt based stem cell. Isaacson *et al*^[6] in 1981 demonstrated presence of IgA, lysozyme in GCC suggestive of possible role of Paneth cells in this tumor^[3-6].

GCC exhibits clear distinction when compared to appendiceal NETs or primary adenocarcinoma in terms of demographics, biology and clinical aggressive behavior. The prognoses of GCC lays intermediate between appendiceal NETs and primary appendiceal adenocarcinoma^[1,2].

CLINICAL PRESENTATION

GCC are diagnosed in less than 1% of appendectomy specimens^[7,8]. Most commonly, patients present with abdominal pain and acute appendicitis (> 50%). They are most often diagnosed incidentally during appendectomy

or ileocecal resection and confirmed by the pathologist in post-surgical specimens. About 27% of patients may present with perforated appendicitis^[9]. Patients may also present sub-acutely in advanced stages with vague abdominal pain and mass^[7,8]. Common in Caucasians, there is equal distribution in male and females with the average age of diagnosis in the fifth decade^[1,2]. Up to 50% of patients present with metastatic disease^[8,10-12]. Similar to carcinoids a significant number of these patients may harbor a second primary malignancy^[12-14].

Morphologically the tumor circumferentially involves the appendiceal wall with transmural extension. Sub-mucosal involvement with mucosal sparing is noted. Most tumors are generally > 2 cm in size. The native appendiceal epithelium may show fibrous obliteration without adenomatous or dysplastic changes^[8,15].

GCC display a wide range of histologic patterns both in primary and metastatic sites. Common to all GCC is the presence of mucin containing goblet shaped epithelial cells arranged in clusters in the lamina propria and submucosa. These cells stain positive for mucicarmine, periodic acid-Schiff and alcian blue stains suggestive of goblet cell mucin. Extracellular pools of mucin may also be present. Also seen are cells, which demonstrate focal, inconsistent scattered immunoreactivity for neuroendocrine markers (*i.e.*, chromogranin, synaptophysin)^[8,16].

Since GCCs show a submucosal growth pattern, it has a tendency to spread to surrounding bowel. The most common metastatic sites include direct extension into the right colon and ileum, followed by spread to lymph nodes, peritoneum and omentum. The ovaries are common site of metastases in women presenting as Krukenberg tumor. Up to 80 % of women with stage 4 disease present with ovarian metastases^[8,12]. Solid organ metastases to liver, lung, bones are uncommon^[8]. A previous study reports the rate of metastases to lymph nodes increases with the T stage of the tumor T2 (0%), T3 (13%), T4 (60%)^[9].

Metastatic lesions from GCC are more aggressive tumors and often show poorly differentiated signet ring cell or undifferentiated adenocarcinoma morphology with minimal neuroendocrine features. They may not share features of primary tumor and carry poorer prognosis. Metastatic tumors usually do not stain for chromogranin A or synaptophysin and stain heavily for mucin, suggestive of degeneration into signet ring cell morphology. The population of endocrine cells and Paneth cells seem to decrease in metastatic lesions. Yan *et al*^[17] in their series of 26 patients reported that nine patients (35%) with metastatic GCC failed to stain for neuroendocrine marker. The explanation for this finding remains elusive^[17-21].

CLASSIFICATION

Currently multiple classification systems exist to describe GCC.

The 2010 World Health Organization (WHO) cla-

Classification for tumors of the appendix, classifies GCC under the category of neuroendocrine neoplasms based on differentiation and histological grading. Grade refers to the proliferative activity measured with mitotic counts and Ki-67 index. They are further sub-classified as low grade: G1 (< 2 mitosis/10 HPF and ≤ 2% Ki index), intermediate grade: G2 (2-20 mitosis/10 HPF, 3%-20% Ki index) and high grade: G3 (> 20 mitosis/10 HPF, > 20% Ki index). Differentiation refers to resemblance of tumor cells to the normal neuroendocrine cells. Carcinoids (well differentiated neuroendocrine neoplasm) generally belong to G1 and G2 categories while G3 is considered as a neuroendocrine carcinoma (NEC). Goblet cell tumors are subtyped under mixed adenoneuroendocrine carcinoma (MANEC). To qualify for this definition at least 30% of tumor should have gland forming epithelial and neuroendocrine components^[22].

The 2010 American joint commission on cancer (TNM classification) stages these tumors based on the tumor size, nodal status and metastatic disease into stages (I - IV). Stage I (T1, N0, M0), stage II (T2/T3, N0, M0), stage III (any T/N1, M0), and stage IV (any T /any N/ M1)^[23].

Tang *et al*^[8] in 2008, proposed a system of classification specific for GCC of appendix based on histologic features of the tumor at the primary site. They include the arrangement of the goblet cells, degree of atypia and desmoplasia to label these tumors into three groups. Typical GCC (group A); adenocarcinoma ex GCC, signet ring cell (group B); adenocarcinoma ex GCC, poorly differentiated (group C). Almost all patients in group C presented in advanced stages with wide metastases. This suggests that GCCs display a spectrum of histologic features with the potential to progress to an aggressive adenocarcinoma phenotype^[8].

These multiple pathologic definitions and differing terminologies have led to inconsistent reporting and difficult to characterize this disease.

MANEC per the 2010 WHO classification are tumors harboring both epithelial and neuroendocrine components. However based on this definition it requires tumors to have at least 30% representation of each component. In general this is not true for all GCC tumors. Further advanced stages of GCC losses its neuroendocrine differentiation and acquires an aggressive signet ring cell or poorly differentiated morphology.

This tumor may need further investigations to better clarify and define their heterogeneous, molecular profile and classification.

IMMUNOCHEMISTRY AND MUTATIONAL FINDINGS

GCC specimens demonstrate focal, inconsistent immunoreactivity for neuroendocrine markers. In contrast diffuse staining is observed in most classic carcinoids of the appendix. Common positive markers are synaptophysin, chromogranin A, serotonin, neuron specific enolase,

pancreatic polypeptide. Ultrastructural immunohistochemistry staining has shown tumor nests resembling normal crypts in the submucosa. Separate goblet cell and neuroendocrine cells are often located in close proximity to each other^[24] (Table 1).

In addition GCC do not exhibit mutations as conventional colorectal adenocarcinoma. These tumors are negative for KRAS, SMAD4 and BRAF mutations^[25]. They show negative staining for nuclear β-catenin and for p53. MUC2 expression is preserved^[8]. Normal colorectal and appendicular epithelium expresses MUC2 only. GCC show strong carcinoembryonic antigen, caudal type homeobox transcription factor 2, cytokeratin 7 (CK7), CK20 expression suggestive of intestinal epithelial origin while these markers remain negative in classic carcinoids^[26]. A single study showed allelic loss in chromosomes 11q, 16q, and 18q in GCC similar to ileal carcinoids^[25].

The proliferative Ki67 index remains low in typical GCC but rises with advanced stages (Tang's group C). The significance remains unknown as some groups have shown worsening survival rates with rising Ki67 index^[19,27] while other have shown no correlation^[9,28,29]. Positive staining for p53 and MUC1 with loss of MUC2 expression is suggestive of transformation to adenocarcinoma phenotype similar to colorectal adenocarcinoma^[8]. This also correlates with the rising Ki67 index as reported with Tang's *et al*'s classification.

In general patients with GCC do not present with carcinoid syndrome and urinary 5HIAA levels are within normal range^[16]. Unlike classic midgut carcinoids, serum chromogranin A levels are normal and have no value in detecting and monitoring GCC. Somatostatin expression is sparse and erratic and therefore functional scans such as 111-Indium pentetreotide scintigraphy (Octreoscan) and Gallium 68-octreotide positron emission tomography (PET) scans are usually normal in patients with GCC, and thus are of limited use^[11,19]. Fluorodeoxyglucose PET scan may be useful in advanced disease to detect peritoneal metastatic disease^[7,27,30].

GCC also express transcription factor Math-1 and HD5 (Defensins) a known marker for Paneth cells^[26]. Math-1 is a basic helix-loop-helix transcription factor essential for development of the pluripotent stem cell towards secretory stem cell lineage and may play a role in pathogenesis of GCC.

PATHOGENESIS

The pathogenesis of GCC remains unclear. Unlike adenocarcinomas of the GI tract which arises through an adenoma-carcinoma sequence GCC is thought to arise from pluripotent intestinal epithelial crypt base stem cells^[6,26].

An understanding of the embryological origin and signaling pathways associated with development of small bowel and appendix may provide clues and explain the origin and progression of GCC. The epithelial lining of

Table 1 Immunomarkers and mutations for appendiceal goblet cell carcinoids, typical neuroendocrine tumors and adenocarcinoma

Markers	Goblet cell carcinoid	Typical carcinoid	Adenocarcinoma
CEA	+	-	+
CK7	+	-	+
CK20	+	-	+
CDX2	+	-	+
CD56	+/-	++	-
CAM5.2	+	-	+
Synaptophysin	+/-	++	-
Chromogranin A	+/-	++	-
B-Catenin (nuclear)	-	-	+
p53	+/-	-	++
Ki67%	+/-	+/-	++
MUC1	-	-	++
MUC2	++	-	+/-
E-cadherin expression	N	N	U
MATH-1 expression	+	+	-
KRAS mutation	-	-	+
SMAD4 mutation	-	-	+
Notch signaling inhibition	U	+	-
MMR (MSH2, MSH6, MLH1, PMS2)	-	-	+/-

(+): Present; (-): Absent; (+/-): Present sometimes. CEA: Carcinoembryonic antigen; CK: Cytokeratin; CDX2: Caudal type homeobox transcription factor 2; CD56: Neural cell adhesion molecule; CAM 5.2: Antibody against CK8; p53: Tumor protein 53; Ki-67: Cellular proliferative marker; MUC: Mucin; Math-1: Protein atonal homolog 1 (a basic helix-loop-helix family of transcription factors); KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; SMAD4: Mothers against decapentaplegic homolog 4, transcription factors in the TGF pathway; MMR: Mismatch repair genes; N: Normal expression; U: Unknown.

small gut consists of a single layer of columnar cells. This differentiated epithelium arises from the crypts and projects up as villi into the lumen forming the absorptive lining of the gut (Figure 1). Villi begin to form by embryonic day 15 and crypt form by invagination of intervillus pockets at post-natal day 7^[31,32]. The four main types of differentiated cells are absorptive enterocytes, goblet cells, neuroendocrine and Paneth cells. The crypt thus forms the proliferative stem cell compartment, where these cells originate, differentiate, amplify and move up into the villi akin to a system of conveyor belt in an assembly line^[33]. Paneth cells which also originate from the crypt in an exception and migrates downward into the base of the crypt. These four cell types are the main differentiated cell types found in the epithelial lining of the small intestine.

How is the stem cell niche created and defined? What molecular signaling mechanisms keep the niche intact and regulated? Information on these fundamental questions comes from mouse studies. Advances in development and stem cell biology have also occurred to generate complex three dimensional human intestinal tissues *in vitro* through directed differentiation of human pluripotent stem cells. These human intestinal organoids called mini-gut have expanded our ability to study development, genetics, intestinal pathogens and metabolic disease and cancer^[34]. Cheng and Leblond^[35,36] in 1974 were first to characterize crypt based columnar cells as intestinal stem cells. Barker *et al*^[37] identified a marker Lgr5/GPR49, a leucine rich orphan G-protein coupled receptor that labels these stem cells. Tritiated radioactive thymidine labelling experiments have confirmed that these Lgr5 cells are the multipotent stem

cells. Stem cell division occurs every 24 h and these cells are localized to the crypts. Subsequently cells migrate up from the crypt to the villus in 3-5 d^[34,38]. These stem cells by itself are not terminally differentiated and can divide without a limit. The daughter cells have to choose between committing to terminal differentiation or remain as a stem cell. The rapidly dividing groups of cells derived from the crypt stem cells that have committed to differentiation are known as transit amplifying cells. As they migrate further up the crypt they amplify according to their prospective destined fate and differentiate as enterocyte, goblet cell, neuroendocrine and Paneth cell. They cease to divide further once they reach the neck of the crypt at the crypt villous junction^[31,33].

Thus this slim, columnar crypt based Lgr5 positive stem cells along with the post mitotic Paneth cells form the stem cell niche through which begins the growth and renewal of all the differentiated cells of the small intestinal epithelium.

There are two major groups of cell signaling mechanisms which govern the crypt-villus axis (Figure 1). The first is an epithelial-epithelial cell communication. The key mediators of these mechanisms are Wnt, Notch, Eph-ephrin and Math 1 signaling pathways. Together and sequentially they are primarily responsible for maintaining the gut stem cells in a proliferative state, differentiation into secretory or absorptive lineage and establish boundaries between these clones of cells. Mutation in these critical pathways has been implicated with excessive uncontrolled, ectopic crypt formation, adenomas, excessive goblet cell or neuroendocrine cells and other risks for colorectal malignancies.

The second major group of cellular signaling comprises

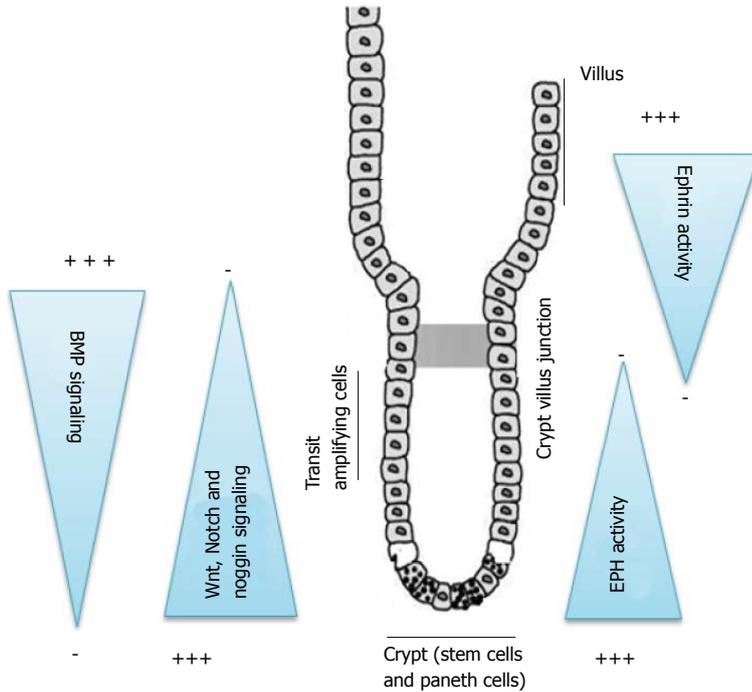


Figure 1 Schematic diagram of crypt-villus axis. The initial signaling mechanisms in a crypt-villus axis begin with Wnt and Notch pathways. The Wnt pathways maintain the gut stem cell compartment. The Paneth cell which constitutes part of the stem cell niche generates Wnt signals that act over a short range and keep cells in the crypt in a proliferative state. There exists a gradient in Wnt, Notch and noggin signaling which is highest in the crypt base and diminishes towards the crypt-villus junction. BMP signaling is low in the crypt and higher in the crypt villus junction. A definitive gradient exists for Eph-ephrin pathways too. The cells acquiring a differentiated fate switch off the expression of Eph-B and switch on the expression of Ephrin B ligands which progressively increases as they migrate up the axis.

of epithelial-mesenchymal (EMT) communications and the mediators in these pathways consist of hedgehog, BMP and PDGAF signaling pathways. The essential function of EMT pathways is to maintain a proper spacing between one crypt and the next. They are negative regulators of crypt formation. Hedgehog signaling increases the expression of BMP in the mesenchyme which further represses the Wnt signaling. Noggin, a BMP inhibitor is expressed in the crypts to maintain unsuppressed Wnt activity in the crypt epithelium (Figure 1). Mutation in these pathways or inhibition of BMP signaling by overexpression of its inhibitors, Noggin or inactivation of its receptor BMPRIA lead to excessive and ectopic crypt formation as seen with juvenile polyposis syndrome due to BMP knock out mutations^[39].

We will limit our discussion to the epithelial-epithelial signaling mechanisms which may hold clues to the pathogenesis of GCC.

The initial signaling mechanisms in a crypt-villus axis begin with Wnt and Notch pathways in the crypts (Figure 1). Both the development of small intestine and its homeostasis require canonical Wnt signaling. The Wnt pathways maintain the gut stem cell compartment. The Paneth cell which constitutes part of the stem cell niche generates Wnt signals that act over a short range and keep cells in the crypt in a proliferative state^[31,33]. There exists a gradient in Wnt signaling which is highest in the crypt base and diminishes towards the crypt-villus junction (Figure 1). Wnt signaling further drives the expression of Notch pathway. Notch pathway through its ligands such as Delta and jagged and effectors such as Hes and NF- κ B transcription factors mediate lateral inhibition within the Wnt activated cell population thus driving cells towards different fates. Delta expressing cells escape Notch activation (Wnt⁺, Notch⁻) and commit to secretory

fate through the downstream Math-1 signaling pathways and exit into a committed fate^[32,33,40]. Meanwhile (Wnt⁺/Notch⁺) cells continue to migrate up the crypt and divide, generating daughter cells and diversify till they lose Wnt activation as they move up the villus and differentiate as absorptive enterocytes. Inactivation of Notch pathway by deletion of Hes 1 or nonsense mutation of Delta ligands leads to excessive formation of goblet cells and neuroendocrine cells^[32,33,40]. Further studies have shown that inhibiting transcription factors in the Notch pathways by deletion of RBP-jk or by use of γ -secretase inhibitors prevents proteolytic cleavage and the release of notch intracellular domain complex. This result in epithelial cells composed exclusive of goblet cells^[41]. Conversely experiments have shown that increased Notch activity results in severe reduction of differentiated secretory cells, suggesting a tumor suppressor role of Notch signaling in neuroendocrine tumors^[42].

In addition to Wnt-Notch signaling another significant pathway in the crypt-villus axis known to play a role in maintaining cellular boundaries, segregation and establish migratory path are the Eph-ephrin molecules (Figure 1). Expression of Eph B receptors and the Ephrin-B ligands within the intestine is regulated *via* the β -catenin-TCF transcription complex through the Wnt pathway. A definitive gradient exists with proliferative cells in the crypt expressing higher density of Eph-B receptors and progressively decreases at the crypt villus axis. The cells acquiring a differentiated fate switch off the expression of Eph-B and switch on the expression of Ephrin B ligands which progressively increases as they migrate up the axis. Paneth cells express only Eph receptors and therefore remain at the crypt base. In general cells expressing Eph receptors are repelled by contact with cells expressing ephrins on their surface.

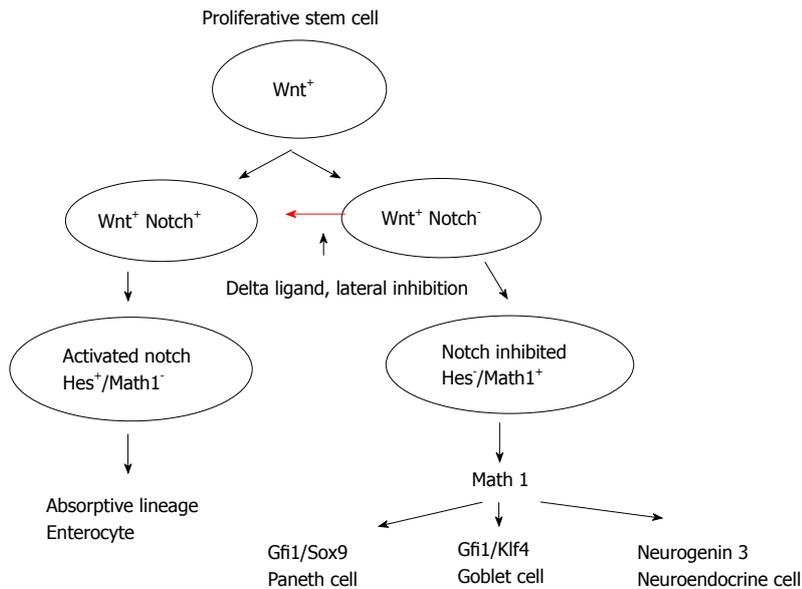


Figure 2 Intestinal stem cell signaling (Wnt, Notch, Math-1 pathways, lateral inhibition).

These mechanisms keep the cells segregated in their respective niches. Dysregulation of the eph-ephrin axis leads to cellular derangement with proliferating cells are not restricted to the bottom of the crypt and abnormally scattered along the crypt-villus axis^[33]. Eph B mediated compartmentalization restricts the spreading of Eph B expressing tumor cells into ephrin B1-positive territories *in vitro* and *in vivo*. Loss of EphB-mediated compartmentalization may lead to invasiveness of the tumor cells^[43].

All three secretory cell types derive from a precursor expressing Math-1 (mouse atonal homologue 1), also known as Atoh1, Hath-1 (humans) (Figure 2). As explained earlier Delta expressing cells escape Notch activation (Wnt^+ , $Notch^-$) and commit to secretory fate through the downstream Math-1 signaling pathways^[32,33,40]. It is a basic helix-loop-helix transcription factor that is required for secretory cell lineage through downstream Neurogenin 3 for neuroendocrine cells, Gfi1 and Klf4 for goblet cells, β -catenin and sox9 for Paneth cells and subsequent cell cycle exit^[31,32,44,45]. Mice deficient in Math1 lack goblet cells and the epithelial cells continue to maintain their proliferative state^[32,40]. Overexpression of Math1 results in ectopic secretory cells^[46]. The immunohistochemical expression of Math-1 in GCC suggests that this transcription factor is essential for normal development of the pluripotent stem cell towards secretory stem cell lineage and may play a role in its pathogenesis. Possible somewhere along its differentiation a mutation occurs with altered signaling pathways which causes excessive clones of goblet cells and neuroendocrine cells and may explain the hybrid nature of this tumor^[18,26].

NETs including GCC appear to be heterogeneous group of tumors with varying signaling mechanisms and gene expressions in different tissue of origin. A number of questions remain to be answered. Is there a Notch signaling dysfunction or inhibition leading to loss of Hes regulated inhibition of Math-1? Studies have confirmed

the potential oncogenic role of Notch signaling and its transcription factor in certain solid organ abdominal, lung, breast, and genitourinary, neural and hematological malignancies^[47]. However Notch signaling also appears to have a tumor suppressor role in gastrointestinal, thyroid and pulmonary neuroendocrine tumors^[42,48,49]. In another recent study of 31 ileal carcinoids, Notch signaling was uniformly absent in ileal neuroendocrine tumors suggestive of loss of tumor suppressive role^[50]. Is the loss of Notch signaling, the driving mutation and occurs after the first stem cell division at the level of transit amplifying cells with subsequent progeny showing dysfunction? Could there be a concurrent Eph-ephrin pathway mutation along with loss of notch signaling, leading to loss of compartmentalization of cells and portending invasiveness^[43]?

Why does metastatic GCC show minimal neuroendocrine expression and more of signet ring cell and poorly differentiated morphology? Are there further successive mutations downstream in the Math-1 signaling pathway? Are there subsequent epigenetic modifications, chromatin remodeling and inactivation of tumor suppressor genes which further amplify the carcinogenesis?

Further investigations at these levels are needed that may lead to our understanding of the pathogenesis of these tumors and may have therapeutic implications. Targeted therapies to activate Notch signaling with varying concentrations for metastatic GCC may have potential benefits. The origin of goblet cells carcinoid and its transformation from typical GCC and to advanced signet ring cell, poorly differentiated adenocarcinoma could be due to spontaneous, sporadic mutation in the mentioned crypt-villus architecture and or the surrounding mesenchyme and is yet to be successfully identified. Characterizing the levels of expression of Notch pathway components in tumor samples from patients with GCC could serve as a tumor marker. This reinforces the need to further investigate the presence of these mutations in larger cohorts and in institutions

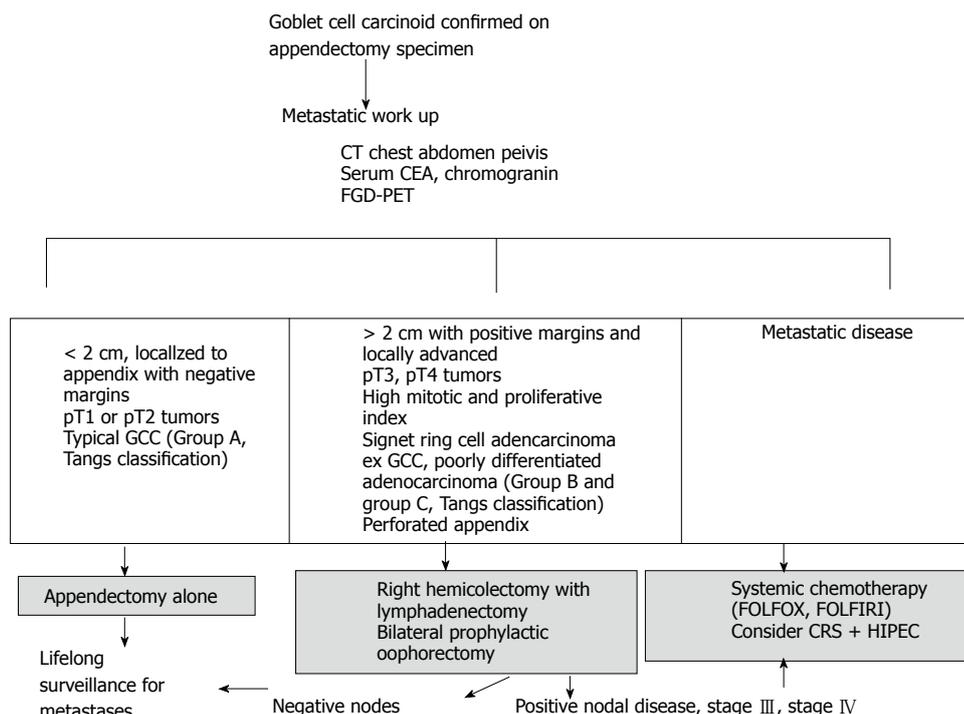


Figure 3 Treatment algorithm for goblet cell carcinoid. FDG-PET: Fluorodeoxyglucose positron emission tomography; GCC: Goblet cell carcinoids.

treating patients with GCC and appendiceal NETs.

TREATMENT

Most patients typically present with acute appendicitis and undergo appendectomy. The dilemma arises after GCC is diagnosed and confirmed, whether simple appendectomy is adequate or further oncologic resection is required (Figure 3). A multi-disciplinary evaluation is recommended for the optimal treatment. Both European and North American Neuroendocrine tumor societies guidelines recommend right hemicolectomy after appendectomy due to the high rate of metastases and its impact on prognosis^[30,51]. However other authors have argued against right hemicolectomy in their series^[8,13,52,53]. In a meta-analysis evaluating 13 studies with 100 patients, the authors concluded no benefits of right hemicolectomy in all patients. Selective criteria were recommended^[53]. In another recent retrospective analysis of a larger number of appendiceal NETs, GCC and signet ring cell adenocarcinoma from seer database showed a benefit of right hemicolectomy and statistically improved survival only for signet ring cell cancer when compared to appendectomy alone ($P = 0.01$). There was no significant difference in survival for typical NETs ($P = 0.21$) or GCC ($P = 0.94$) based on type of surgery^[54]. Based on Tangs classification the histology of the tumor in the appendectomy specimens and not the size of the tumor should determine the extent of oncologic resection^[8]. In patients who fulfill all the following criteria: Tumor less than 2 cm localized to appendix with negative margins, pT1 or pT2 tumors, and typical GCC histology group A (Tang *et al*^[8] classification) tumors, an

appendectomy alone may be sufficient as the definitive treatment^[13]. Right hemicolectomy is recommended in tumors greater than two centimeters, locally advanced, positive margins, T3, T4 tumors and histology suggestive of group B, group C (Tangs classification) in the appendectomy specimens^[8,11,12,55].

The impact of perforated appendicitis in patients with GCC remains unclear. In a meta-analysis of 18 cases of GCC diagnosed upon perforated appendicitis showed no impact on survival and prognosis^[56]. In another retrospective series of 20 GCC patients with perforated appendicitis, a lower rate of peritoneal metastases was observed in the perforated group (15%) compared to the non-perforated group (42%) with no difference in peritoneal relapse between the two groups^[9].

A complication of GCC of the appendix is their propensity to spread to the ovaries. GCC of the appendiceal origin express elevated MUC2 and MUC5AC. In contrast mucinous tumors arising from ovarian primaries express only MUC5AC^[57]. This could be of benefit in differentiating the origin of these tumors in females with primary ovarian mucinous malignancy^[58]. In postmenopausal female patients with GCC prophylactic bilateral oophorectomy, although not evidence based should be considered^[7,8,12]. In female patients with mucinous ovarian and pelvic malignancies an appendectomy should always be performed in staging laparotomy as these may represent metastatic GCC^[12,19,57].

Adjuvant systemic chemotherapy is prescribed for stage III and stage IV diseases and disease recurrence. Due to rarity of GCC a randomized control trial cannot be accomplished. Data is available from scattered anecdotal reports and small series of GCC and therefore guidelines

for choice of chemotherapy is lacking. Since metastatic GCC shows clinical and histological resemblance to colorectal adenocarcinoma and not metastatic carcinoids the choice of adjuvant therapy in GCC is similar to colorectal adenocarcinoma. 5-fluorouracil (5-FU) and leucovorin based FOLFOX (5-FU, leucovorin, oxaliplatin) and FOLFIRI (5-FU, folic acid, irinotecan) chemotherapy are standard regimens recommended^[11,30].

With locally advanced or recurrent peritoneal disease, cytoreductive surgery with hyperthermic intraperitoneal mitomycin and systemic chemotherapy (CRS+ HIPEC) may improve median survival^[11,12,17,59,60]. In a recent study of 45 patients with GCC and peritoneal metastases who received CRS+ HIPEC, the therapy was successfully completed in 71% of patients and 3 years, overall survival (OS) was 63.4 %^[60]. Another study on 26 patients report median survival of 51 mo and an overall five-year survival of 43%^[17]. However a recent retrospective study on 25 patients who received CRS plus HIPEC therapy reports no reduction in relapse rates or improvement in disease free survival in either stage I and II compared to stage III and IV^[9].

The other treatment options generally available for metastatic carcinoids such as interferon, somatostatin analogues (octreotide), targeted agents such as everolimus and sunitinib and radionuclide targeted therapy is not useful for metastatic GCC due to the absence of adequate uptake on Octreoscan or Gallium 68 PET scan and no confirmed mechanistic target of rapamycin or vascular endothelial growth factor pathway dysregulation.

PROGNOSIS

The overall disease specific survival for all GCC subtypes is 40%-80% depending on different series^[7-9,11,12,54]. The five-year survival for localized, regional and distant metastatic disease based on Tang's classification of group A, B, C are 100%, 36% and 0% respectively. This correlates with the AJCC (TNM) staging system where reported five-year survival with stage I (100%), stage II (76%), stage III (22%), stage IV (14%), respectively.

CONCLUSION

GCC are a separate entity from carcinoids and adenocarcinoma. The pathogenesis is unclear however the tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Successive mutations likely favor them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. Metastatic lesions differ from the primary appendiceal site in terms of histology and tumor aggressiveness. A multidisciplinary approach is suggested for optimal outcomes. Surgery remains the main treatment modality. Due to its heterogeneity, this tumor should not be classified according to a single system and a combination of size of the tumor (T classification), grade and mitotic index (WHO classification) and arrangement of the goblet cells, degree of atypia

and desmoplasia (Tang *et al*^[8]'s histopathologic classification) should dictate further definitive therapy. Simple appendectomy may be sufficient in early stages while right hemicolectomy is recommended for advanced tumors. CRC with HIPEC may improve survival in a select few with metastatic peritoneal disease. These tumors have an unpredictable behavior even in early stages and local recurrence and delayed metastases may be frequently seen. Therefore lifelong surveillance is warranted.

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Advances in minimally invasive neonatal colorectal surgery

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Abstract

Over the last two decades, advances in laparoscopic surgery and minimally invasive techniques have

transformed the operative management of neonatal colorectal surgery for conditions such as anorectal malformations (ARMs) and Hirschsprung's disease. Evolution of surgical care has mainly occurred due to the use of laparoscopy, as opposed to a laparotomy, for intra-abdominal procedures and the development of trans-anal techniques. This review describes these advances and outlines the main minimally invasive techniques currently used for management of ARMs and Hirschsprung's disease. There does still remain significant variation in the procedures used and this review aims to report the current literature comparing techniques with an emphasis on the short- and long-term clinical outcomes.

Key words: Neonatal surgery; Laparoscopy; Anorectal malformation; Colorectal surgery; Hirschsprung's disease

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Core tip: This review describes the recent evolution of neonatal colorectal surgery. It details the advances and current techniques since the introduction of laparoscopic surgery and minimally invasive approaches to the surgical management of anorectal malformations and Hirschsprung's disease. This review focuses on the various surgical options available and the benefits of these different techniques, outlining the current literature reporting the short- and long-term outcomes for these procedures.

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INTRODUCTION

The application of minimal access techniques within

paediatric surgery has evolved considerably in the last thirty years since the advent of laparoscopic surgery in the late 1980s. Advances in laparoscopic techniques and the development of new entirely transanal procedures has transformed the operative management of paediatric colorectal conditions, in particular Hirschsprung's disease and anorectal malformations (ARMs). Improving technology and refinement of techniques over the last decade has allowed these minimally invasive approaches to be used in increasingly challenging cases.

ARMS

History and evolution of technique

The posterior sagittal anorectoplasty (PSARP), a perineal approach to the correction of ARMs, has been standard practice since it was first described by Peña in the 1980s^[1]. Laparoscopy in the operative management of ARMs was first described in 1998. The laparoscopic-assisted anorectal pull-through (LAARP) was popularised in 2000^[2]. Proponents advocated this approach to avoid a laparotomy to ligate a high fistula and aimed to reduce post-operative pain and recovery time.

The LAARP is beneficial for recto-bladder neck fistulae and it may facilitate clear identification of the levator muscles so the surgeon can be sure of the correct position of the anus, avoiding the risks of sagittal dissection^[3]. It was hoped this small perineal wound, opening only in the centre of the muscle complex, would improve functional outcomes by its relative preservation of the sphincter muscles^[4].

Indications and use of laparoscopy initially expanded rapidly due to the benefit of avoiding extensive perineal dissection which was postulated to reduce soft tissue rectal scarring and lead to improved rectal compliance. However, the management of low anorectal malformation in males (recto-perineal and retro-bulbar fistulae) *via* a laparoscopic approach has resulted in an increased risk of urethral injury due to a difficult and extensive pelvic dissection as well as injury to the rectal nerves and pelvic plexus. This results in poor bowel function and therefore laparoscopy in these cases is unwarranted^[5,6].

CURRENT TECHNIQUES

Single or staged laparoscopic procedure?

ARMs with a recto-urethral fistula have been traditionally managed with colostomy formation in the newborn period, followed by definitive anorectoplasty at a later stage. Good positioning of the colostomy is vital to avoid problems in mobilizing the rectum^[3]. There is an argument in favour of the use of laparoscopy for stoma formation to ensure that it is appropriately sited and also to allow for fistula assessment and consideration of primary repair^[7]. Laparoscopy has therefore allowed surgeons to treat patients with recto-

bladder neck fistula ARMs with a single procedure without an initial colostomy. Small case series have shown that this is feasible and without the presumed difficulties of abdominal distension when the patient is operated within 48 h after birth^[7]. Though the rectum may be dilated with meconium, it has been shown to be feasible with laparoscopic manipulation to perform the dissection safely. Initial concerns about handling of friable bowel leading to injuries have not been seen in the published series reporting this technique^[7].

LAARP

We prefer a three stage operation in case of high ARMs with or without fistula. Following stoma formation, a colostogram is performed to identify the presence and level of fistula^[4]. Laparoscopic assisted pull-through is usually performed at 3 mo of age^[4].

In recto-bladder neck fistula, the fistula is located approximately 2 cm below the peritoneal reflection, and the rectum communicates with the urinary tract in a T fashion, which means that there is a minimal common wall between the distal part of the rectum and the urinary tract. The laparoscopic approach provides an excellent view of the peritoneal reflection, the ureters and the vas deferens, which must be visualised to prevent injury when dividing a recto-bladder neck fistula^[2].

The operation is begun by dividing the peritoneum around the distal rectum to create a plane of dissection to be followed distally. The dissection should occur on the rectal wall. The rectum rapidly narrows as it reaches its communication with the bladder neck. Dividing the fistula as close to the urinary tract as possible is required to prevent the formation of a diverticulum in the future^[8]. This can be confirmed by noting that the rectum has narrowed sufficiently to allow the 3 mm Maryland laparoscopic instrument to completely clamp across the fistula. A suture with 3/0 PDS is used to ligate the fistula. A submucosal dissection plane to create a mucosal tube of the distal rectum has been advocated as this facilitates easier ligation, further limiting the amount of fistula tissue left attached to the urethra^[9]. Initial reports described clip or endoloop ligation of the fistula but later studies have shown that simple sharp ligation flush with the bladder is the best technique^[10,11].

The distal rectum is then mobilized by dividing feeding vessels until there is enough length to pull the rectum comfortably down to the perineum. If the colostomy was created too distal in the sigmoid it may prevent this mobilisation.

The pubococcygeus muscle is then identified by inspection of the pelvic floor. A hiatus is located along the anterior surface of the two muscle bellies just posterior to the urethra which is the anatomical landmark where the rectum will be delivered from the pelvic side of the dissection^[2,5].

Various techniques have been described for creation

of the pull-through channel at the optimal site. The laparoscopic Peña electrostimulator has been used to identify accurately the centre of the muscle complex in the perineum^[10,12]. This can be particularly useful in cases of immature and unclear levator muscles^[3,13]. The positioning of the channel can be further guided with perineal and endoscopic ultrasound which can also serve as a useful tool for ensuring that the dissection is not risking injury to genitourinary structures^[14,15].

Entry into the pelvis from below can be facilitated under laparoscopic vision with a Verees needle and serial dilatation until a 10-12 mm trocar can be placed to allow the bowel to be pulled through and the anoplasty completed^[4,9].

Robotic assistance has been used to perform these operations in a limited series. The increased range of movement added with 3D vision technology aims to make the pelvic dissection easier for the surgeon. Currently this is hampered by the size of these infants but, as these technology advances, robotic assistance may prove a valuable tool in minimally invasive pull-through surgery for ARMs^[16].

As with other laparoscopic procedures, surgeons aiming for improved cosmesis have reported successful completion of LAARP using single-port techniques but such techniques are not commonplace due to the technical challenges and cosmetic benefits^[17].

OUTCOMES FOR LAPAROSCOPIC REPAIR OF ARMS

Short-term outcomes

Anal stenosis is a significant complication following PSARP and remains so in case series of LAARP. Ischaemia of the pull-through and tension on the anastomosis are causes of stenosis but it can also result from non-compliance with the postoperative dilatation regimes^[10].

Initial pitfalls encountered with the laparoscopic approach have been bladder/urethral injuries, bladder/urethral diverticulum and rectal prolapse but as the technique has become more established these problems do not appear to be encountered any more frequently in this group^[18].

There is evidence of reduced operating times, post-operative stay and blood loss in the LAARP group compared with open PSARP for high ARMs but again in these case series no clinical outcome difference was found^[19,20].

Long-term outcomes

It has been well documented that constipation is a major problem for patients that have undergone corrective surgery for high ARMs^[21]. Reviews have indicated a 80%-100% constipation rate following corrective surgery for recto-vesical fistulae^[22,23]. Some degree of soiling has been shown to occur in 42%-63% of cases of recto-vesical fistula^[23]. It has been noted that the majority of these patients experience resolution of constipation

by the time they have progressed through puberty^[24]. Long term follow up suggests that approximately half of patients managed with PSARP for high anorectal malformation have an excellent functional result by adulthood^[25]. It remains to be seen whether LAARP will improve this figure.

Outcome data for patients that have had LAARP remains limited to small series with relatively short follow up. The incidence of the most commonly described outcomes after PSARP and LAARP are shown in Table 1. These rates are calculated from pooled data used in a meta-analyses^[26]. An increase in preserved recto-anal relaxation reflex has been shown in patients undergoing LAARP compared to PSARP by performing follow up anorectal manometry^[27]. MRI imaging has revealed less peri-rectal fibrosis and sphincter asymmetry in these patients. However, neither of these measures has shown a correlation with a significant clinical improvement in the studies to date^[26-29].

It has been shown that the objective feedback using a continence evaluation questionnaire is significantly better at 3-4 years post-op in the LAARP group compared to PSARP, however this significance did not persist in patients that had been followed up for 5 years or more^[30]. The possible significance of this data remains limited by its small numbers.

Currently the main benefit of the laparoscopic approach is to replace the laparotomy in cases of recto-bladder neck and recto-prostatic urethra fistula. Other potential benefits remain to be confirmed^[18,31]. Attempts to review and combine the data of existing studies to ascertain if there are significant benefits have been unsuccessful due to the lack of standardisation of outcome measures reporting between paediatric surgical centres^[26,29].

HIRSCHSPRUNG'S DISEASE

History and evolution of technique

The surgical management of Hirschsprung's disease has evolved since the basic principles of repair described by Swenson *et al*^[32] in 1948. Progression occurred from a two- or three-stage procedure to a primary operation in the early 1980s^[33]. In the single stage primary operation, a laparotomy is used to mobilise the colon followed by an endorectal pull-through. Three main endorectal pull-through techniques are popularly used: Swenson, Soave and Duhamel.

The laparoscopic-assisted primary pull-through was first described by Georgeson *et al*^[34] in 1995. Following this, surgeons quickly began to replace the laparotomy for the transabdominal portion of each of the different pull-through procedures with laparoscopy^[35,36]. Subsequently, the entirely transanal endorectal pull-through emerged in 1998^[37].

More recent technical advances have also been described in conjunction with the pull-through procedure. Single-incision laparoscopic surgery has been used safely

Table 1 Comparison of outcomes of the open posterior sagittal anorectoplasty and the laparoscopic-assisted anorectal pull-through for management of anorectal malformations, subdivided into high and low malformations

	Open PSARP			LAARP		
	High	Low	All	High	Low	All
Short-term outcomes						
Mucosal prolapse (%)	10.7	21.2	16.4	9.8	2.9	6.2
Long-term outcomes						
Defecation dysfunction (%)	33.3	41.8	40.3	36.4	27	29.2
Rectoanal inhibitory reflex positive (%)	-	-	57.4	-	-	72.7

Rates extrapolated from pooled data from a meta-analysis comparing the different techniques^[26]. PSARP: Posterior sagittal anorectoplasty; LAARP: Laparoscopic-assisted anorectal pull-through.

to compliment the transanal endorectal pull-through and the Duhamel's procedure^[38-40]. One series used robotic assistance for the Swenson pull-through in 7 cases. They hypothesize that the increased dexterity as compared to laparoscopic surgery may improve the accuracy of the endorectal dissection and thus improve future outcomes, however this is as yet unproven^[41].

Main current techniques

The majority of patients with Hirschsprung's disease are suitable for a definitive primary procedure, using either the laparoscopic-assisted or the primary transanal approach^[42]. Both of these techniques can be performed at any age and are routinely performed within the first few months of life^[43,44].

Relative contraindications for a primary procedure include severe dilatation of the proximal bowel, significant clinical deterioration due to enterocolitis or long segment Hirschsprung's disease^[42]. These patients may be more appropriately managed with an initial levelling colostomy, which can be achieved with a laparoscopic approach, and a definitive pull-through procedure performed at a later stage. Laparoscopy offers the advantage of visualising the entire bowel, allowing for identification of the transition zone and biopsies prior to creating a stoma at the appropriate level.

Long segment Hirschsprung's disease is defined as a transition zone proximal to the mid-transverse colon. The most common type is total colonic aganglionosis, which can involve a portion of the terminal ileum. Although any of the three pull-through techniques can be used, the laparoscopic assisted Duhamel's procedure is favoured in these patients.

Laparoscopic-assisted endorectal pull-through

Laparoscopy is first used to take intra-operative frozen section levelling biopsies in order to identify normal ganglionated bowel. The bowel is inspected to identify the transition zone. A seromuscular biopsy is taken from above the transition zone in what appears to be normal bowel. Any perforation or bleeding at this site can be closed with a braided suture (Figure 1). If ganglion cells are absent or there is evidence of thickened nerve fibres then biopsies should be continued proximally until

normal ganglionated colon is identified. No dissection of the mesentery or rectum should be started until the level of normal bowel has been confirmed.

At this stage, in those patients found to have a long Hirschsprung's segment, it may be preferred to create a stoma above the suspected transition zone and delay the definitive procedure to a later stage, in order to await formal histology results.

Once the proximal level of the pull-through has been established, mobilisation of the colon with dissection of the mesocolon and mobilisation of the rectum below the peritoneal reflection can be continued laparoscopically (Figure 2). This is usually achieved with hook diathermy or the harmonic scalpel in older children. The transanal dissection of the surgeon's choice then follows. This involves a trans-anal endorectal dissection of the rectum starting 2-3 mm above the dentate line until the rectum and colon is completely free. In a Soave procedure, the first part of the dissection includes only the mucosa and submucosa, leaving a muscular cuff of aganglionated rectum. The posterior wall of this cuff should be incised in order to prevent stenosis. At this stage the pneumoperitoneum can be re-instated, using the laparoscope to visualise the mobilised aganglionic rectum and colon as it is pulled through. This ensures that the bowel has not been kinked or rotated during this process and there is sufficient mobilisation of the colon to prevent tension on the anastomosis. The mesenteric defect or window should then be closed to prevent the risk of an internal hernia. The aganglionated segment is excised and anastomosis of the colon to the rectal mucosa is performed, followed by closure of the laparoscopic port sites^[45].

Laparoscopic Duhamel procedure

The procedure for the initial levelling biopsies for the laparoscopic Duhamel procedure is the same as for the laparoscopic-assisted endorectal pull-through, as described above.

After the level of normal ganglionated bowel has been identified, the colon needs to be mobilised adequately and the mesentery of the distal aganglionated bowel can be divided. Once dissection has reached the peritoneal reflection, the rectum is closed to create the rectal

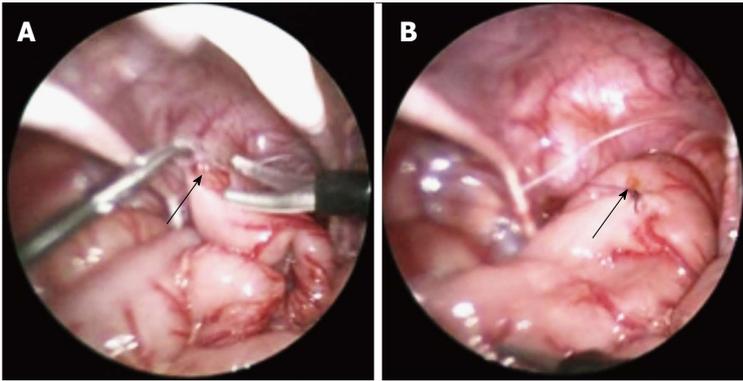


Figure 1 Photographs demonstrating a laparoscopic colonic biopsy taken in the sigmoid colon. A: Maryland grasper holding the sigmoid colon, while scissors are used to take the biopsy specimen; B: The biopsy site is then sutured closed. Arrow indicates the biopsy site.

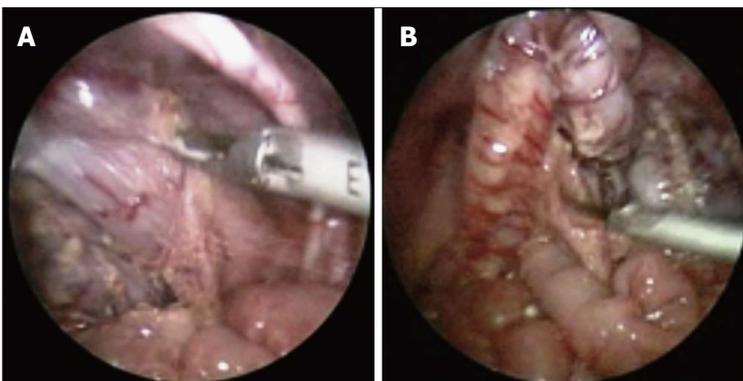


Figure 2 Photographs demonstrating the laparoscopic mobilisation of the colon and rectum using a harmonic scalpel. A: Mobilisation of the rectum at the peritoneal reflection; B: Division of the sigmoid colon mesentery.

pouch, either by oversewing the bowel or using an automatic stapler. Following this, the posterior rectum is then incised transanally, approximately 1 cm proximal to the dentate line. This creates an opening for the pull-through. A tunnel behind the rectum is created with a smooth dissector and dilated up to an adequate size with Hegar dilators. The proximal colon is pulled through the tunnel using a traction suture under laparoscopic vision. The colon is then anastomosed to the posterior wall of the rectum at the incision site. This can be completed with an automatic stapler to remove the wall between the rectal stump and the colon. Correct positioning of the pulled-through colon, without twisting or tension, is then confirmed using the laparoscopic view prior to closure^[46,47].

Primary trans-anal endorectal pull-through

The totally trans-anal endorectal pull-through was derived from the laparoscopic-assisted endorectal pull-through. It excludes the initial biopsies and proceeds directly to the trans-anal endorectal dissection, assuming that if the infant is responding to rectal wash-outs there is a classic Hirschsprung’s disease, with the transition zone at the recto-sigmoid colon. Either a lonestar retractor or retracting sutures are placed between the perianal skin and the dentate line. The rectal mucosa dissection begins 2-3 mm above the dentate line. In a Soave procedure, the dissection then proceeds submucosally until the peritoneal reflection at the level of the pouch of Douglas is reached. At this point the bowel can be dissected full-thickness after separating the sero-muscular plane 360

degrees. The muscular cuff should be vertically split posteriorly to avoid stenosis. The dissection continues along the rectal wall until a clear difference in calibre is noted, representing the transition zone. Alternatively in the Swenson procedure, the dissection of the rectum is full thickness from the beginning, leaving no muscular cuff. Once the peritoneal reflection has been reached the colon will be pulled through and the mesentery is divided trans-anally. Care must be taken to avoid rotating the bowel as the dissection progresses. Biopsies can be taken and sent as frozen section during the procedure to confirm the level of the transition zone. Once normal bowel has been reached the aganglionic segment can be excised and the anastomosis performed^[37,44].

The trans-anal pull-through has gained popularity due to its simplicity. It avoids the intra-peritoneal dissection and the need for laparoscopic expertise and equipment, which may be particularly important in low-income countries. However, in cases where the transition is proximal to the sigmoid colon mobilisation of the descending colon is usually required in order to perform an anastomosis without tension. This can be achieved laparoscopically if necessary.

The main benefit of using the laparoscopic-assisted approach over the primary trans-anal approach is early identification of the transition zone prior to dissection of the mesentery so that long segment Hirschsprung’s can be identified and dealt with appropriately. Laparoscopy also allows full mobilisation of the colon on a mesocolic pedicle to minimise tension on the anastomosis, and reduces the risk of rotational abnormalities during the

Table 2 Comparison of short-term and long-term outcomes of various approaches to the pull-through procedure for Hirschsprung's disease

	Open pull-through		Laparoscopic-assisted pull-through		Transanal endorectal pull-through
	Swenson/soave	Duhamel	Endoanal	Duhamel	
Short-term outcomes					
Length of stay (d)	12.5	9.8	7.8	7.3	5.1
Enterocolitis (%)	26	15	28	10	25
Long-term outcomes					
Constipation (%)	12	23	15	30	11
Faecal incontinence (%)	26	11	35	4	20

Rates taken from pooled data from meta-analyses comparing the different techniques^[52,57,60].

pull-through^[48]. Additionally, it reduces the need for a lengthy trans-anal dissection resulting in less dilatation of the anal sphincter, a factor that may be associated with faecal incontinence in the long-term^[49].

OUTCOMES

Short-term outcomes

Quoted benefits of laparoscopic surgery over traditional open techniques include reduced post-operative pain, quicker recovery of bowel function, shorter length of stay and improved cosmesis^[43,46,50]. On the contrary, the disadvantage is thought to be a longer operative time^[46,50]. Reported operative time for the open approach ranges from 91.3-297 min, laparoscopic approach from 150-257 min, and trans-anal approach from 43.5-258 min. Meta-analyses directly comparing these techniques demonstrated a shorter operating time in laparoscopic procedures and trans-anal procedures^[51,52]. Reported length of stay for open procedures range from 6.9 to 18.7 d, laparoscopic-assisted procedures from 3.6 to 10.4 d and trans-anal endorectal procedures from 2.6 to 9.8 d. Two studies comparing laparoscopic vs open procedures showed a significantly shorter average length of stay with laparoscopic procedures; 4 d following the laparoscopic endorectal pull-through, 7 d with the laparoscopic Duhamel pull-through and 10 d after an open Duhamel pull-through^[46,53]. When compared to the transabdominal approach, both the laparoscopic-assisted pull-through and the trans-anal endorectal pull-through have been shown to have a shorter length of stay^[51,52].

Conversion of a laparoscopic to an open procedure usually occurs for technical reasons and conversion rates range between 1%-2.5%^[39,43,54].

Recognised early post-operative complications of the pull-through procedure for Hirschsprung's disease include bleeding, anastomotic leak, perforation, adhesive bowel obstruction and post-operative enterocolitis. Late complications include anastomotic stenosis, enterocolitis, need for re-do surgery. These have all been described in association with the minimally-invasive techniques^[39,43,54-56]. Rates of these post-operative complications are comparable in laparoscopic and open approaches and may favour laparoscopic procedures. Although no individual comparative study has shown any

significant difference in complication rates, pooled data from a meta-analysis demonstrated fewer complications in the laparoscopic operations^[51]. A meta-analysis comparing laparoscopic vs open Duhamel procedure showed lower rates of further surgery in the laparoscopic group, with 14% compared to 25% of patients after the open procedure. The incidence of post-operative enterocolitis is 10% after the laparoscopic Duhamel's procedure and 15% after the open procedure, however this did not reach significance^[57].

A large cohort study investigating the transanal endorectal pull-through suggested lower rates of early complications compared to the transabdominal approach^[58]. The reported incidence of enterocolitis following the transanal endorectal pull-through ranges from 4.6%-54%, with a systematic review suggesting an incidence of 10.2%^[59]. Comparison with both the transabdominal approach and laparoscopic-assisted approaches have not demonstrated any difference in the rates of post-operative enterocolitis^[52,60].

Long-term outcomes

Functional outcomes after surgery for Hirschsprung's disease relate to impaired bowel function. Both severe constipation and faecal incontinence are experienced by these patients even into adulthood, although bowel function has been demonstrated to improve with increasing age^[61]. The rate of severe constipation does decrease by young adulthood^[62]. Additionally, faecal incontinence, impacting on quality of life, was reported less frequently with longer follow-up. It seems that puberty is the critical age for this improvement as bowel function in late adolescence and adulthood remains similar^[63].

Investigation of the long-term outcomes of Hirschsprung's disease managed with minimally invasive techniques has been carried out, with on average up to 5 years of follow-up. There have been 3 meta-analyses undertaken comparing different techniques; laparoscopic to open Duhamel procedure, trans-anal endorectal approach to transabdominal approach, and trans-anal endorectal approach to laparoscopic endoanal approach^[52,57,60]. Unfortunately, the data has a significant degree of heterogeneity, both in terms of the actual surgical techniques used and in how

the outcomes, constipation and faecal incontinence, were defined. The incidence of the most commonly described outcomes across the different techniques is demonstrated in Table 2. These rates are calculated from pooled data used in the meta-analyses.

Meta-analysis comparing the laparoscopic Duhamel to the open Duhamel procedure indicated that the incidence of faecal incontinence seems to be significantly lower with the laparoscopic approach (4% and 11% respectively; $P = 0.02$), while the incidence of severe constipation does not seem differ (30% and 23% respectively; $P = 0.12$)^[57]. Another study suggested lower constipation rates and better continence at 1-year follow-up for the laparoscopic-assisted endoanal pull-through over the Duhamel procedure^[53].

Initial early evidence with the transanal endorectal pull-through raised concerns about higher rates of faecal incontinence^[49]. This was hypothesized to be related to overstretching of the anal sphincter muscles during the neonatal procedure. Recently comparison of the transanal endorectal approach to the trans-abdominal approach suggested reduced rates of incontinence and constipation^[52]. While a comparison between the transanal endorectal approach to the laparoscopic-assisted endoanal approach demonstrated no difference in outcome^[60].

Currently it remains too early to fully evaluate the longer term outcomes into adulthood of minimally invasive techniques vs the traditional open procedures^[63].

CONCLUSION

Over the past two decades, there has been significant evolution in the surgical management of neonatal colorectal conditions. Advances in the technology and understanding of minimally invasive surgery have allowed these techniques to be adapted for use in small infants for correction of ARMs and Hirschsprung's disease. Laparoscopy and minimally invasive techniques are now safely and routinely used in the management of these major congenital anomalies. As experience grows, these techniques will be used for increasingly complex and challenging cases.

Benefits of minimally invasive surgery have been demonstrated, in terms of shorter hospital stay and improved cosmesis, and other potential benefits are hypothesized. Major improvements in functional outcomes remain as yet unproven. Significant variation does still exist in the specific operative techniques. High quality data investigating different techniques and comparing both short-term and long-term outcomes is still needed to determine which procedures are most effective for our patients.

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Case Control Study

Increasing trend in retained rectal foreign bodies

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Abstract

AIM

To highlight the rising trend in hospital presentation of foreign bodies retained in the rectum over a 5-year period.

METHODS

Retrospective review of the cases of retained rectal foreign bodies between 2008 and 2012 was performed. Patients' clinical data and yearly case presentation with data relating to hospital episodes were collected. Data analysis was by SPSS Inc. Chicago, IL, United States.

RESULTS

Twenty-five patients presented over a 5-year period with a mean age of 39 (17-62) years and M: F ratio of 2:1. A progressive rise in cases was noted from 2008 to 2012 with 3, 4, 4, 6, 8 recorded patients per year respectively. The majority of the impacted rectal objects were used for self/partner-eroticism. The commonest retained foreign bodies were sex vibrators and dildos. Ninety-six percent of the patients required extraction while one passed spontaneously. Two and three patients had retrieval in the Emergency Department and on the ward respectively while 19 patients needed examination under anaesthesia for extraction. The mean hospital stay was 19 (2-38) h. Associated psychosocial issues included depression, deliberate self-harm, illicit drug abuse, anxiety and alcoholism. There were no psychosocial problems identified in 15 patients.

CONCLUSION

There is a progressive rise in hospital presentation of impacted rectal foreign bodies with increasing use of different objects for sexual arousal.

Key words: Rectal foreign bodies; Rigid sigmoidoscopy;

Eroticism; Examination under anaesthesia; Psychosocial issues

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Core tip: There is a progressive rising incidence of retained rectal foreign bodies with increasing use of different designed and improvised objects for sexual arousal. The clinicians in the emergency settings must be well informed about the approach to the care of the patients with foreign bodies retained in the rectum.

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INTRODUCTION

Hospital presentation with foreign bodies retained in the rectum is no longer rare although concrete epidemiological data are still lacking^[1,2]. The earliest report of rectal foreign body dates back to the sixteenth century^[3]. There have been recent reports to suggest an increasing incidence and hospital presentations with foreign bodies retained within the rectum^[1-6]. Our prediction is that it is very much likely that such increasing hospital presentations shall continue to rise with the use of different objects for anal sexual fantasy. Objects retained in the rectum are mainly encountered in the adults following either intentional or non-intentional insertion. Occasionally, the retained objects may result from accidental or deliberate ingestion which had travelled through the whole of the gastrointestinal tract only to be impacted in the rectum^[1-3,6,7].

These patients usually present to the Emergency Department (ED) due to anorectal, pelvic or lower abdominal pain^[1,4]. Typically, the patients have delayed hospital presentation after several failed attempts at retrieving the object^[1-7]. The delayed presentation, particularly due to the perceived shame and/or associated embarrassment, presents both diagnostic and management challenges to the emergency staff^[1,2]. The fact that significant numbers of these patients are often reluctant to volunteer the truth about the circumstances surrounding their presentation in the ED further contributes to the diagnostic delay. Therefore, the care of the patients with foreign bodies retained within the rectum requires a methodical approach for diagnosis, retrieval of the foreign body and post-extraction clinical observation^[1,2]. The desired ultimate outcome for every case is a safe and successful per anum extraction of foreign body, in a manner as to respecting the patients' right to dignity, privacy and confidentiality.

We present our experience with retained rectal

foreign bodies to highlight a rising trend in presentation over a 5-year period and the approach to management.

MATERIALS AND METHODS

We retrospectively reviewed the cases of all retained rectal foreign bodies that were managed in our hospital over a 5-year period, 2008 to 2012. Patients coded on the hospital Patient Administrative System (PAS) with a diagnosis of rectal foreign bodies were identified. Patient and clinical related data were collected from the hospital records right from the ED presentation through to the admission episode until discharge. Data collected relate to patients' demography, clinical presentation, types of the objects, circumstance relating to insertion, the time from insertion to presentation, physical examination findings, investigations and treatment offered. The yearly case presentation, types of retained rectal foreign bodies, length of hospital stay, associated complications and psychosocial problems were recorded.

RESULTS

A total of 25 patients presented to our ED and treated for retained rectal foreign bodies over the 5 years study period. The mean age was 39 (17-62; SD 13.98) years with 17 males and 8 females giving a gender ratio of 2 to 1. We noted a progressive rise in the number of cases that presented per year from 2008 to 2012 with 3 recorded cases in 2008 and rising to the highest level of 8 cases in 2012 (Figure 1). Various objects impacted in the rectum and the reasons for insertion are shown in Tables 1 and 2 respectively. The presenting complaint were anorectal pain^[4], failure to self-retrieve the object, persistent vibration and anorectal pain^[2], anorectal pain and failure to retrieve the object^[3] and anorectal pain and rectal bleeding^[2]. The mean period between rectal object insertion and the visit to the ED was 14 (1-72; SD 14.6) h. Fifty-two percent (13/25) of the patients volunteered having had previous anorectal insertion of the same object ranging from 2 to 5 episodes with no problem.

Physical examination findings were completely normal in 11 while elicited clinical findings were tender lower abdomen in 3, palpable rectal foreign bodies on digital rectal examination (DRE) in 10 and blood in the rectum with palpable object in 1. Plain abdominal and pelvic X-ray were performed in all patients and erect chest X-ray was selectively performed only in 4 cases where indicated to exclude any free peritoneal gas under the diaphragm. Plain X-ray film confirmed the presence of retained rectal foreign objects in all cases but in one patient with apple in the rectum where it was not so obvious on the plain film. There was no specific indication for computerised tomography (CT) scan in any these patients and therefore this investigation was not done.

Extraction of the retained rectal objects was required

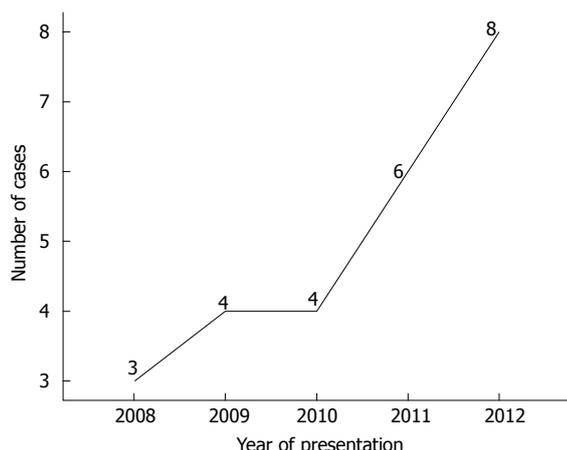


Figure 1 Line chart showing progressive rise in the number of cases over a 5-year period.

in 24 of the 25 patients. One patient passed the object spontaneously while waiting to be taken to the operating theatre. Two patients whose retained foreign bodies were easily palpable had the objects retrieved in the ED by digital manipulation and discharged. Three patients underwent digital removal of the retained rectal foreign bodies on the surgical assessment ward and were kept for a period of observation. Nineteen patients needed examination under anaesthesia (EUA) and extraction of retained foreign bodies in the operating theatre. Of the 19 patients, 15 had the objects extracted with grasping forceps with the aid of a proctoscope and/or a rigid sigmoidoscope, 2 were retrieved using small Keilland's forceps, 1 was digitally removed and one patient with impacted apple in the rectum was broken down and removed piecemeal. Rigid sigmoidoscopy was performed in 19 of 25 patients post extraction to exclude anorectal injury with the status of the anal sphincters assessed and recorded in each case. Two patients sustained anorectal mucosal tear, one of which developed significant bleeding per rectum post extraction; in one patient the sex toy had broken in ano; otherwise there was no complication recorded in 22 patients. There was no evidence of perforation identified in any of our patients in this series either during the EUA and/or following the period careful in hospital clinical observation.

The mean length of hospital stay was 19 (2-38; SD 9.56) h. All our patients had successful per anum extraction of the object with no one requiring a laparotomy or laparoscopy. Identified psychosocial issues in some of the patients included depression and deliberate self-harm in 3, illicit drug abuse in 2, anxiety in 2, depression in 1 and excess alcohol consumption in 2. There were no psychosocial problems identified in 15 patients. There was no correlation between the presence of psychosocial issues and either repeat insertion or number of previous insertions of rectal foreign bodies.

DISCUSSION

Rectal insertion of objects and retention are commonly

Table 1 Table showing types of retained rectal foreign bodies

Retained rectal objects	Frequency	Percentage (%)
Apple fruit	1	4
Glass jar	2	8
Nail varnish bottle	1	4
Sex toy (dildo)	5	20
Sex vibrator	12	48
Denture (accidentally ingested and retained in the rectum)	1	4
Roll on deodorant bottle	2	8
Ceramic candle holder	1	4

Table 2 Reasons for retained rectal foreign bodies

Reasons for insertion of retained rectal foreign body	Frequency	Percentage (%)
Self erotism	9	36
Partner erotism	13	52
Self-massage of rectal prolapse	1	4
Self-harm	1	4
Accidental ingestion of denture	1	4

seen in the adults. These are either used in the majority of cases for anal sexual stimulation or sometime for criminal intent^[1-9]. Occasionally, retained rectal foreign body may have resulted from self-treatment of anorectal conditions, attempts at concealment of illicit drugs or weapons and accidental ingestion of objects which eventually get impacted in the anorectum as in one of our patients^[1,2,4,8,10-13]. There is a wide range of objects finding their ways into the rectum and we and other authors have previously predicted a possible rise in the incidence and presentations in the ED following the of various objects for erotic fantasy^[1-4,6,8].

The current study shows a progressive increase in the number of cases that presented over a 5-year period from 2008 through to 2012 from a single centre. This outlook confirmed what we and some other authors have predicted previously^[1-4,6,8]. This most recent study has demonstrated a significant rise in the number of cases per year compared with studies by Safioleas *et al*^[5] who reported 34 patients over a 25-year period, Coskun *et al*^[6] with a report of 15 patients over a 10-year study period (1999-2009), Rodríguez-Hermosa *et al*^[7] with 30 patients over an 8-year period (1997-2004) and our previous report of 16 cases over a 4-year period (2001-2004)^[8]. We can only expect a continuing rise in the hospital presentations of impacted foreign bodies within the rectum given the increasing fantasy with a wide variety of improvised household and designed objects. Table 3 summarises the trend in the published literature over the last few decades. The sudden surge in the incidence reported by Lake *et al*^[4] covering a 10 year study period was a data from a very large United States population and stands as the largest published data on this subject in the literature. The current data and our previous report^[8] have shown a rising trend in the ED cases of objects impacted in the rectum.

Table 3 Table showing published trend in retained rectal foreign body

Ref.	Study years	No of cases	Average cases per year	M:F ratio
Huag <i>et al</i> ^[14]	1979-2000 (21 yr)	10	0.48	10:00
Lake <i>et al</i> ^[4]	1993-2002 (10 yr)	87	8.7	17:01
Clarke <i>et al</i> ^[13]	1995-2005 (10 yr)	13	1.3	13:00
Rodríguez-Hermosa <i>et al</i> ^[7]	1997-2004 (8 yr)	30	3.75	15:01
Ayantunde <i>et al</i> ^[8]	2001-2004 (4 yr)	16	4	15:01
Safioleas <i>et al</i> ^[5]	1971-2006 (25 yr)	34	1.36	6:1
Coskun <i>et al</i> ^[6]	1999-2009 (10 yr)	15	1.5	15:00
Ayantunde <i>et al</i> ^[8]	2008-2012 (5 yr)	25	5	2:1

This study also affirmed the persistent male preponderance as it was variously reported in the published literature although there seems to be a slightly higher female population in the current study than previously reported^[1-10]. The gender ratio showed that the male population was only twice affected as female gender in the current study. This reduced male to female ratio may have been due to a significant increase in the group of female gender using objects for partner-erotism in this cohort than previously reported. The majority of our patients were young adults who were using the retained objects for either self-erotism or partner-erotism. Eighty eight percent of our patient population were using the foreign bodies for erotic stimulation and this is in agreement with the previous published reports^[1-4,7-10]. The changing pattern with increasing female gender and predominantly younger population than previously reported may likely be the emerging trend in the presentations of retained rectal foreign bodies.

Our previous work^[8] and that of Cohen *et al*^[9] have shown objects used for sexual interaction accounted for more than three-quarter of the cases impacted foreign bodies in the rectum presenting to hospitals. One patients in this study inserted an apple fruit for self-harm. This patient disclosed that he was abused as a child and became very depressed after the loss of his wife. One patient was using the object for self-massage of rectal mucosal prolapse in an attempt to reduce it while one accidentally swallowed their dentures, which later became impacted in the rectum prompting the presentation to the ED. We did not encounter any patient in the current series with retained rectal foreign bodies with history of sexual rape or other violent sexual practices as previously reported by some authors^[1,2,8,14,15].

Generally speaking, patients with rectal foreign bodies do not attend the ED early unless attempts have been made to retrieve the objects by the patient or their partners because of the perceived embarrassment and shame^[1-4,7,8,12-14]. The majority of our patients attended the ED because of failure to retrieve the foreign bodies after several attempts while few others presented with anorectal pain and/or bleeding. Two of our patients in particular presented because of persistent vibration of the powered sex toys causing them significant anorectal and lower abdominal pain. The delay in presentation may be due to the hope of a spontaneous passage of the foreign objects by the patient and the eventual failure to

pass against their expectation leads to some measure of anxiety^[1].

The initial evaluation at presentation should include a careful history, abdominal and digital rectal examinations (DRE) including the assessment of the status of the perianal region and anal sphincters with the findings clearly documented before and after the extraction of the foreign body in the clinical notes^[1-4,8,14-16]. Confirmation of the type, size, number and location of the objects should be by biplanar plain abdominal and pelvic films^[1-3,8,14]. Biplanar plain X-rays in this study showed the foreign objects in all but one of our patients. The one patient with retained apple fruit was not so obvious on the plain films. Erect chest X-ray and CT scan should only be selectively performed where indicated. Plain erect chest radiograph is recommended to exclude the presence of free peritoneal gas under the diaphragm indicating rectosigmoid perforation^[1]. There was no patient in this series with any specific indication requiring a CT scan evaluation. CT scan where indicated is excellent for localization of non-opaque foreign bodies, detection of perforation or obstruction and diagnosis of pelvic abscess^[1].

The basic approach to the management of patients with retained foreign bodies include achieving a safe per anum extraction, direct visualisation of the rectosigmoid mucosal to exclude bowel injury and a period of close clinical observation in the hospital for early detection of complications^[1-4,8,16]. Extraction of impacted rectal foreign bodies should be achieved under direct vision where possible using an anoscope or sigmoidoscope to avoid iatrogenic anorectal injury^[1-4,8,14,16].

Generally speaking, the determination of level of the retained foreign bodies in the rectosigmoid segment is important and useful for the purpose of management. Most low-lying rectal foreign objects are reachable by the examining finger and can be removed per anum whereas those higher up in the sigmoid colon can prove to be difficult to retrieve^[1,2,7,13,14]. Foreign bodies that are impacted above the rectum are usually not easily visualized and therefore transanal retrieval is difficult^[1,2,7,13,14]. Generally speaking, a foreign body located below the rectosigmoid junction that is easily palpable by the clinician's examining finger can be extracted in the ED. However, an uncooperative and anxious patient with associated anal sphincter muscles contractions will make ED extraction undesirable. The

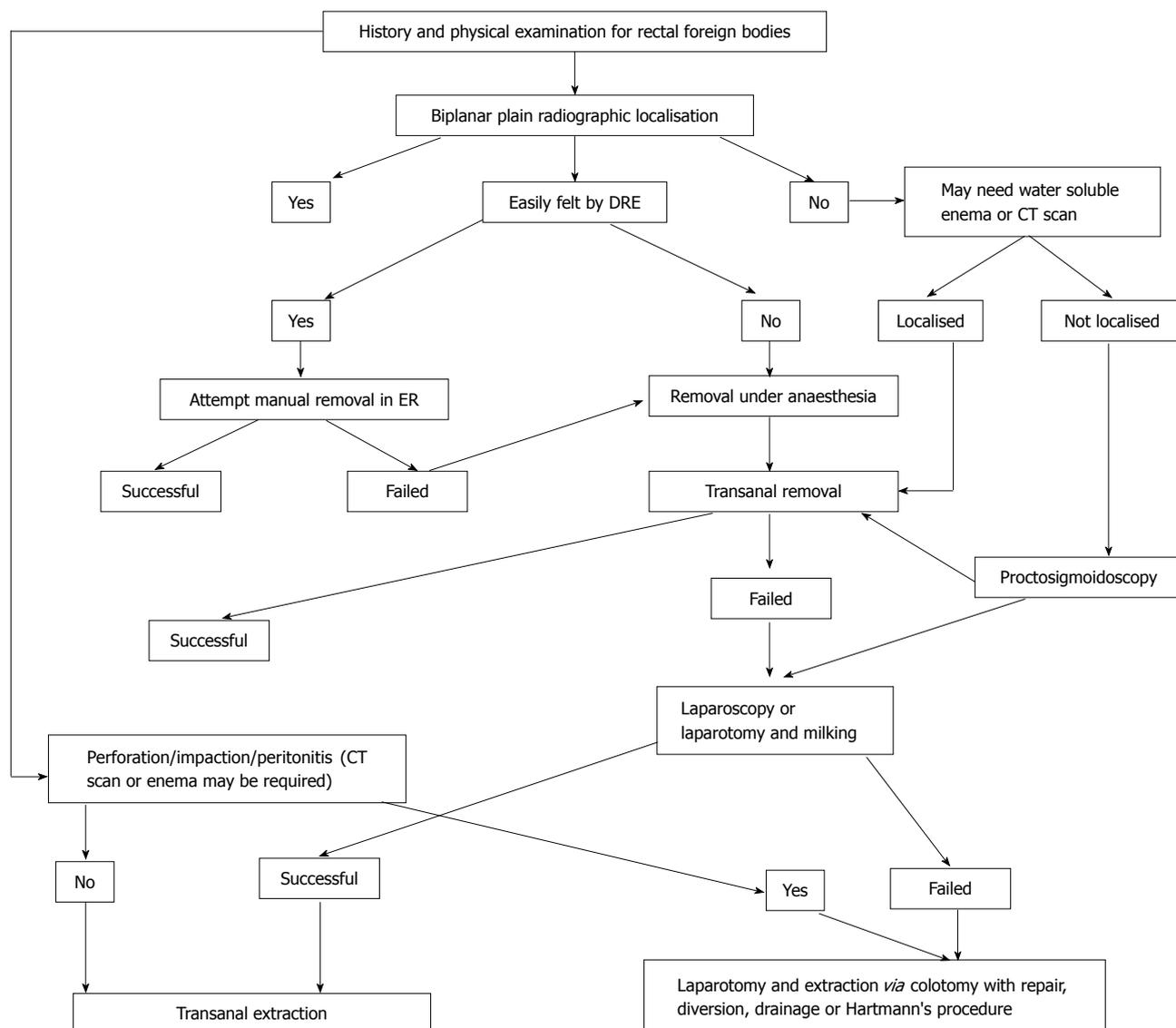


Figure 2 Algorithm for management of retained rectal foreign bodies.

use of anaesthesia in the treatment of these patients reduces anal sphincter muscles spasm and therefore improves direct visualization and good exposure with a successful chance of extraction per anum^[1,8].

There has been a significant evolution addressing the various management challenges of wide spectrum of different types of objects impacted in the rectum over the last few years^[1,2,4,8,10,14,16]. The majority of retained low-lying foreign bodies can be removed with a guided grasping forceps or a clamp introduced a proctosigmoidoscope. This approach can be aided by an initial examining finger manoeuvre to disengage the impacted object from the oedematous anorectal mucosa^[1,8]. The majority of our patients in this study required their retained rectal objects to be removed in the operating theatre under direct vision with proctosigmoidoscope using a grasping forceps or a small Keilland's forceps. All of them underwent successful transanal retrieval with no need for laparoscopy or laparotomy.

The failure of transanal retrieval of impacted foreign bodies in the rectum can be predicted preoperatively. Lake *et al*^[4] in their experience cited several factors responsible for failure of transanal removal including the impaction of a an object longer than 10 cm, hard or sharp objects, objects that have migrated upward into the sigmoid colon and those that have been impacted for more than 2 d. There are specific indications for the use of emergency laparotomy for extraction of impacted objects including failure of attempts at transanal removal, presence of perforation and/or peritonitis^[1,2,4,8,16]. The use of minimally invasive operative techniques for impacted rectosigmoid foreign bodies has been described which is a combination of laparoscopic downward milking of the object followed by per anal extraction^[1,2,17-19]. This approach however is only recommended for smooth foreign bodies and if successful, avoids the need for a full laparotomy and provides the benefit of early discharge from the hospital^[1,2,17-19]. Figure 2 is adapted from reference 1.

In conclusion, this study confirms a rising trend in the

number of patients with retained rectal foreign bodies with hospital presentations and most of these objects were used for erotic stimulation. There was also a slightly higher female population in the current study than previously reported and this may be the emerging trend of this entity. It is very much likely that the increasing trend would be encountered in most hospitals and therefore, the clinicians in the emergency settings need to be well informed about the approach to the care of patients with retained rectal foreign bodies.

COMMENTS

Background

Hospital presentation with retained rectal foreign bodies is no longer rare although concrete epidemiological data are still lacking. They are usually encountered in the adults and are either inserted intentionally or non-intentionally. The delay in the presentation and the associated patient's vague history usually lead to significant diagnostic and management challenges.

Research frontiers

There are recent anecdotal reports suggesting an increasing trend in the hospital presentations with impacted foreign bodies in the rectum. The present authors' and other authors' prediction from the previous published reports was a likelihood of an increasing presentation with the use of different objects for anorectal eroticism. Therefore, the clinicians in the emergency settings should be well familiar with the approach and the principles of care of these patients.

Innovation and breakthroughs

The authors predict that from the current study and the paucity of the available published epidemiological data that there is likely going to be an increasing trend in the incidence and presentations with the retained objects in the rectum.

Applications

The diagnosis and treatment patients presenting to hospital rectal foreign bodies should be orderly and methodical including safe retrieval and post-extraction period of observation. The desired ultimate outcome for every case is a safe and successful per anum extraction of foreign body, in a manner respecting the patients' right to dignity, privacy and confidentiality.

Terminology

Retained lower GIT foreign bodies may be located low or high based on their positions relative to the to the rectosigmoid junction. Most low-lying rectal foreign objects are easily reachable by the examining finger and can be removed per anum whereas those higher up in upper rectum or sigmoid colon may be difficult to reach and retrieved.

Peer-review

This is an interesting case series of rectal foreign bodies.

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Retrospective Cohort Study

Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: Need for routine histological analysis?

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Abstract

AIM

To analyse the range of histopathology detected in the largest published United Kingdom series of cholecystectomy specimens and to evaluate the rationale for selective histopathological analysis.

METHODS

Incidental gallbladder malignancy is rare in the United Kingdom with recent literature supporting selective histological assessment of gallbladders after routine cholecystectomy. All cholecystectomy gallbladder specimens examined by the histopathology department at our hospital during a five year period between March 2008

and March 2013 were retrospectively analysed. Further data was collected on all specimens demonstrating carcinoma, dysplasia and polypoid growths.

RESULTS

The study included 4027 patients. The majority (97%) of specimens exhibited gallstone or cholecystitis related disease. Polyps were demonstrated in 44 (1.09%), the majority of which were cholesterol based (41/44). Dysplasia, ranging from low to multifocal high-grade was demonstrated in 55 (1.37%). Incidental primary gallbladder adenocarcinoma was detected in 6 specimens (0.15%, 5 female and 1 male), and a single gallbladder revealed carcinoma *in situ* (0.02%). This large single centre study demonstrated a full range of gallbladder disease from cholecystectomy specimens, including more than 1% neoplastic histology and two cases of macroscopically occult gallbladder malignancies.

CONCLUSION

Routine histological evaluation of all elective and emergency cholecystectomies is justified in a United Kingdom population as selective analysis has potential to miss potentially curable life threatening pathology.

Key words: Gallbladder; Incidental; Cholecystectomy; Histopathology; Carcinoma

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Core tip: The selective use of histopathological examination of gallbladders removed during routine cholecystectomy has been advocated by several authors in the literature. We present a large single centre study demonstrating a full range of gallbladder disease from cholecystectomy specimens, including more than 1% neoplastic histology and two cases of microscopic gallbladder malignancies in macroscopically normal gallbladders. On this basis, routine histological evaluation of all elective and emergency cholecystectomies is justified in an United Kingdom population as selective analysis has potential to miss potentially curable life threatening pathology.

Patel K, Dajani K, Iype S, Chatzizacharias NA, Vickramarajah S, Singh P, Davies S, Brais R, Liao SS, Harper S, Jah A, Praseedom RK, Hugué EL. Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: Need for routine histological analysis? *World J Gastrointest Surg* 2016; 8(10): 685-692. Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/685.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.685>

INTRODUCTION

Cholecystectomy is among the most commonly performed surgical procedures worldwide, principally indicated in patients with symptomatic gallstone-associated disease. Approximately 5.5 million people in the United Kingdom

have gallstones^[1], with 70000 undergoing operative intervention each year in the United Kingdom^[2]. The indication for cholecystectomy is usually benign disease, though the histology can reveal incidental premalignant or malignant gallbladder pathology warranting appropriate further surgical resection.

Incidental gallbladder malignancies are rare in the United Kingdom with reported rates between 0.17%-0.81% of cholecystectomy resected specimens^[3-6]. Further revision surgery with curative intent is generally indicated in those without metastatic disease and tumour staging worse than T1a. Potentially curative resection may be offered in up to 50% of patients with incidental gallbladder malignancy post-cholecystectomy, however, some of these patients are ultimately found to have unresectable or metastatic disease at the time of laparotomy^[7,8].

Recognised premalignant conditions leading to gallbladder carcinoma include gallbladder dysplasia and those arising from adenomatous polyps^[9]. Dysplastic changes are often difficult to predict pre-operatively due to absence of macroscopic abnormalities detectable on imaging, hence emphasizing need to histologically examine all gallbladders resected^[9]. Strategies for gallbladder polyp surveillance and indications for operative management have been previously recommended, however this remains a controversial topic with widely varied practice in reality^[10,11].

Some authors have advocated selective, rather than routine, histopathological analysis of resected gallbladders, primarily due to rarity of incidental disease, financial implications and time burden on histopathology departments^[4-6,12]. Others have suggested macroscopic examination of resected gallbladders intra-operatively, to determine whether further histological analysis is required depending on presence of suspicious macroscopic lesions or significant patient risk factors for gallbladder cancer^[4].

The primary aim of this study was to review the range of histopathology detected in the largest United Kingdom series of routine cholecystectomy specimens from a single centre teaching hospital, in particular pre-malignant and malignant pathology. Secondary aims were to further analyse patients with incidental gallbladder malignancy, dysplasia and polyps and to make recommendations for future practice and necessity of routine histological examination of gallbladder specimens.

MATERIALS AND METHODS

This descriptive study was designed as a retrospective review of a database of all gallbladder specimens histopathologically examined at Cambridge University Hospital (Cambridge, United Kingdom) during a five year period between March 2008 and March 2013. This hospital is a tertiary referral centre for management of hepatopancreatobiliary malignancies. Exclusion criteria included gallbladders resected as part of another procedure (*e.g.*, Whipple's resection) and instances where malignancy was strongly suspected pre-

Table 1 Summary of histopathological findings

Histology	Subgroup	No (n = 4027)	% Total
Normal		182	4.50%
Cholecystitis		3480	86.3%
Acute		45	
Chronic	Gangrenous	3435	
	Empyema	29	
	Follicular	6	
	Xanthogranulomatous	3	
		5	
Cholesterosis		246	6%
Polypoidal Lesion		44	10%
	Cholesterol-based	42	
	Hyperplastic	1	
	Adenoma	1	
Metaplasia		13	0.3%
Dysplasia		55	1.4%
	Focal LGD*	40	
	Multi-Focal LGD	9	
	Focal HGD	2	
	Multi-focal HGD	4	
	(Multi-focal HGD + AC)	(2)	
Carcinoma <i>in situ</i>		1	0.02%
Adenocarcinoma		6	0.15%

LGD: Low grade dysplasia; HGD: High grade dysplasia; AC: Adenocarcinoma.

operatively, including ultrasonographically suspicious lesions or polyps greater than 1 cm in size. Histology reports were retrospectively analysed for presence of gallbladder disease, including benign and malignant pathology.

Further information was obtained on gallbladders demonstrating incidental gallbladder malignancies, dysplastic changes and polypoid structures including patient demographics, pre-operative symptoms and imaging, operative details, tumour histology and post-operative clinical outcomes. In patients with incidental malignancies, extensive data was collected on staging, tumour type, further resectional surgery and survival time. Survival times were calculated from time of cholecystectomy to date of death or latest follow up. In those with detected dysplasia, additional data were collected, including type of dysplasia, presence of tumour foci and associated risk factors (*e.g.*, primary sclerosing cholangitis). For gallbladder specimens containing polyps, further information was obtained including uptake into our gallbladder surveillance programme, polyp type, size and number, preoperative ultrasonography findings and indications for surgery. Hospital electronic medical records and patient hard copy notes were used to extract relevant data.

Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS Windows Version 22.0, Chicago, IL, United States) with a *P*-value less than 0.05 representing statistical significance. Continuous data analysed was described with median values accompanied with ranges [Median (range)].

RESULTS

A total of 4027 resected gallbladders from elective and emergency cholecystectomies were examined by the histopathology department at Addenbrooke's Hospital in the 5 years period studied. Overall, we report an incidental gallbladder invasive adenocarcinoma rate of 0.15% (6/4027) and one gallbladder demonstrating carcinoma-*in-situ* (0.02%, 1/4027). The majority of resected specimens exhibited gallstone or cholecystitis related disease. Table 1 displays the range of histopathological findings demonstrated from our patient sample.

Gall bladder carcinoma

Primary invasive gallbladder adenocarcinoma was identified in 6 patients with a median age of 66.5 years (range 45-71) and a female majority (5/6) (Figure 1 is an illustration of typical macroscopic and microscopic appearances of a gallbladder cancer specimen). All but one patient (5/6) had co-existing cholelithiasis on pre-operative ultrasonography, while half (3/6) had ultrasonography evident thickened gallbladder walls consistent with cholecystitis. All patients were symptomatic with right upper quadrant pain pre-operatively, however none presented with a palpable mass, clinical jaundice or weight loss. In none of these patients was gallbladder malignancy considered a potential differential diagnosis on decision to perform a cholecystectomy. Surgery in 4 of these of these cases were reported as more challenging than usual, but not in the other 2, which were both reported as macroscopically normal from histopathological examination, but microscopic examination revealed T1 disease, one T1a and the other T1b. Otherwise, tumour staging varied significantly with T3 disease the most advanced. To present date, 3 patients have died from progressive metastatic disease with a post-cholecystectomy mean survival time of 20.6 mo.

A single case of carcinoma-*in-situ* (0.02%, 1/4027) was identified in a 66-year-old gentleman with known gallstones. No lesion was identified on macroscopic examination, however microscopic analysis revealed foci of adenocarcinoma within surrounding extensive high grade dysplasia. Further details of all carcinoma patients including operation details and clinical outcome postoperatively are depicted in Table 2.

Gall bladder dysplasia

The overall incidence rate of gallbladder dysplasia was 1.37% (55/4027) with a wide spectrum of dysplastic changes as illustrated in Table 1. Median age was 53 years (range 22-82) with the majority of patients being female (85.5%, 47/55). From all 55 cases of dysplasia, 47.3% (26/55) had co-existing gallstone disease on final histology. Primary sclerosing cholangitis was pre-existent in 3.6% (2/55) patients. Four gallbladders exhibited multifocal high grade dysplasia from which half

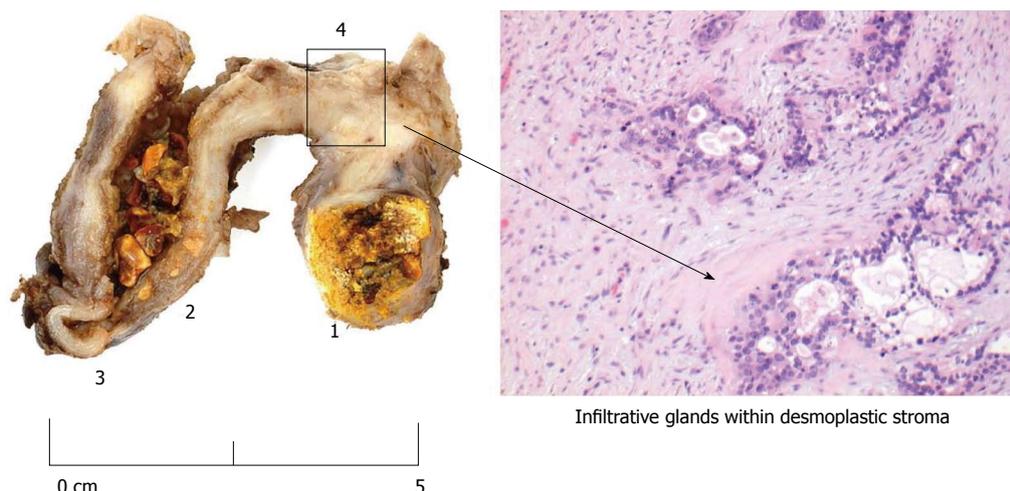


Figure 1 Typical macroscopic and microscopic appearances of gallbladder cancer. 1: Cholesterol gallstones, impacted; 2: RA sinuses containing impacted stones; 3: Chronic cholecystitis; 4: Ruptured gallbladder carcinoma.

Table 2 Pre- and post-operative characteristics of cases with incidental gallbladder adenocarcinoma							
Age	Sex	Pre-operative imaging	Operation details	Operative findings	Tumour type/staging	Further management	Survival (mo)
71	F	USS: Multiple gallstones	Lap	Smooth GB wall with multiple calculi	T1a N0 M0, Adenocarcinoma	No further operation, surveillance CT scans	Alive (64)
68	F	USS: Multiple stones, dilated CBD; CT: Multiple stones, no mass seen	Open	Large GB calculi, no CBD stones on CBD exploration	T2 N0 M0, Adenocarcinoma (MD)	Not fit for further resection (known chronic leukaemia – already on chemotherapy)	Alive (22)
45	F	USS: Stones, thickened GB wall; CT: Inflammatory changes on GB wall	Lap converted to open	Small abscess on GB bed, gross GB wall thickening	T3 N1 M0, Adenocarcinoma (PD)	Revision operation – abandoned as nodules on umbilical port and peritoneum, palliative chemotherapy	12
70	F	USS: Grossly thickened GB wall and multiple gallstones	Lap	Thick dense adhesions with fistulous communication between GB tumour and transverse colon	T3 N1 M1, Adenocarcinoma (PD)	Chemotherapy	12
65	F	USS: Stones, cholecystitis; CT: Marked GB wall thickening, ?cholecystitis	Lap	GB wall inflamed, disintegrated with biliary spillage++	T2 N0 M0, Adenocarcinoma (MD)	Not medically fit for revision surgery; developed nodal disease but not fit for chemo; palliative therapy	37
65	M	USS: Sludge and gallstones (pancreatitis patient)	Lap	Mildly inflamed GB with calculi	T1b N0 M0, Adenocarcinoma (PD)	Revision surgery and lymphadenectomy, chemotherapy	Alive (36)
66	M	USS: Multiple small gallstones	Lap	Smooth GB wall with calculi	Tis N0 M0	No further management	Alive (54)

USS: Ultrasonography; CT: Computed tomography; GB: Gallbladder; MD: Moderately differentiated; PD: Poorly differentiated.

(2/4) exhibited foci of adenocarcinoma, both previously mentioned in our cancer cohort (Table 2). One gallbladder (1.8%, 1/55) demonstrated a tubular adenoma with surrounding focal high grade dysplastic changes. No gallbladder specimen revealed evidence of dysplasia at the cystic duct resection margin.

Gall bladder polyps

Gallbladder polyps were identified in 1.09% (44/4027). The median age was 51 years (range 28-84). Pre-operative imaging identified 77.3% (34/44) of these polyps, with a measured median size of 7.4 mm (range

2-13 mm). All but three polyps were cholesterol in nature (93.2%, 41/44). The other three polyps varied in histology including one hyperplastic polyp, one xanthomatous polyp and one tubular adenomatous polyp. None of these polyps exhibited malignant features.

DISCUSSION

This study is the largest United Kingdom series to date evaluating range of histopathology demonstrated from cholecystectomy resected gallbladder specimens. Our main findings include observed overall rates of 0.17%

incidental gallbladder adenocarcinomas and 1.37% incidental premalignant gallbladder dysplasia. The most common histology reported in our study was chronic cholecystitis (85.3%).

Incidental gallbladder malignancy identified in cholecystectomy specimens make up the majority of all diagnosed gallbladder cancers^[12]. There is a well-documented heterogeneity in the incidence of gallbladder cancer, varying according to various patient demographic factors including worldwide location, ethnicity and age^[13]. Along with most of Europe, the United Kingdom is considered a low risk area with an associated low rate of incidental gallbladder malignancies when compared to high risk areas such as India and Japan^[14]. Previous United Kingdom studies have reported incidence rates between 0.17%-0.81%, however some of these studies have included gallbladders in which tumour was suspected on preoperative imaging^[3-6]. Our study observed a 0.17% rate of incidental gallbladder malignancies. This relatively low incidence may reflect the ethnicity of our study population with a strong European-Caucasian representation as only one patient from all carcinoma and dysplasia-revealing gallbladders was non-Caucasian in ethnicity (Indian). Furthermore, those patients in whom gallbladder malignancy was strongly suspected on pre-operative imaging were strictly excluded from our study and this may have contributed further to the low incidence rate.

Chronic gallstone-related irritation is a known significant risk factor for dysplastic changes and development of carcinoma^[15]. Increased gallstone weight, number and volume have also been associated with an increased risk of gallbladder cancer^[16]. In this study, 6 out of the 7 carcinoma patients had co-existing gallstones.

In contrast, only 47.3% of dysplastic gallbladders demonstrated final histology cholelithiasis, perhaps implying other pathogenesis factors involved in development of gallbladder dysplasia. In this regard, 2 patients exhibiting high grade dysplasia had a pre-operative diagnosis of primary sclerosing cholangitis, a known risk factor for gallbladder malignancy with previous reports of up to 30% of resected gallbladders displaying dysplasia/carcinoma pathology^[17]. Consistent with this, our policy is to adopt a low threshold in recommending cholecystectomy in patients with primary sclerosing cholangitis presenting with clinical or radiological evidence of gallbladder pathology.

In our institution, routine pre-operative investigations for patients presenting with symptomatic biliary pathology includes the assessment of liver function tests alongside ultrasonographic assessment of the gallbladder and biliary tree. Should these provide any suspicious features then further assessment with cross sectional imaging (CT scan or MRCP) and endoscopic ultrasound are performed, followed by discussion in the regional multi-disciplinary meeting where decision on further management is made.

Six patients in our cohort were identified as having

gallbladder carcinoma on post-operative histology (Table 2), with a median age of 66.5 years. The youngest patient was a 45-year-old female who was found to have T3N1 disease which progressed rapidly with peritoneal spread. None of these were suspected pre-operatively. In 2 of the 6 cases, the pre-operative ultrasound identified gallstones within a thin walled gallbladder with the absence of any worrying features to necessitate further investigations. Operative findings for these 2 cases were of thin walled gallbladders (macroscopically normal) and hence gallbladder cancer was not suspected. Post-operative histology described early gallbladder carcinoma (T1a and T1b respectively), despite these microscopic findings, the histopathological examination reported these specimens as macroscopically normal looking. The remaining 4 cases, were identified on pre- and intra-operative examinations as having macroscopic abnormalities. In 3 of these cases, further pre-operative investigations with cross sectional imaging (CT scan) were performed. The CT findings were reported as inflammatory, with the absence of a mass lesion and abnormal lymphadenopathy. Operative findings were of thickened gallbladder walls, while one had an associated abscess in the gallbladder fossa. The clinical suspicion here was of severe inflammatory changes. Although the presence of gallbladder cancer in such cases is always a possibility, the clinical suspicion was low and hence standard cholecystectomy was performed. Post-operative histology identified T2 disease in 2 cases and T3 N1 disease in the remaining case.

The final case was of a 70-year-old female with pre-operative ultrasonography describing a thickened and inflamed gallbladder with calculi; at the time of surgery she was found to have dense adhesions a thickened shrunken gallbladder, as well as a fistulous communication between the gallbladder and the transverse colon. These findings were thought to be inflammatory in nature, however, the diagnosis of gallbladder carcinoma is regarded as a possibility in such cases. An intra-operative decision on whether a simple cholecystectomy or a more radical should be taken. The majority of such cases will ultimately prove to be benign and inflammatory in aetiology. Factors such as pre-operative co-morbidities and the potential stage of disease, should this turn out to be malignant, are taken into account. If clinical suspicion of cancer is high, co-morbidities are limited and the patient is suitable for a potentially curative resection, then frozen section may be performed to confirm the diagnosis and the surgical plan amended as deemed necessary. However, if the patient or tumour factors render potentially curative surgical intervention impossible then a standard cholecystectomy to achieve a tissue diagnosis may be deemed appropriate.

Several United Kingdom papers have recommended selective histopathological analysis of cholecystectomy resected specimens^[4-6,14]. This recommendation is based on the assumption that incidental gall bladder malignancy is associated with macroscopic lesions which can be identified on examination of the resected gall bladder

in the operating theatre. Our study, the largest United Kingdom series to date and the only one with over 3000 patients, demonstrates that this assumption is not reliable, as evidenced by the finding of gallbladder malignancy in macroscopically normal gallbladders, including T1b disease for which revision surgery is generally advocated, on account of published data showing a survival benefit of 3.4 years from radical resection over simple cholecystectomy^[18]. The patient with T1b disease underwent further liver segmental resection with lymphadenectomy and is disease free three years later to this day. This is the first United Kingdom series to report a patient with macroscopically occult incidental gallbladder malignancy with no preoperative or intra-operative suspicion of carcinoma who subsequently underwent successful R0 resectional surgery.

A systematic review in 2014 by Jamal *et al*^[14] examined 20 previous studies, including 6 United Kingdom studies, evaluating the necessity of routine histological analysis in macroscopically normal gallbladders. The authors concluded that in gallbladders deemed normal from macroscopic examination by the operating surgeon, selective histological analysis was feasible in the "low risk" European ethnicity under the age of 60^[14]. However, the systematic review did not include a recent histopathology paper by Hayes *et al*^[19] examining gallbladder specimens sent for histology after cholecystectomy. This study reported a striking 50% (5/10) of incidental invasive gallbladder malignancies presenting with no macroscopic abnormalities on histopathologist examination with a mean age of 54.6 years. This proportion of macroscopically occult malignancies in a "low risk" population of that age range challenges the recommendations from Jamal *et al*^[14] recent systematic review. In addition, United Kingdom Royal College of Pathologists 2005 recommendations state that all gallbladders removed for presumed benign disease warrant histological examination in order to ensure no significant subtle pathology is missed from macroscopic examination^[20].

Solaini *et al*^[3] in 2014 reported almost 3% incidental neoplastic findings from cholecystectomy gallbladders with inclusion of dysplastic changes and is one of few United Kingdom papers supporting routine histological analysis of all gallbladder specimens. The authors reported dysplasia rates of 2.3% (18/771) with a median age of 45 years in a population with strong Asian ethnicity representation (66%). Our study observed lower rates of dysplastic changes at 1.37% (55/4027) with a higher median age of 53 years, perhaps partly explained by the lack of representation of the Asian population in our study group^[21].

Whether the finding of dysplasia is of clinical significance may be debated, but our opinion is that this is not merely academic. Positive cystic duct margins and gross high grade dysplastic changes can indicate further potential pancreatobiliary disease, with further operative exploration warranted in certain circumstances. Bickenbach *et al*^[22] in 2011 reported five cases of high

grade dysplasia at the cystic duct resectional margin following cholecystectomy, all of whom subsequently underwent further resectional surgery, either with excision of cystic duct remnant or excision of extrahepatic bile duct. Of these, one patient was found to have adenocarcinoma within the resected cystic duct remnant. No gallbladders in our study demonstrated cystic duct margin positive disease, however half our cases of multifocal high grade dysplasia had associated foci of adenocarcinoma. In our practice, the finding of high grade dysplasia on the cystic duct margin would warrant further surgical exploration and frozen section of cystic duct margin to ascertain whether further radical resection would be required to ensure R0 resection.

Gallbladder polyps are common with a reported incidence rate in a recent multi-ethnic United Kingdom series of 3.3%, with higher rates observed in the Asian ethnic groups^[23]. Our series reports a 1.09% (44/4027) incidence of polypoid lesions of the gallbladder, however we excluded all polyps reported as sonographically suspicious of malignancy or more than 1 cm in size pre-study in order to focus on incidental gallbladder pathology. Our largely Caucasian study population may also reflect the observed lower polyp incidence rate. All but one polyp demonstrated benign pseudotumour characteristics, predominantly cholesterol in nature (41/44). We did however observe one true polyp adenoma (1/44, 2.3%) occurring in a 67-year-old male and of 3mm in size, which had been reported as a gallstone on preoperative sonography with biliary colic as indication for surgery. Cairns *et al*^[24] in 2013 examined a large cohort of gallbladder polyps in a United Kingdom population and observed a similar 2.2% incidence rate of adenomas as well as 0.7% adenocarcinoma rate. Although adenomas are histologically benign, there is a well-recognised adenoma-carcinoma path of carcinogenesis to gallbladder malignancy^[21]. This has led to polyp surveillance implementation in HPB centres with indications to operatively remove gallbladders displaying polypoid lesions above 1 cm, rapidly growing in size or symptomatic in nature^[24]. Marangoni *et al*^[10] surveyed United Kingdom surgeons regarding their practice of gallbladder polyp surveillance with indications for operative management and revealed significant variation and identified a need for formal national guidelines to tackle this area of conflicting opinions. Although polyp surveillance was not analysed in further detail as part of this study, it is our practice to actively monitor polyps with ultrasonography particularly with recent literature to support it is cost effective^[24].

In conclusion, our study has demonstrated a broad spectrum of histopathology from examination of cholecystectomy resected gallbladders for preoperatively diagnosed benign gallbladder disease. This is the largest United Kingdom series within the literature and observed 0.17% incidence of primary adenocarcinoma and 1.37% gallbladder dysplasia. The study is the first United Kingdom study to report cases of macroscopically normal gallbladders harbouring adenocarcinoma lesions

with subsequent successful R0 resection. We also report a single case of adenocarcinoma in a patient aged 45 years. With over 1% rate of pre-malignant and malignant disease, we conclude that routine histological evaluation of all elective and emergency cholecystectomies is justified in a United Kingdom population and that selective histological evaluation has the potential to miss life threatening gallbladder pathology amenable to subsequent curative surgery.

COMMENTS

Background

Cholecystectomy is among the most commonly performed surgical procedures worldwide. Routine histopathological examination of the resected specimens is usually performed. However, selective histopathological analysis has been proposed in the literature, primarily due to rarity of incidental disease (0.17%-0.81% in the United Kingdom), financial implications and time burden on histopathology departments.

Research frontiers

The authors aimed to analyse the range of histopathology detected in the largest published United Kingdom series of cholecystectomy specimens and to evaluate the rationale for selective histopathological analysis.

Innovations and breakthroughs

This large single centre study demonstrated a full range of gallbladder disease from cholecystectomy specimens, including more than 1% neoplastic histology and two cases of macroscopically occult gallbladder malignancies.

Applications

Routine histological evaluation of all elective and emergency cholecystectomies is justified in a United Kingdom population as selective analysis has potential to miss potentially curable life threatening pathology.

Peer-review

The authors described an incidental non-benign gallbladder histopathology after cholecystectomy in a United Kingdom population. More than 4000 cases of resected gallbladder specimens were analyzed histopathologically. Although several reports regarding incidental gallbladder cancer have been already published from high prevalence areas, studies from infrequent area such as the United Kingdom are worth publishing.

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Retrospective Cohort Study

Acute appendicitis: Epidemiology, treatment and outcomes-analysis of 16544 consecutive cases

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Abstract**AIM**

To investigate the epidemiology, treatment and outcomes of acute appendicitis (AA) in a large population study.

METHODS

This is a retrospective cohort study derived from the administrative dataset of the Bergamo district healthcare system (more than 1 million inhabitants) from 1997 to 2013. Data about treatment, surgery, length of stay were collected. Moreover for each patients were registered data about relapse of appendicitis and hospital admission due to intestinal obstruction.

RESULTS

From 1997 to 2013 in the Bergamo district we collected 16544 cases of AA, with a crude incidence rate of 89/100000 inhabitants per year; mean age was 24.51 ± 16.17 , 54.7% were male and the mean Charlson's comorbidity index was

0.32 ± 0.92. Mortality was < 0.0001%. Appendectomy was performed in 94.7% of the patients and the mean length of stay was 5.08 ± 2.88 d; the cumulative hospital stay was 5.19 ± 3.36 d and 1.2% of patients had at least one further hospitalization due intestinal occlusion. Laparoscopic appendectomy was performed in 48% of cases. Percent of 5.34 the patients were treated conservatively with a mean length of stay of 3.98 ± 3.96 d; the relapse rate was 23.1% and the cumulative hospital stay during the study period was 5.46 ± 6.05 d.

CONCLUSION

The treatment of acute appendicitis in Northern Italy is slowly changing, with the large diffusion of laparoscopic approach; conservative treatment of non-complicated appendicitis is still a neglected option, but rich of promising results.

Key words: Acute appendicitis; Conservative treatment; Epidemiology; Laparoscopic appendectomy; Intestinal obstruction

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Core tip: Acute appendicitis is the most common surgical emergency around the world. In the Bergamo district, northern Italy its incidence is 89/100000 inhabitants per year with a negative trend during the last years. Percent of 95 patients were treated with appendectomy, 48% of whom laparoscopically; 1.3% of operated patients had an intestinal obstruction during the follow-up. Conservative treatment resulted in a reduced length of stay but 23% of patients had a relapse during follow up. Cumulative length of stays during the study period was similar for the two treatment option.

Ceresoli M, Zucchi A, Allievi N, Harbi A, Pisano M, Montori G, Heyer A, Nita GE, Ansaloni L, Coccolini F. Acute appendicitis: Epidemiology, treatment and outcomes-analysis of 16544 consecutive cases. *World J Gastrointest Surg* 2016; 8(10): 693-699 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/693.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.693>

INTRODUCTION

Acute appendicitis is probably the most common surgical emergency worldwide. Since its first accurate description by Fitz^[1] in 1886 and the first appendectomy performed by Treves^[2] in England, appendectomy became the preferred treatment of acute appendicitis. Although appendicitis is a very common disease, nowadays it has a still poorly understood etiology, with a very heterogeneous clinical pattern of presentation, varying from simple uncomplicated appendicitis to generalized peritonitis due to perforation. For each clinical pattern the proposed treatment is the same: Appendectomy.

This results in an overtreatment with a described rate of negative appendectomy (a histopathological diagnosis of normal appendix) ranging from 6% to 20%^[3,4]. Appendectomy has also a complication rate ranging from 8% to 11%, depending on the surgical technique^[5]. Several reports described spontaneous resolution of uncomplicated appendicitis without the need of an operation and, since the high rate of negative appendectomy and the significative complications rate, some authors proposed and advised conservative management for uncomplicated appendicitis^[6,7]. Conservative management for appendicitis has been described in 1930 by the "Ochsen-Sherren delayed^[8] treatment", which consisted of resting and fasting followed by delayed elective appendectomy; nowadays, a conservative approach based on antibiotic therapy is gaining popularity, as documented by several randomized studies and meta-analyses that analyze this peculiar issue^[9-17]. Conservative treatment has been shown to be safe and effective as primary treatment compared to surgical treatment with a significative reduction in morbidity, even with a considerable one year recurrence rate of 23%^[17].

Despite this positive evidence, great uncertainty and skepticism remain concerning conservative treatment among surgeons.

The aim of the study was to describe the epidemiology of acute appendicitis in a large population study during the last seventeen years in order to analyze the evolution of the treatment throughout the years - appendectomy or conservative treatment, open or laparoscopic surgery - and to study the long term follow up of patients, in order to investigate the relapse rate of acute appendicitis in conservatively-treated patients and the incidence of intestinal occlusion after surgery.

MATERIALS AND METHODS

This is a retrospective analysis of patients discharged from the hospital between 1997 and 2013 with a diagnosis of acute appendicitis. Data were extracted from the administrative health care database of Bergamo's district, a large area (2723 km²) in Northern Italy with 1094062 inhabitants. This database collects all discharge records for each citizen of the district from any hospital, public and private, intra and extra-district. On the basis of this register, patients are assigned to the respective DRG, and reimbursements are supplied to the hospitals from the regional health care system.

Patients were retrieved on the basis of the concomitant presence of an unplanned hospital admission, with a ICD9-CM code of AA (ICD9-CM code 540.X, 541.X, 542.X, 543.X) in the first three diagnostic fields and with an Italian DRG code of Acute Appendicitis.

For each patient tracked, data regarding age, sex, Charlson's comorbidity index, surgical procedures (ICD9-CM code 47.X), length of hospital stay, time intervals between admission and operation and mortality were

Table 1 Distribution of patients among age categories and sex

Age category	Sex		Total	
	F	M	n	Among total
0-1	1	0	1	0.01%
1-6	239	369	608	3.68%
7-13	1673	2322	3995	24.15%
14-17	1314	1119	2433	14.71%
18-25	1904	1628	3532	21.35%
26-35	1167	1556	2723	16.46%
36-45	529	889	1418	8.57%
46-55	255	514	769	4.65%
56-65	165	352	517	3.13%
66-75	135	205	340	2.06%
76-85	89	79	168	1.02%
> 85	23	17	40	0.24%
Total	7494	9050	16544	100.00%

recorded.

For each patient further data on hospitalization related to acute appendicitis (same code) and bowel occlusion (ICD9-CM code 560.X) were collected, as well as the number of further hospitalizations, interventions, length of stay of each hospitalization and cumulative length of stay during the study period.

Continuous variables were expressed as mean \pm SD and were compared with the Mann-Whitney *U* test; association was tested with the Pearson's χ^2 test. Correlations were calculated with the Pearson's correlation test. Multivariate analyses were performed with the logistic regression method. Survivals were calculated with the Kaplan Meier method. Statistical analysis was performed with SPSS software (SPSS version 20, IBM, United States). Trends were studied with the Joinpoint model: Joinpoint regression analysis was performed using the Joinpoint software from the Surveillance Research Program of the United States National Cancer Institute (Joinpoint Regression Program, Version 4.1.1 - August 2014; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Trends were summarized with Average Annual Percent Change (AAPC). Calendar years started from 1997, until 2013. Crude rates are per 100000 inhabitants.

RESULTS

From 1997 to 2013 in the Bergamo district we collected 16544 cases of AA, with a crude incidence rate of

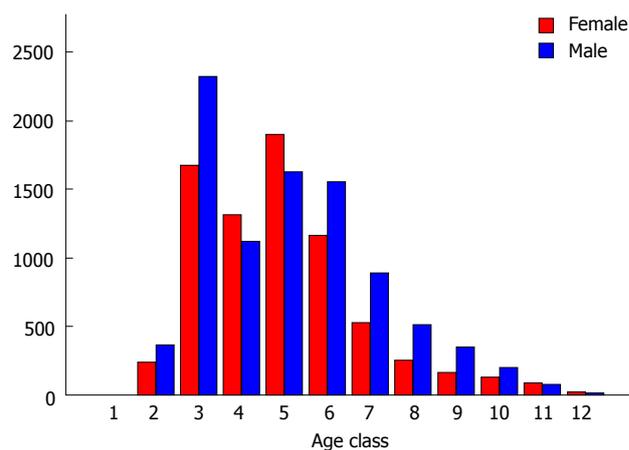


Figure 1 Age class and sex distribution. 1: 0-1; 2: 1-6; 3: 7-13; 4: 14-17; 5: 18-25; 6: 26-35; 7: 36-45; 8: 46-55; 9: 56-65; 10: 66-75; 11: 76-85; 12: > 85.

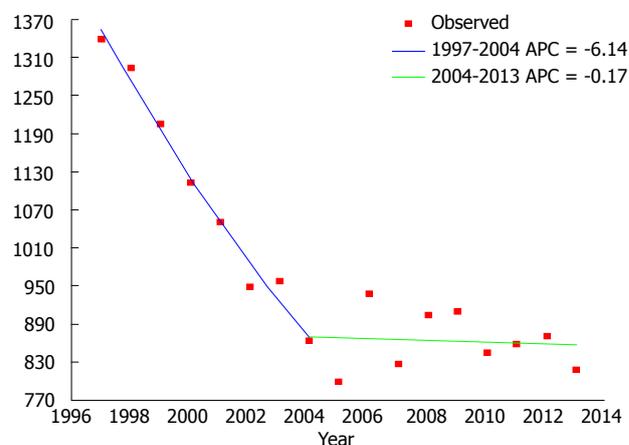


Figure 2 Number of patients discharged with acute appendicitis diagnosis during the years.

89/100000 per year; mean age was 24.51 ± 16.17 , 54.7% were male and mean Charlson comorbidity index was 0.32 ± 0.92 . Mortality was recorded for 7 patients ($< 0.0001\%$). Table 1 and Figure 1 show the distribution of age categories and sex: differences among sex in the different age categories were statistically significant ($P < 0.001$). The incidence of AA decreased during the years starting from 120/105 in 1997 to 73/105 in 2013 with a statistically significant negative value (AAPC = -2.8 , $P < 0.001$) (Figure 2).

Operative treatment

An appendectomy was performed in 94.7% of the patients: Mean age was 24.39 ± 15.98 , mean Charlson's comorbidity index was 0.31 ± 0.90 and 53.1% were male. Patients were operated after a mean of 0.85 ± 1.46 d and the mean length of stay was 5.08 ± 2.88 d with a negative trend over the considered period, starting from 6.09 ± 2.94 in 1997 to 4.58 ± 2.33 in 2013 (AAPC -1.5 , $P < 0.001$). Mortality was $< 0.0001\%$.

Data about laparoscopic procedures was available only after the year 2000: 48% of the patients were operated with the laparoscopic technique with a positive

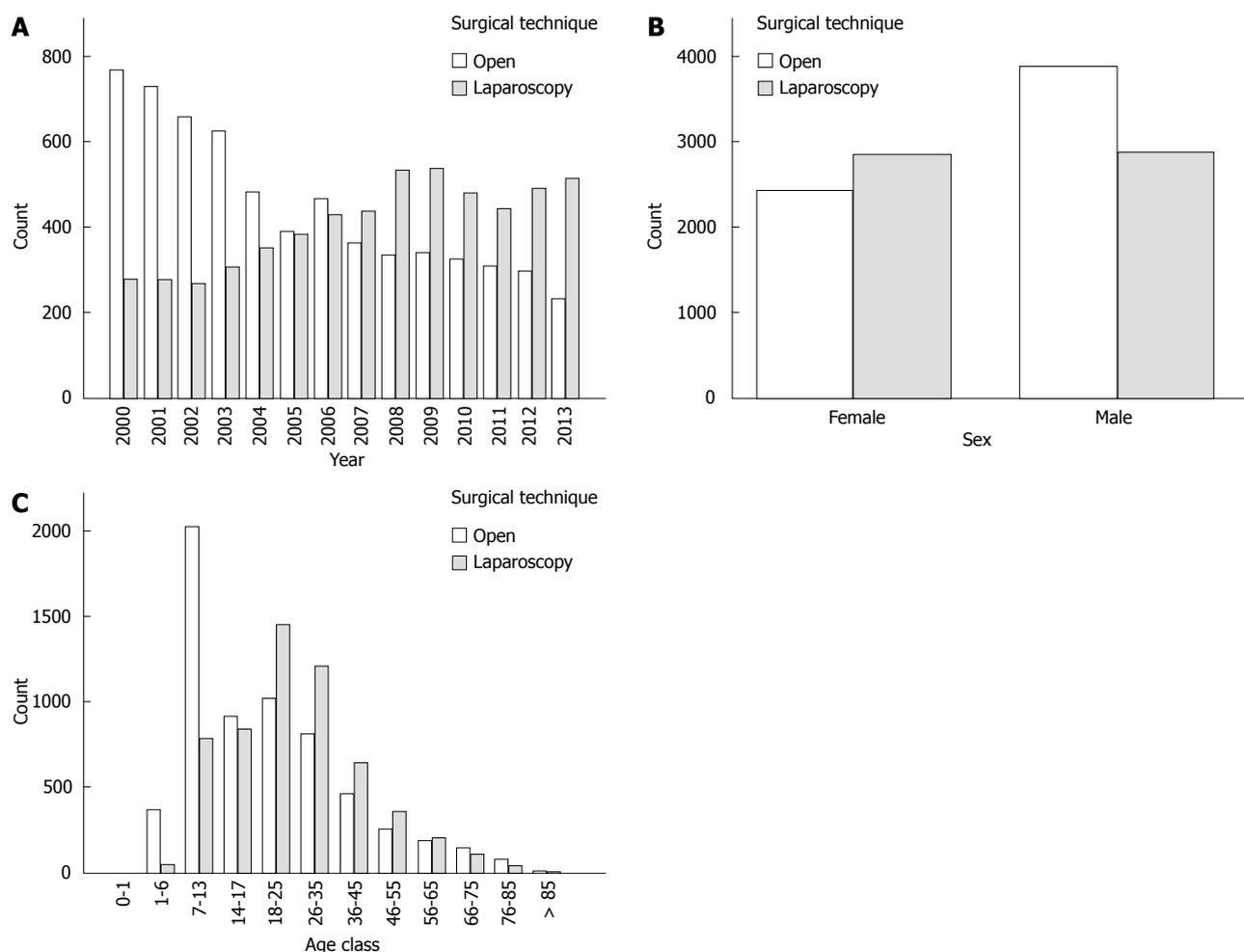


Figure 3 Surgical technique during the years (A), between sex (B) and among age classes (C).

trend during the years, starting from 26% in 2000 to 68.8% in 2013 (AAPC 5.2, $P < 0.001$) (Figure 3A) and with a mean length of stay of 4.47 ± 2.66 d (compared to 5.43 ± 2.94 with the open technique, $P < 0.001$). Laparoscopy was associated with a higher age, female sex and year in both univariate and multivariate analysis ($P < 0.0001$) (Table 2, Figure 3B and C).

The cumulative hospital stay during study period was 5.19 ± 3.36 d with a mean of 1.01 ± 0.13 hospital admissions. One hundred and ninety-two patients (1.2%) had at least one further hospitalization due intestinal occlusion after a mean of 30.53 ± 41.23 mo (median 11 mo) and 59.9% of them were operated on (Figures 4 and 5).

Conservative treatment

In general, 5.34% of the patients were treated conservatively: Mean age was 26.68 ± 19.04 ; 56.1% were male and mean Charlson's comorbidity index was 0.51 ± 1.26 ; mean length of stay was 3.98 ± 3.96 d; mortality was 0.1%. The proportion of patients treated conservatively increased during the years, from 6.1% in 1997 to 8.7% in 2013, although the trend was not significant ($P = 0.6$) (Figure 6).

Overall, relapse rate was 23.1% and a new episode of acute appendicitis occurred after a mean of 6.5 ± 15 mo (median 32 d); 89% of patients were operated on at relapse. The mean number of hospital admissions was 1.26 ± 0.47 with a cumulative hospital stay during the study period of 5.46 ± 6.05 d (Figures 4 and 5).

After univariate analysis, conservative treatment was associated with higher age, higher comorbidity index, and year of treatment ($P < 0.0001$); after multivariate analysis only Carlson's comorbidity index ($P = 0.004$) and year of treatment ($P < 0.0001$) remained significant (Table 3).

DISCUSSION

Acute appendicitis in Northern Italy has a crude rate of 89 cases per 100000 inhabitants per year, and this data is comparable to similar studies in other country worldwide^[18-21]. Surprisingly, during the study period the incidence decreased significantly, from 120 to 73 cases per 100000 inhabitants. This data contrasts with the data reported by Buckius *et al*^[20] in the United States over a similar period of time. Acute appendicitis is already a poorly understood disease and its diagnosis is still

Table 2 Surgical technique: Data about surgical techniques were available only after year 2000

	Open appendectomy	Laparoscopic appendectomy	Total	Univariate analysis P value	Multivariate analysis	
					OR	P value
n (%)	6321 (52)	5734 (48)	12055			
Age	22.79 (17.01)	27.57 (15.19)	25.06 (13.55)	< 0.0001	1.018 (1.018-1.0121)	< 0.0001
Sex	M: 61.5%	M: 50.2%	M: 54.6%	< 0.0001	1.80 (1.66-1.94)	< 0.0001
Charlson's	0.33 (0.97)	0.35 (0.87)	0.34 (0.92)	0.385		
Year	0.277 (Pearson Correlation)			< 0.0001	1.15 (1.14-1.16)	< 0.0001
Time to surgery (d)	0.66 (1.35)	0.97 (1.53)	0.81 (1.45)	< 0.0001		
Length of stay (d)	5.28 (3.00)	4.47 (2.66)	4.89 (2.85)	< 0.0001		
Mortality	5 (0.1%)	1 (0.001%)	6 (< 0.0001)	0.13		

Data are expressed as mean ± SD or number and proportion. Multivariate analysis was calculated for the correlation with laparoscopic approach.

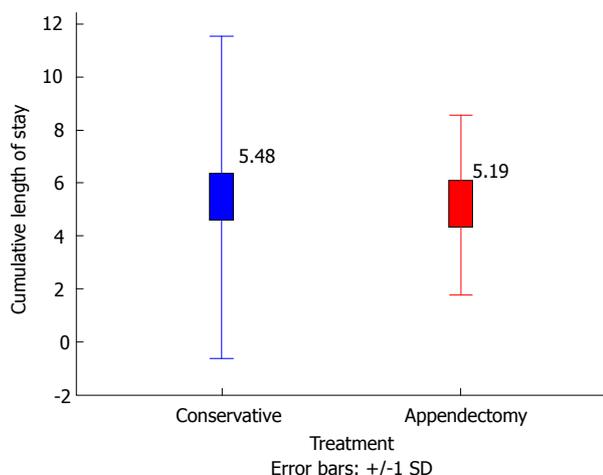


Figure 4 Cumulative length of stay between treatment options. Data are expressed in days (SD).

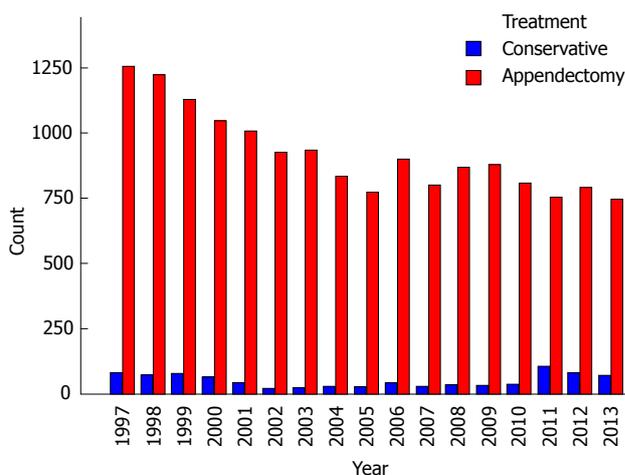


Figure 6 Treatment option during the years.

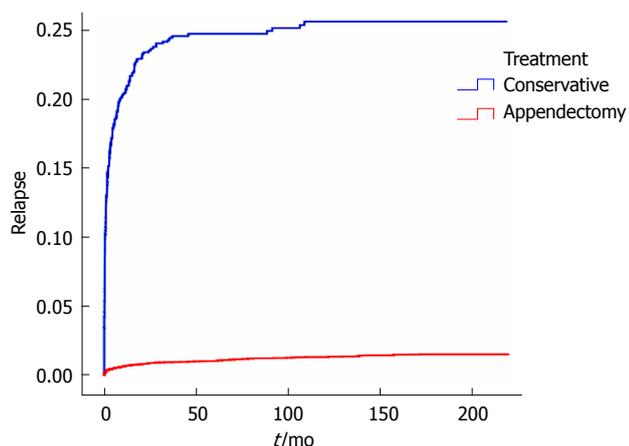


Figure 5 Kaplan-Meier curve of failure of conservative treatment (blue line) and incidence of intestinal obstruction in operated patients (red line).

based on clinical judgment, with great variability among surgeons. Clinical scores have been developed and proposed in the last years to help surgeons reaching a diagnosis of acute appendicitis, such as the Alvarado and the Andersson score^[22,23]. The decrease in the incidence rate could be explained by the diffusion of these scores and a consequent increased attention in the diagnosis of

acute appendicitis, in order to reduce the rate of negative appendectomies. As expected, acute appendicitis is more frequent in young and male patients (Figure 1), as reported by the literature^[18-20], with augmented incidence among patients in the 7-25 years categories. In the years categories 14-25, acute appendicitis is more frequent in females: A possible reason is the starting of childbearing ages and the sexual transmitted disorders that could mime acute appendicitis - with lower quadrant abdominal pain - and a consequent higher rate of negative appendectomies, as reported by Seetahal *et al*^[3]. Unfortunately there are no data available on the rate of negative appendectomies to confirm this hypothesis. The possibility of a diagnosis other than appendicitis in women justifies the higher frequency in this subgroup of the laparoscopic technique, which give the possibility to thoroughly explore the peritoneal cavity, as shown in Figure 3B. Laparoscopic appendectomy was performed in 48% of the cases, with an enormous increase across the years, from 26% to 69% (Figure 3). This data demonstrates the gradual diffusion of the laparoscopic technique, as shown by a similar study in the same contest for acute cholecystitis^[24]. After multivariate analysis, the laparoscopic approach was correlated to the year of treatment, female sex and older age: Figure 3C demonstrates that open appendectomy is still the

Table 3 Different treatments

	Total	Treatment		Univariate analysis <i>P</i> value	Multivariate analysis	
		Appendectomy	Conservative		OR (95%CI)	<i>P</i> value
<i>n</i> (%)	16544	15661 (94.7)	883 (5.3)			
Age	24.51 (16.17)	24.39 (15.98)	26.68 (19.04)	< 0.0001	1.006 (0.999-1.013)	0.095
Sex	M: 54.7%	M: 54.6%	M: 56.1%	0.424		
Charlson's	0.32 (0.92)	0.31 (0.90)	0.51 (1.26)	< 0.0001	0.826 (0.703-0.868)	< 0.0001
Year		-0.33 (Pearson Correlation)		< 0.0001	0.973 (0.959-0.986)	< 0.0001
Time to surgery (d)		0.85 (1.46)				
Length of stay (d)	5.02 (2.92)	5.08 (2.88)	3.98 (3.46)	< 0.0001		
Mortality	7 (< 0.0001%)	6 (< 0.0001%)	1 (0.1%)	0.292		
Relapse		1.20%	23.10%	< 0.0001		
Time to relapse (mo)	Mean	30 (45)	6.5 (15)	< 0.0001		
Time to relapse (mo)	Median	11 (1.17-49)	1 (0.16-6.63)			
number of hospitalization	1.03 (0.18)	1.01 (0.13)	1.26 (0.47)	< 0.0001		
Cumulative LOS	5.20 (3.56)	5.19 (3.36)	5.47 (6.05)	0.02		

Data are expressed as mean \pm SD or number and proportion. Multivariate analysis was calculated for the conservative treatment.

preferred technique for children.

Conservative treatment for acute appendicitis in Northern Italy is still a neglected option, with only 5% of patients treated not operatively; however, over the period of study there was a small increase in the proportion of patients treated conservatively. Despite the small number, conservative treatment seems to be an effective treatment option, showing a reduced length of stay and, notwithstanding an overall relapse rate of 23%, a similar cumulated length of stay and number of hospital admissions during the study period, with a clinically not significant difference (Figure 4). Conservative treatment, as shown in Figure 5, fails after a median of 32 d and leads to an operative treatment in the majority of cases. Factors involved in the choice of this approach are represented by the comorbidities of the patient and the year of treatment, showing that this option is slowly spreading, but still depends on the surgeon's preference. Conservative treatment resulted in 77% reduction of surgical procedures for appendicitis during the study period, maintaining a similar length of stay; moreover, appendectomy exposes patients to the risk of intestinal obstruction due to adhesions in 0.7%-10.7%^[25-27]: In our group of patients, 1.3% of the patients needed a further hospitalization due to bowel obstruction after a median of 11 mo and required a further surgical operation in 60% of cases. Laparoscopic appendectomy has been shown to reduce the risk of intestinal obstruction^[28] and our results confirm this evidence, although the clinical effect is not significant (Table 2). A cost-effectiveness study demonstrated that conservative treatment, with a failure rate of less than 40% is more cost effective than operative management: Our results on a large population study during a long period show that treating a patient with acute appendicitis conservatively could be considered the better treatment option.

The study was performed retrieving data from an administrative register that allows for a long-term follow up for each patient included; unfortunately,

administrative registries do not include data about histopathological diagnosis. Moreover, figures about failure of conservative treatment could be slightly underestimated, considering the lack of data about the immediate failure during the first hospital admission.

In conclusion the treatment of acute appendicitis in Northern Italy is slowly changing, with the large diffusion of laparoscopic approach; conservative treatment of non-complicated appendicitis is still a neglected option, but full of promising results.

COMMENTS

Background

Acute appendicitis is the commonest surgical emergency. Despite appendectomy is considered the definitive treatment there is great interest in the conservative management.

Research frontiers

Epidemiology and treatment of acute appendicitis.

Innovations and breakthroughs

The study outlines the current epidemiology of acute appendicitis giving an overview on the state of the art of the treatment's choice in the daily clinical practice.

Applications

The study gives the state of the art of the treatment of acute appendicitis and its changes during the last years.

Terminology

Conservative treatment: Medical therapy based on antibiotics administration.

Peer-review

This is a well-written article with good statistical analysis.

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Retrospective Study

Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula

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Author contributions: Liu MY and Hu SH carried out the studies and data analyses; Liu MY drafted the manuscript; Chang SJ supervised the procedure, provided significant advice and revised the manuscript; Tang HC developed the protocol, cared the patients, provided advice and revised the manuscript; Hu SH collected the data and provided nutrition care; all of the authors have read and approved the final manuscript; Liu MY and Hu SH contributed equally to this work.

Institutional review board statement: The study was eligible for a determination of “exempt review” status by the ethics committee of the Tainan Sin-Lau Hospital (Grant No. SLH919-02).

Informed consent statement: A retrospective study was deployed to investigate the effects of a dipeptide- and tripeptide-based enteral formula. Patients were screened from the ICU database, therefore we did not seek informed consent. Acquisition of patient data and its subsequent use were approved by the ethics committee of the Tainan Sin-Lau Hospital (Grant No. SLH919-02). Patient information was anonymized and de-identified prior to analysis.

Conflict-of-interest statement: No conflicts of interest to declare.

Data sharing statement: No additional data are available.

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Abstract**AIM**

To compare a dipeptide- and tripeptide-based enteral formula with a standard enteral formula for tolerance and nutritional outcomes in abdominal surgery patients.

METHODS

A retrospective study was performed to assess the differences between a whole-protein formula (WPF) and a dipeptide- and tripeptide-based formula (PEF) in clinical outcomes. Seventy-two adult intensive care unit (ICU) patients with serum albumin concentrations less

than 3.0 g/dL were enrolled in this study. Patients were divided into two groups (WPF group = 40 patients, PEF group = 32 patients). The study patients were fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days.

RESULTS

The mean serum albumin level on postoperative day (POD) 10, prealbumin levels on POD-5 and POD-10, and total lymphocyte count on POD-5 were significantly higher in the PEF group compared to those in the WPF group ($P < 0.05$). The average maximum gastric residual volume of the PEF patients during their ICU stays was significantly lower than that for WPF patients.

CONCLUSION

Dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas.

Key words: Dipeptides and tripeptides; Enteral nutrition; Abdominal surgery; Gastric residual volume; Absorption

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Core tip: Few trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients. The results of the present study suggest that dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas and could shorten the intensive care unit stays of malnourished abdominal surgery patients.

Liu MY, Tang HC, Hu SH, Chang SJ. Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula. *World J Gastrointest Surg* 2016; 8(10): 700-705 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/700.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.700>

INTRODUCTION

Malnutrition is a common finding in critically ill patients. Enteral nutrition is a preferred means of support for stimulating gut hormones, modulating immunity, and maintaining the barrier function of the intestinal mucosa. However, malabsorption, poor emptying, and hypoalbuminemia often occur in patients given enteral nutrition.

Proteins are hydrolyzed to small peptides in the intestines, which are then efficiently absorbed through a variety of specific transport mechanisms, as has been previously described^[1]. Some investigators have reported that peptide-based enteral diets are associated with better protein responses and less diarrhea compared to

intact-protein diets^[2,3]. On the other hand, others have reported that peptide-based formulas seem to offer no benefits over intact-protein diets in acutely injured, hypoalbuminemic patients^[4]. However, while previous studies have described the small peptide formulas, no particular dipeptide- or tripeptide-based formulas have been investigated.

Studies have demonstrated that dipeptides and tripeptides are the major products of proteins that are absorbed. Proteins are hydrolyzed in the intestines to small peptides, which are then efficiently absorbed through specific transport mechanisms. The major mechanism for absorption of the dipeptides and tripeptides of protein digestion products across the brush border is absorption through proton-coupled oligopeptide transporters (POTs)^[5-11]. Dietary proteins are converted into large peptides by gastric and pancreatic proteases in the gastrointestinal lumen and then undergo further hydrolysis into small peptides (80%) and free amino acids (20%) by various peptidases in the brush border membrane of the intestinal epithelium^[12]. Previously, Yoshihara *et al.*^[13] studied the absorption of a 100% free amino acids formula, a 60% dipeptides and tripeptides with 40% free amino acids mixture, a 100% dipeptides and tripeptides mixture, and a lactalbumin mixture. Absorption was evaluated by calculating the area under the curve of amino acid concentration in portal vein plasma of rats for 120 min after administration of each nitrogen source^[13]. The results indicated that the absorption was maximal upon administration of the nitrogen source when the 60% dipeptides and tripeptides with 40% free amino acids mixture was used.

Few clinical trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas. In our hospital, however, critically ill patients in the intensive care unit (ICU) began receiving such a formula from July 2015. The aim of this study, then, was to compare this dipeptide- and tripeptide-based enteral formula with a standard enteral formula in terms of tolerance and nutritional outcomes in abdominal surgery patients.

MATERIALS AND METHODS

Patients

A retrospective study was deployed to investigate the effects of a dipeptide- and tripeptide-based enteral formula. Patients screened from the ICU database for abdominal surgery with serum albumin concentrations less than 3.0 g/dL were included in the study. The patients who received dipeptide- and tripeptide-based enteral formula from July 2015 to December 2015 were classified as the dipeptide- and tripeptide-based formula (PEF) group. Other patients who were fed a whole-protein formula were classified as the WPF group. These patients were generally included the study, although any patients with renal failure, hepatic

failure, or who required parenteral nutrition intervention were excluded. This study was approved by the ethics committee of Tainan Sin-Lau Hospital (Grant No. SLH 919-02). Patient information was anonymized and de-identified prior to analysis.

Enteral nutrition care

Patients in both groups received the same feeding protocol, when they were transferred to the ICU. Each patient received 18 kcal per kilogram of body weight on postoperative day (POD-) 1, 23 kcal on POD-3, and 28 kcal on POD-7. The patients were fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days. The composition of the WPF (Osmolite HN, Abbott Laboratories) was 16.7% of protein, 54.3% of carbohydrate, and 29.0% of lipid. The composition of the PEF (Twinline, Otsuka Pharmaceutical Co, Ltd) was 16.0% of protein, 59.0% of carbohydrate, and 25.0% of lipid. The WPF contained only whole proteins (*e.g.*, calcium-potassium caseinate), whereas the protein source of the PEF (from enzymatically hydrolyzed milk protein) consisted of amino acids and peptides with molecular weights < 500 Da (approximately 78%), peptides with molecular weights between 500 and 1000 Da (approximately 15%), and peptides with molecular weights between 1000 and 3000 Da (approximately 7%).

On POD-1 with stable hemodynamic status, the full-strength diet was administered at 30 mL/h through a naso-gastric (NG) tube or *via* percutaneous endoscopic gastrostomy (PEG) feeding tubes, with the rate increasing as tolerated to a goal of 75-100mL/h. A gastric residual volume (GRV) of over 150 mL was the threshold for suspension of feeding^[14], which was followed by re-evaluation to reduce the feeding rate 2 h later. The GRV was calculated every 4 h by refractometry (Model N.O.W. 507-1; Nippon Optical Works, Tokyo, Japan) during each patient's stay in the ICU. A refractometer measures the "total soluble solids in solution" and a Brix value (BV) is assigned to the liquid. We examined the BV in order to measure the actual GRV^[15,16]. The GRV was recorded when volumes exceeded 150 mL. At such times, feeding of the patient was suspended for re-evaluation and reduction of the feeding rate 2 h later. No prokinetic drugs were used within 10 d in both groups.

Data collection

Demographic data obtained at the start of the study included gender, age, body mass index (BMI), APACHE II score, and major diagnoses. Additional data including the length of stay in the ICU, total enteral volume, GRV, and the prevalence of diarrhea were also collected for this study. The occurrence of diarrhea was defined as greater than three loose stools per day or greater than 300 mL/d. Serum albumin, prealbumin, C-reactive protein (CRP) and total lymphocyte count (TLC) were measured at baseline, day 5, and day 10.

Table 1 Comparison of demographic and clinical characteristics between the whole-protein formula group and the dipeptide- and tripeptide-based formula group

	WPF group	PEF group	P-value
<i>n</i>	40	32	
Gender (Male/Female)	23/17	19/13	0.873
Feeding route (PEG ¹ /NG ²)	2/38	3-29	0.468
Major diagnoses			
Esophageal cancer	4	5	0.473
Colon cancer	22	16	0.673
Gastric cancer (subtotal gastrectomy)	2	3	0.468
Bile duct cancer	4	2	0.567
Ischemic bowel	8	6	0.894
Age	67.5 \pm 10.5	64.7 \pm 10.1	0.263
APACHE II score	11.6 \pm 2.3	12.4 \pm 2.6	0.201
Ventilator dependence, <i>n</i> (%)	15 (37.5)	13 (40.6)	0.787
Body mass index	22.3 \pm 2.1	21.9 \pm 2.2	0.398

¹Percutaneous endoscopic gastrostomy; ²Naso-gastric tube. Values are presented as number of patients or mean \pm SD. WPF: Whole-protein formula; PEF: Dipeptide- and tripeptide-based enteral formula.

Statistical analysis

Data were analyzed using SPSS version 12.0 (SPSS, Inc). The differences between the two groups were analyzed by Student's *t*-test. Data are presented as mean \pm SD. χ^2 analysis was used for comparisons of the proportions of subjects in the two groups. A *P*-value < 0.05 was considered significant.

RESULTS

Study population

A total of 86 abdominal surgery patients with serum albumin concentrations less than 3.0 g/dL were identified who were admitted to the ICU during the study period. Seven of these 86 patients developed renal failure, one patient developed hepatic failure, and 6 patients required parenteral support; these 14 patients (WPF group = 6 patients, PEF group = 8 patients) were excluded from the study. The remaining 72 patients were divided into two groups (WPF group = 40 patients, PEF group = 32 patients), and the patient characteristics of the two groups are provided in Table 1. Colon cancer was the most common major diagnosis in both groups. Most colonic surgery patients can resume oral intake on POD-1. Some colon cancer patients were elderly, confused and had comorbid diseases such as diabetes, heart disease, and chronic obstructive pulmonary disease; thus they could not resume oral intake on POD-1. Therefore, we used an NG tube for intervention. There were no significant differences between the two groups in terms of age, APACHE II score, ventilator dependence, and BMI (Table 1).

Serum albumin, prealbumin, TLC and CRP

The patients were fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days. On

Table 2 Differences in nutritional status between the whole-protein formula group and the dipeptide- and tripeptide-based formula group

	WPF group	PEF group	P-value
Albumin (g/dL)			
POD ¹ -1	2.59 ± 0.21	2.57 ± 0.19	0.652
POD-5	2.60 ± 0.26	2.68 ± 0.28	0.198
POD-10	2.70 ± 0.30	2.89 ± 0.27	0.010
Prealbumin (mg/dL)			
POD-1	11.1 ± 1.4	10.6 ± 1.3	0.201
POD-5	11.6 ± 1.2	12.8 ± 2.1	0.006
POD-10	12.9 ± 1.7	15.1 ± 1.5	< 0.001
TLC ² (cell/mm ³)			
POD-1	1069 ± 135	1077 ± 148	0.801
POD-5	1082 ± 149	1192 ± 168	0.012
POD-10	1231 ± 162	1311 ± 182	0.052
CRP ³ (mg/L)			
POD-1	43.7 ± 7.8	43.0 ± 9.4	0.742
POD-5	32.7 ± 4.9	33.4 ± 5.2	0.824
POD-10	19.7 ± 5.0	18.5 ± 5.4	0.416

¹Postoperative day; ²Total lymphocyte count; ³C-reactive protein. Values are presented as mean ± SD. WPF: Whole-protein formula.

POD-1 with stable hemodynamic status, a full-strength enteral formula (1.0 kcal/mL) was administered through NG or PEG. The prealbumin levels and TLCs were similar between the two groups on POD-1. There was also no significant difference between the serum albumin levels on POD-1 and POD-5 for the two groups, but the level for the PEF group was significantly higher than that of the WPF group on POD-10 (2.89 ± 0.27 vs 2.70 ± 0.30 , $P = 0.01$; Table 2). Prealbumin levels on POD-5 and POD-10 were significantly higher in the PEF group than in the WPF group ($P < 0.01$). The TLC of the PEF group was higher than that of the WPF group on POD-5, but there was no significant difference on POD-10. In critical patients protein parameters depend on inflammation. We checked the CRP levels, and there was no significant difference between the two groups.

Clinical outcomes

The prevalence of suspended feeding due to high gastric residuals and maximum caloric intake during ICU stay was similar between the two groups (Table 3). The average maximum GRV for the PEF group patients during their ICU stays was significantly lower than that for the WPF group (Table 3). There was no significant difference between the groups in terms of the caloric intake on POD-5, but the average intake for the PEF group on POD-10 was higher than that of the WPF group. There was no significant difference between the two groups in terms of the prevalence of diarrhea and pneumonia. The average length of stay in the ICU for the PEF group was 6.2 ± 0.8 d, which was significantly shorter than that for the WPF group (6.8 ± 1.5 d).

DISCUSSION

Providing enteral nutrition care for critically ill patients is challenging in general, but it is even more difficult to

Table 3 Clinical outcomes for the whole-protein formula group and the dipeptide- and tripeptide-based formula group

	WPF group	PEF group	P-value
Length of stay in the ICU ¹ (d)	6.8 ± 1.5	6.2 ± 0.8	0.047
Maximum caloric intake during ICU stay (kcal/kg)	22.5 ± 1.9	23.2 ± 2.4	0.063
Caloric intake (kcal/kg body weight/d)			
POD ² -5	20.7 ± 2.3	21.5 ± 1.7	0.116
POD-10	23.5 ± 2.4	25.1 ± 2.9	0.010
Maximum GRV ³ during ICU stay (mL)	183.6 ± 88.0	138.0 ± 63.9	0.016
Prevalence of suspended feeding due to high GRV (%)	21.8	15.2	0.071
Prevalence of diarrhea (%)	19.9	13.2	0.056
Prevalence of pneumonia (%)	5	3.1	0.692

¹Intensive care unit; ²Postoperative day; ³Gastric residual volume. Values are presented as mean ± SD. WPF: Whole-protein formula.

provide such care for abdominal surgery patients. In this study, except the enteral formulas used, the care received by the two groups of patients was the same. Both groups of patients would be unable to achieve their caloric intake goals under normal circumstances. As noted above, there were no significant differences between the two groups in terms of their average caloric intakes and rates of diarrhea and pneumonia complications. The average maximum GRV recorded for each patient during ICU stay among the WPF group patients was higher than that among the PEF group patients, but there was no significant difference between the two groups in terms of the prevalence of suspended feeding due to high GRV ($P = 0.071$). It was easy and effective to calculate GRV values by refractometry. More specifically, BV measurements and the following equation were used: $(GRV \times \text{pre-dilution BV}) = (GRV + 30 \text{ mL water}) \times \text{post-dilution BV}$. We accurately grasped the GRV values to avoid the risk of aspiration pneumonia and to assess the digestion conditions. The dipeptide- and tripeptide-based enteral formula seemed to have been efficiently absorbed and resulted in better prealbumin, albumin (POD-10), and TLC (POD-5) levels in the PEF group, in addition to shortening the ICU stay. Prealbumin is a rapid-turnover protein (half-life < 48 h), which is a more sensitive indicator to assess the nutritional status than albumin (half-life 21 d). When patients' nutrition is improved, the serum prealbumin will increase rapidly (POD-5 and 10).

Four members of the POT superfamily have previously been identified, namely, PepT1 (SLC15A1), PepT2 (SLC15A2), PHT1 (SLC A4), and PHT2 (SLC A3). In humans, PepT1 expressed in the small intestine epithelium is involved in the absorption of nutritional peptides^[17,18]. Previously, the effects of PepT1 activity on a variety of pathological conditions have been studied. Ziegler *et al.*^[19] found that patients with short-bowel syndrome may experience up-regulation of the expression of colonic PepT1 adapted to malabsorption of dipeptides and

tripeptides, independent of changes in the mucosal surface area. In other studies, intestinal villous atrophy due to prolonged fasting was investigated in fasting animals, and it was observed that PepT1 expression increased during metabolic fasting phases^[20,21]. Ogiwara *et al.*^[22] showed that 4 d of starvation markedly increased the PepT1 in the jejunum, while a study by Ihara *et al.*^[23] demonstrated that starvation for 4 d and semistarvation for 10 d increased PepT1 mRNA and protein in the rat jejunum. That the cell population of PepT1 is increased in starvation may explain these results of earlier studies. In a study by Vazquez *et al.*^[24] this increase was expected to reduce the absorption of amino acids in human volunteers' jejunum after 14 d of hunger. In fact, while the absorption of amino acids was decreased, surprisingly, no significant change in the absorption of peptides was observed. In the present study of malnourished abdominal surgery patients, we conjectured that the patients' PepT1 levels would result in an increase in the absorption of dipeptides and tripeptides.

A randomized trial by Heimbürger *et al.* demonstrated that 10 d of feeding with a small-peptide diet produced slightly greater increases in serum rapid-synthesis proteins than did a whole-protein diet, especially between days 5 and 10^[25]. Our study found a similar result. The PEF group patients received the dipeptide- and tripeptide-based enteral feeding formula, and this formula was more efficacious and better tolerated than the whole-protein formula received by the patients in the other group. The present study suggests that 7 d of feeding of the dipeptide- and tripeptide-based enteral feeding formula may benefit a patient's nutritional status. Peptide formulas, however, are more expensive than whole-protein formulas, costing approximately five times more. More specifically, feeding a patient for 7 d with a peptide formula rather than whole-protein formula will cost roughly \$140 more. The mean cost of ICU is \$350 per day in Taiwan. However, peptide formulas seem to shorten the average ICU stay by about one day, and this should be factored into overall consideration of the cost and quality of care.

There were no significant differences in the prevalence of GRV, diarrhea, and pneumonia complications between the two groups, but the PEF group did exhibit a lower tendency for GRV and diarrhea than the WPF group. Two limitations of this study were its retrospective study design and low number of admitted patients. Well-designed clinical trials are needed to survey the efficacy, tolerance, and cost effectiveness of using dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients.

In conclusion, the results of the present study suggest that dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas and could shorten the ICU stays of malnourished abdominal surgery patients.

intolerance often occurs in these patients. Few trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients. The aim of this study, then, was to compare this dipeptide- and tripeptide-based enteral formula with a standard enteral formula in terms of tolerance and nutritional outcomes in abdominal surgery patients.

Research frontiers

The previous studies have described the small peptide formulas, but no particular dipeptide- or tripeptide-based formulas have been investigated.

Innovations and breakthroughs

The dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas, which shortened intensive care unit stay by about one day.

Applications

Early initiation of feeding with a dipeptide- and tripeptide-based enteral formulas for 7 d is a feasible approach in malnourished abdominal surgery patients.

Peer-review

This study is acceptable and very useful.

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COMMENTS

Background

Early enteral nutrition in critically ill patients is important, however, gut

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Clinical Trials Study

Phase II study of docetaxel, cisplatin and capecitabine as preoperative chemotherapy in resectable gastric cancer

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Abstract

AIM

To investigate the feasibility of preoperative docetaxel, cisplatin and capecitabine (DCC) in patients with resectable gastric cancer.

METHODS

Patients with resectable gastric cancer fulfilling the inclusion criteria, were treated with 4 cycles of docetaxel (60 mg/m², cisplatin (60 mg/m²) and capecitabine (1.875 mg/m² orally on day 1-14, two daily doses) repeated every three weeks, followed by surgery. Primary end point was the feasibility and toxicity/safety profile of DCC, secondary endpoints were pathological complete resection

rate and pathological complete response (pCR) rate.

RESULTS

All of the patients (51) were assessable for the feasibility and safety of the regimen. The entire preoperative regimen was completed by 68.6% of the patients. Grade III/IV febrile neutropenia occurred in 10% of all courses. Three patients died due to treatment related toxicity (5.9%), one of them (also) because of refusing further treatment for toxicity. Of the 45 patients who were evaluable for secondary endpoints, four developed metastatic disease and 76.5% received a curative resection. In 3 patients a pCR was seen (5.9%), two patients underwent a R1 resection (3.9%).

CONCLUSION

Four courses of DCC as a preoperative regimen for patients with primarily resectable gastric cancer is highly demanding. The high occurrence of febrile neutropenia is of concern. To decrease the occurrence of febrile neutropenia the prophylactic use of granulocyte colony-stimulating factor (G-CSF) should be explored. A curative resection rate of 76.5% is acceptable. The use of DCC without G-CSF support as preoperative regimen in resectable gastric cancer is debatable.

Key words: Gastric cancer; Preoperative chemotherapy; Docetaxel; Capecitabine

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Core tip: The use of the combination of docetaxel, cisplatin and capecitabine in resectable gastric cancer has resulted in a high curative resection rate of 77%, although it also resulted in a high rate of febrile neutropenia, and in treatment related mortality.

Dassen AE, Bernards N, Lemmens VEPP, van de Wouw YAJ, Bosscha K, Creemers GJ, Pruijt HJFM. Phase II study of docetaxel, cisplatin and capecitabine as preoperative chemotherapy in resectable gastric cancer. *World J Gastrointest Surg* 2016; 8(10): 706-712 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/706.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.706>

INTRODUCTION

Although declining, gastric cancer is still ranking in the top 5 of incidence and mortality rates of malignancies in Europe^[1]. Loco-regional and metastatic recurrence rates are high and prognosis remains poor, with a 5-year survival rate of 20%-31% for stage I -III disease^[2]. Surgery is still the cornerstone of treatment for gastric cancer, although survival can be improved by adding perioperative treatment. In 2006, the results of the MAGIC trial were published showing that perioperative chemotherapy with epirubicin-cisplatin-5-fluorouracil

(FU) (ECF) improved survival compared to surgery alone (5-year survival 36% vs 23%, respectively). Although most patients assigned to the perioperative chemotherapy tolerated the preoperative chemotherapy well, only 55% of them started the postoperative chemotherapy due to postoperative complications with only 42% of the patients completing the entire regimen^[3]. These results demonstrate the problems encountered with the perioperative approach, *i.e.*, many patients do not complete the full number of post-operative chemotherapy cycles.

In an attempt to increase efficacy and tolerability of chemotherapy regimen in gastric cancer other cytotoxic agents have been explored. The combination of docetaxel, cisplatin and fluorouracil has shown to be effective in advanced gastric cancer with reported overall response rates of 37%-43% and an acceptable safety profile^[4-6]. Capecitabine, an orally substitute of 5-FU, offers a clear advantage in terms of convenience and safety without compromising efficacy^[7]. The combination of cisplatin and capecitabine showed an overall response rate of 46%-54.8% in advanced gastric cancer^[8,9]. In addition, in a phase II study using preoperative docetaxel, capecitabine and cisplatin in initially locally advanced unresectable gastric cancer a R0 resection could still be achieved in 63% of the patients with an acceptable toxicity (febrile neutropenia 4%, no treatment related mortality)^[10].

Taking these promising results into consideration we decided to conduct a one arm phase II trial investigating the feasibility of 4 cycles of preoperative chemotherapy with docetaxel, cisplatin and capecitabine in patients with resectable gastric cancer, followed by a standardized gastric resection and lymphadenectomy.

MATERIALS AND METHODS

Patient selection

Inclusion criteria were histologically proven gastric cancer [including gastro-oesophageal junction/cardia carcinoma (Siewert 2 and 3^[11])], stage I b-IVa (6th TNM classification), WHO performance state 0-1, age \geq 18 years and adequate hematologic, renal and hepatic function. All patients signed an informed consent and were expected to comply with treatment, management of toxicity and scheduled follow-up. Exclusion criteria were non-resectability, previous or current malignancies, other serious illness or medical conditions, known hypersensitivity to any of the chemotherapies used, contraindication for the use of corticosteroids, use of immunosuppressive or antiviral medication, and pregnant or lactating women. A certified ethics committee (METOPP) and the institutional review board at each centre approved the protocol. Screening included a history and physical examination, structural assessment of malnutrition, oesophagoduodenoscopy, blood sampling and CT scan of the chest and abdomen. Evaluation CT-

Table 1 Patient characteristics at baseline

Characteristics	No. of patients	%
Age, yr		
Median	64	
Range	34-84	
Age, category		
< 50 yr	5	9.8
50-59 yr	8	15.7
60-69 yr	22	43.1
70-79 yr	15	29.4
> 80 yr	1	2
Sex		
Male	36	70.6
Female	15	29.4
WHO performance status ¹		
0	37	72.5
1	13	25.5
2	1	2
Clinical T stage ²		
T1	5	9.8
T2	12	23.5
T3	21	41.2
T4	2	3.9
Unknown	11	21.6
Clinical N stage ²		
N0	16	31.4
N1	19	37.3
N2	4	7.8
N3	2	3.9
Unknown	10	19.6

¹WHO: World Health Organization; ²TNM classification.

scans were performed after the second and fourth cycle of chemotherapy.

Treatment

Chemotherapy: Preoperative chemotherapy was administered for four cycles. Based on the described by Sym *et al.*^[10], each 3-wk cycle consisted of docetaxel 60 mg/m² IV infusion and cisplatin 60 mg/m² IV infusion on day 1, and capecitabine 1.875 mg/m² orally on days 1-14 divided into two daily doses (DCC). Prior to each cycle a full physical examination was performed, and a full blood count and chemistry was obtained. The neutrophil count had to be $\geq 1.5 \times 10^9/L$ and the platelet count $\geq 100 \times 10^9/L$. Dose reductions and delays were predefined for granulocytopenia, thrombocytopenia, and non-hematological toxicity. Secondary use of growth factors was not part of the protocol. Any adverse event was collected and registered according to Common Toxicity Criteria (CTC, version 3). A serious adverse event (SAE), defined as an event that is either fatal, life-threatening, requiring or prolonging hospitalization or resulting in persistent or significant disability or incapacity, was reported to the study coordination centre, and evaluated by the principle investigators. Furthermore, these SAE's were reported to the central medical ethics committee.

Surgery and pathology: Patients were scheduled for surgery approximately four to six weeks after the

last cycle of chemotherapy. A (partial) gastric resection and a standardized lymphadenectomy, the so-called D1extra lymphadenectomy specified to tumour location was performed by a local surgeon specialized in gastrointestinal surgery, assisted by a surgeon of the study team. The D1extra lymphadenectomy is a newly defined dissection in which lymph node stations 1-10 and/or 12 (according to the Japanese Classification^[12]) prone to metastases^[13] are removed.

Evaluation and outcome

The primary endpoint of this feasibility study was the toxicity and safety profile of 4 courses of DCC in patients diagnosed with primary resectable gastric cancer. The secondary endpoint of this study was the determination of pathological complete response (pCR) and pathological resection rate (R0). The results, *e.g.*, numbers and proportions of patients reaching the primary and secondary endpoints, will be evaluated using describing statistical analyses.

RESULTS

Patient characteristics

Between November 2008 and November 2012, 53 patients from five participating hospitals were included in the study. Two patients were classified by the monitoring committee as having distal oesophageal cancer instead of gastric cancer and were therefore excluded from the study. In Table 1 the patient characteristics are outlined. The median age was 64 years (range 34-84), and 75% of the patients exhibited an WHO performance state of 0. One patient having a WHO performance state of 2, as re-assessed later on, was not excluded because of an intention-to-treat protocol.

Feasibility

All 51 patient started preoperative chemotherapy. In total, 35 patients completed 4 cycles of chemotherapy (68.6%). In Table 2 the feasibility results are outlined. A total of 169 cycles of chemotherapy were administered. The percentage of intended dose delivered in the intention-to-treat group was 78%-79% for each drug, calculated as the percentage of dose delivered in patients eligible for chemotherapy (deceased patients were excluded). Reasons for dose reduction and discontinuation were treatment related toxicity, including two deaths and a tumour related bleeding in two patients (Figure 1).

Safety

All patients were evaluable for safety. Grade III/IV toxicity is summarized in Table 3. The most common grade III/IV toxicity was febrile neutropenia and diarrhea occurring in 10.1% and 9.5% of the cycles, in respectively 31% and 25% of patients. There were 3 chemotherapy related deaths, resulting in a mortality rate of 5.9%. In two patients, treatment-related death

Table 2 Feasibility: Treatment cycles delivered

	No. of patients	%
Cycles received		
1	51	100
2	44	86.3
3	39	76.5
4	35	68.6
Percentage of intended dose delivered (per evaluable patient, IIT) ¹		
Docetaxel		78.90
Cisplatin		78.70
Capecitabine		78.30
Percentage of intended dose delivered in patients receiving 4 courses (<i>n</i> = 34)		
Docetaxel		92.90
Cisplatin		92.90
Capecitabine		91.60

¹IIT: Percentage of dose delivered of all four courses divided by the amount of patients who could have received the full course.

was infection concomitant with grade III/IV neutropenia. One patient died after refusing further therapy of an initially successful treatment of febrile neutropenia.

Efficacy

Of the remaining 48 patients, 3 patients were considered non-evaluable for the secondary endpoints because of major protocol violation (one patient was operated one year after completion of the preoperative regimen due to myocardial infarction, one patient switched to another chemotherapy regimen, and one patient was operated in a non-participating hospital). Of the remaining 45 patients 39 patients underwent a R0 resection. Two patients developed distant metastases assessed prior to surgery, two patients had peritoneal carcinomatosis diagnosed during explorative surgery and two patients had a R1 resection. Thus, 76.5% of the intention to treat population and 86.7% of the evaluable patients had a R0 resection with curative intend. The surgical results are described elsewhere. A pCR was reported in 3 patients (5.9%).

DISCUSSION

Overall survival of gastric cancer after a curative resection can be improved with perioperative chemotherapy as shown in the MAGIC trial. The additional benefit of perioperative ECF on survival is probably for the larger part attributed to the preoperative part of the treatment^[3]. Postoperative chemotherapy in this patient category is challenging since a high percentage of the patients is not fit enough or willing to start and complete the full postoperative part of the regimen^[3]. To improve the adherence and increase the benefit of preoperative chemotherapy in resectable gastric cancer we designed this phase II study investigating the feasibility of a preoperative regimen of four cycles of docetaxel, cisplatin and capecitabine. To increase

Table 3 Grade 3-4 adverse events related to chemotherapy

Toxicity	No of patients	%	No of cycles	%
Hematologic				
Anemia	3	5.9	3	1.8
Neutropenia	25	49	32	18.9
Febrile neutropenia	16	31.4	17	10.1
Non-Hematologic				
Gastro-intestinal				
Anorexia	8	15.7	10	5.9
Constipation	1	2	1	0.6
Diarrhea	13	25.5	16	9.5
Dysphagia	1	2	1	0.6
Mucositis	6	11.8	6	3.6
Nausea	5	9.8	5	2.9
Vomiting	5	9.8	8	4.7
Constitutional				
Fatigue	4	7.8	4	2.4
Hand-foot syndrome	4	7.8	6	3.6
Neurosensory				
Hearing impairment	1	2	1	0.6
Neuropathy	2	3.6	2	1.2
Renal impairment	3	5.9	3	1.8

the efficacy of the preoperative regimen, we replaced epirubicin by docetaxel, since docetaxel containing combination regimens have shown to be feasible and have good response rates in locally-advanced and metastatic gastric cancer^[4-6]. In our trial however, four courses of DCC as a preoperative regimen showed to be highly demanding for patients with primarily resectable gastric cancer. Only sixty-eight percent of the patients completed all 4 cycles of DCC, the other patients discontinued mainly due to treatment related toxicity. In comparison with results from other trials this percentage is rather low. In a German phase II trial investigating the same regimen as perioperative chemotherapy, with a higher dosage of docetaxel of 75 mg/m², 94% completed all three preoperative cycles^[14]. In the MAGIC trial, 86% completed the intended three preoperative cycles of ECF^[3]. In a French trial the rate of patients completing two cycles of preoperative chemotherapy was 87%^[15], while in an Italian study the rate of completing 4 preoperative docetaxel based cycles was 74%^[16]. Four cycles of preoperative DCC chemotherapy, therefore, might be too demanding whereas 86% and 76% of the patients in our study completed 2 and 3 cycles respectively which is comparable to the results described above. On the other hand, completing postoperative chemotherapy is even more difficult. In the aforementioned Italian study feasibility of preoperative chemotherapy was compared to the feasibility of the same regimen as postoperative chemotherapy. The rate of completing 4 postoperative cycles was 34% in this arm^[16]. In the previous mentioned German and MAGIC trials only 53% and 42% respectively completed the postoperative scheme^[3,14]. Although the rate of completing all 4 cycles was relatively low in our study, the intended delivered dose was reasonable with percentages of 78 for all drugs individually^[7,14]. Accurate

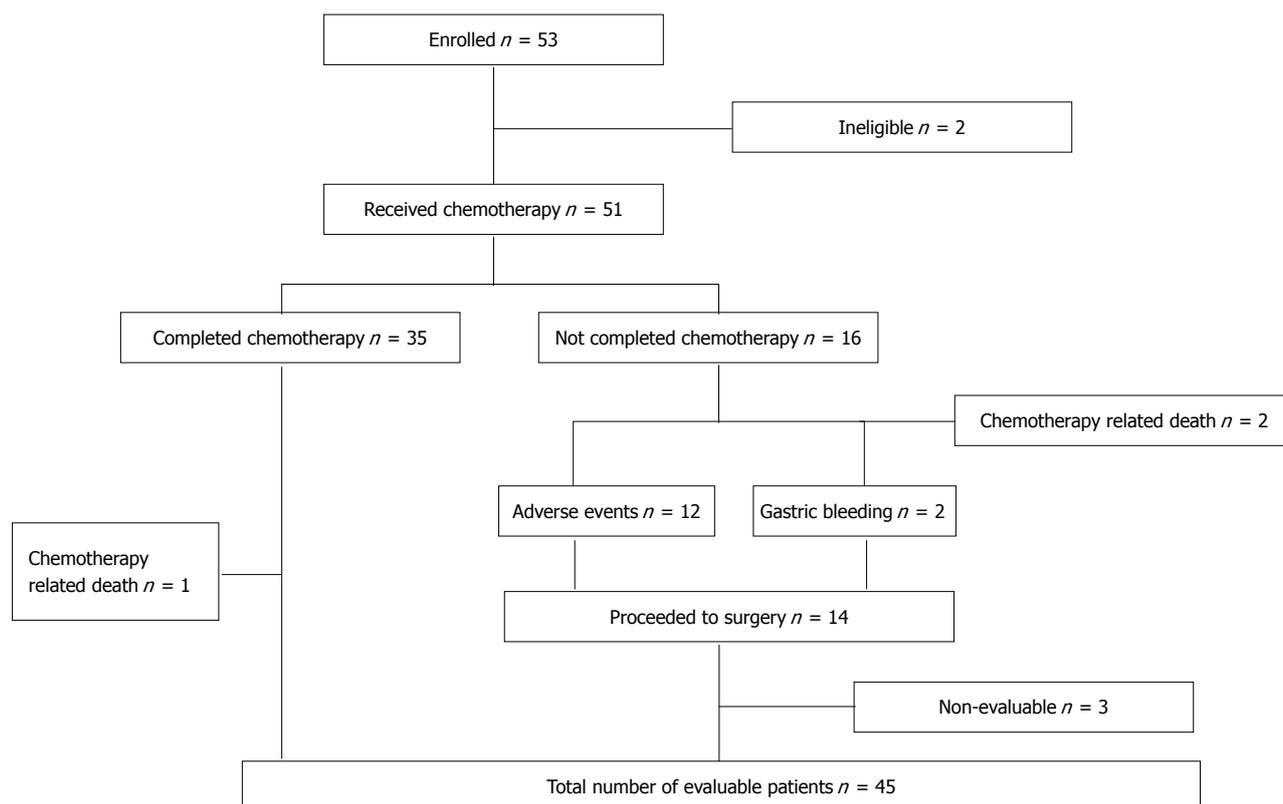


Figure 1 Flow diagram of enrolled patients.

monitoring and early intervention in case of deterioration is imperative to prevent a high amount of patients failing to complete a full chemotherapy regimen.

Treatment related mortality was 5.9% being comparable to mortality rates reported in literature (0%-6%)^[4,5,7,17]. Febrile neutropenia occurred in 10% of all cycles (vs 2%-15% found in other trials^[4,5]), being the cause of death of at least two of three patients. The prophylactic or secondary use of G-CSF was not part of the protocol as no data were available at the time of the study design about the interaction between G-CSF and capecitabine in case of simultaneous administration. In theory, the proliferative activity of bone marrow after the administration of G-CSF might increase the myelotoxicity of capecitabine. In literature, only scarce data are known about the simultaneous use of G-CSF and capecitabine. In a phase II trial in breast cancer, the use of pelfilgastrim was evaluated in a small subset of patients receiving docetaxel and capecitabine based chemotherapy regimen. Minimal grade III/IV neutropenia and no febrile neutropenia was observed^[18]. In one phase II trial in metastatic gastric cancer with a comparable DCC regimen as in our study, patients were treated successfully with G-CSF in case of febrile neutropenia and no toxicity related deaths were reported^[19]. The use of G-CSF as primary or secondary prophylaxis for (febrile) neutropenia in a docetaxel and capecitabine based chemotherapy scheme is therefore promising, and should be further investigated.

Other main toxicities we encountered were grade

III/IV hand-foot syndrome, diarrhea and anorexia. The rate of hand-foot syndrome of 7.8% in this study is acceptable compared to other studies^[7-10,17]. Many patients with gastric cancer experience difficulties with eating. With addition of the toxicity of chemotherapy gastric cancer patients are prone to anorexia and weight loss. It is therefore imperative to monitor their intake and weight to be able to act in time when this is deteriorating. A dietician should be consulted and enteral feeding should be started in an early phase^[20].

In gastric cancer, clinical tumour staging faces several difficulties. The current imaging modalities have low sensitivity rates for T- and N-stage^[21]. It is therefore difficult to clinically assess the efficacy of chemotherapy in these patients. In literature, many modalities have been used to determine response rate^[4,7,15], which makes it difficult to compare ORRs. In our study, we therefore only determined pathological response rate. A pCR was found in 3 patients (5.9%) which is lower than expected looking at other studies investigating DCF or DCC in gastric cancer in which pCRs of 6.1%^[10], 11.7%^[16] and 13.7%^[14] are reported. On the other hand, in the MAGIC trial using ECF as a treatment regimen no pCR was seen^[3].

Thirty-nine (76.5%) patients received a R0 resection. This is in line with rates found in the MAGIC trial (69.3%)^[3], although it is lower compared to other trials using a docetaxel based regimen in which a R0 resection was achieved in 84%^[15], 85%^[16], and 90.2%^[14] of patients. The long-term effects of this docetaxel based

scheme and protocolized D1extra lymphadenectomy have to be awaited.

In conclusion, in our study the benefits defined as R0 resection and complete pathological response rates of four cycles of DCC are lower than expected, although the effects on long-term results have to be awaited. Moreover, this is coupled with a high percentage of grade III/IV toxicity, especially febrile neutropenia. The use of simultaneous G-CSF and capecitabine should be further investigated to decrease toxicity-related non-adherence and mortality. According to the results of this study, the use of DCC without G-CSF support as preoperative regimen in resectable gastric cancer is debatable.

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COMMENTS

Background

Survival rates for resectable gastric cancer are still poor. Resection is the cornerstone of treatment, though the addition of perioperative chemotherapy has additional benefit. In 2006, the results of the MAGIC trial were published, comparing perioperative chemotherapy with surgery alone, which resulted in a survival benefit. Only 42% of patients completed the postoperative regimen consisting of epirubicin, cisplatin and capecitabine. Other regimens have been investigated for their effectiveness in gastric cancer, e.g., docetaxel combined with cisplatin and capecitabine, leading to promising results.

Research frontiers

Improve survival of curable gastric cancer with the use of different regimens of (neo)adjuvant chemotherapy.

Innovations and breakthroughs

At the time of study design, this was one of the first phase II studies to investigate the feasibility of a docetaxel based regimen in resectable gastric cancer. Although the R0 resection rates were high, it was accompanied by a high rate of febrile neutropenia which resulted in a mortality rate of 5.9%.

Applications

The combination of docetaxel, cisplatin and capecitabine could be used as a (neo)adjuvant regimen in the setting of resectable gastric cancer, although the role of granulocyte colony-stimulating factor (G-CSF) to prevent febrile neutropenia should be investigated.

Terminology

Docetaxel can cause neutropenia. In case of an infection, this can be fatal complication. G-CSF could prevent the development of neutropenia, thereby preventing this major complication.

Peer-review

The present study is a phase II clinical trial which had the aim to evaluate the feasibility of three-drug regimen of preoperative chemotherapy of gastric cancer, composed by cisplatin, capecitabine and docetaxel. It is a well-conducted study.

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Acute pain management in symptomatic cholelithiasis

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Abstract

AIM

To review the evidence for the use of different non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of biliary colic.

METHODS

The strategies employed included an extensive literature review for articles and studies related to biliary colic from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane from last 15 years. Keywords: "Biliary colic", "management of biliary colic", "non-steroidal anti-inflammatory drugs", "cholelithiasis" and "biliary colic management". Six randomized control trials, 1 non-randomized trial and 1 meta-analysis were included in this review. The outcomes of these studies and their significance have been reviewed in this paper.

RESULTS

Current evidence suggests there are no set protocols for biliary colic pain management. NSAIDs are potent in the management of biliary colic, not only in terms of symptom control but in disease progression as well. Apart from the studies on diclofenac and ketorolac, there are studies which have shown that intravenous tenoxicam and injectable flurbiprofen are equally effective in managing biliary colic. The efficacy of NSAIDs is superior in terms of lower number of doses and longer duration of action in comparison to other analgesic agents.

CONCLUSION

This literature review has found that NSAIDs are safe and effective for pain control in biliary colic, and reduce the likelihood of further complications.

Key words: Biliary colic; Management of biliary colic; Non-steroidal anti-inflammatory drugs; Cholelithiasis; Biliary colic management

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Core tip: There are currently no set protocols for pain management in biliary colic. This literature review analyses studies from the last 15 years and shows that non-steroidal anti-inflammatory drugs (NSAIDs) provide safe

and effective pain control. It also suggests that NSAIDs play an important role in reducing the complication risk following episodes of biliary colic.

Masudi T, Capitelli-McMahon H, Anwar S. Acute pain management in symptomatic cholelithiasis. *World J Gastrointest Surg* 2016; 8(10): 713-718 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/713.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.713>

INTRODUCTION

In developed countries, including United States, United Kingdom and other European countries, 10% of adults and 20% of people aged > 65 years have cholelithiasis. It is more than twice as common in females as in males^[1]. Biliary colic is seen as a presenting symptom in 75%-80% of the patients with symptomatic cholelithiasis^[2].

This review examines the evidence for the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics in the management of pain in biliary colic as well as their role in the prevention of progression to complications.

MATERIALS AND METHODS

The strategies employed included an extensive literature search for articles and studies related to biliary colic from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane. The keywords used in electronic search were "biliary colic", "management of biliary colic", "non-steroidal anti-inflammatory drugs" and "biliary colic management". The literature searches of the last fifteen years brought up approximately 50 studies and papers in a variety of journals. However, only 6 randomized control trials (RCTs), 1 non-randomized trial and 1 meta-analysis fell within the purview of this review, which was to study the effects of NSAIDs and other pharmacological therapies on symptomatic cholelithiasis.

RESULTS

The studies were examined with the help of a questionnaire devised by the Critical Appraisal Skills Programme^[3] recommended for evaluating RCTs in evidence-based medicine.

Akriviadis *et al*^[4] designed a study investigating the effects of diclofenac in patients suffering from biliary colic. The study aimed to prove the benefits of diclofenac for pain alleviation, and also linked NSAIDs with preventing the development of complications related to cholelithiasis. The study involved 53 consenting patients who were

known to have cholelithiasis and who were diagnosed with biliary colic. One group ($n = 27$) received 75 mg of 3 mL IM diclofenac and the other group ($n = 26$) received 3 mL of saline. The patients were followed up for 3 d and the effect of each treatment was gauged by changes in pain severity and progression to complications. Satisfactory levels of analgesia were obtained in 21 patients from the diclofenac group whilst only 7 from the placebo group were relieved of pain. Nearly 50% of the patients in the placebo group progressed to the development of acute cholecystitis. It was concluded that diclofenac usage could provide cost-effective pain relief in the acute phase of biliary colic and could also prevent development of subsequent complications.

This was a randomized, double-blind and controlled study. The inclusion criteria were based on the presence of right upper quadrant and epigastric pain. These patients were further subjected to sonography to demonstrate the presence of cholelithiasis. The exclusion criteria were strictly monitored. There was a longer follow-up of 3 d in these patients, which aided the adequate monitoring of responses to treatment and the recording of any complications in a surgical ward setting, thus minimizing the chances of observer bias and maintaining uniformity of care. The study also employed the setting up of end points which were based on patient response to treatment and time taken to get relief or symptom progression. This made it a well-controlled study keeping the wellbeing of patients paramount. This is a level-II study with a sound aim and statistically significant results but the only limitation was the fallout of 28 patients from initial enrollment to the final conclusion.

Tomida *et al*^[5] conducted an extensive study on the long-term use of ursodeoxycholic Acid (UDCA) therapy in patients with known cholelithiasis. The aim of this study was to evaluate the effects of this therapy on biliary pain and development of acute cholecystitis. The study included a cohort of 527 patients with uncomplicated cholelithiasis who were either given or withheld UDCA (600 mg/d). These patients were followed for 18 years and the results analysed. It was found that UDCA therapy was associated with reduced risk of developing biliary pain in symptomatic as well as in asymptomatic patients. The risk of conversion to surgery was also reduced in symptomatic patients treated with UDCA. On the basis of these findings it was concluded that UDCA therapy might be considered as a safe option in symptomatic patients and also in patients who carry a significant surgical risk.

This was a non-randomized prospective study designed to cover a large number of patients. The strengths of this study are that it had a large sample size and that the follow-up and data collection were uniform. The inclusion and exclusion criteria were strictly monitored and the allocation of an end-point meant that the patients were given a fair chance of getting an acceptable mode of management for their symptoms. However, the absence of randomization makes this a level-III study and there is

a lack of power calculations to support the representativeness of the study, therefore increasing the likelihood of type 2 error. There is also an element of bias in this type of observational study.

Dula *et al*^[6] compared the efficacy of administering intramuscular ketorolac with intramuscular meperidine in the treatment of acute biliary colic. The study consisted of 30 patients who were divided into two groups and after the diagnosis of acute biliary colic was established, were given either meperidine 1.5 mg/kg (100 mg max.) or ketorolac 60 mg. The patients were asked to rate their pain at two time intervals; before administration and 30 min after the medication was given. This was rated on a visual analogue pain scale. The average pain score was compared between the two groups at time 0 and at 30 min. The average pain score at time 0 was 7.6 for the ketorolac group and 7.3 for the meperidine group. The visual analog scale (VAS) scores for the ketorolac group and the meperidine group were 3.8 and 3.9 at the 30-min time interval after the administration of the respective drugs. It was found that there was indeed improvement in pain control in both groups, but there was no markedly demonstrable difference in the pain relief achieved by either ketorolac or meperidine when administered intramuscularly.

This study had a definite aim and was well-designed but the size of the sample was too small to have any impact on the practice. It was a randomized, prospective and a double-blinded study. However there was an absence of power calculations, making the study less representative of the large number of cholelithiasis patients who present to emergency clinics routinely. Only 15 patients effectively got intramuscular ketorolac and this cannot constitute evidence of any consequence.

Henderson *et al*^[7] conducted a similar study on 324 patients over a 2-year period with a view to comparing analgesic efficacy and systemic tolerability of intravenous Ketorolac and Meperidine in the treatment of acute biliary colic. The patients were between the ages of 18 and 65 years with signs and symptoms consistent with acute biliary colic. Pain scores were quantified by means of a four-point verbal rating system as well as a VAS. These are validated tools for measuring patient satisfaction and drug efficacy and thus lend validity to the findings. The results did not demonstrate any significant differences in pain or drug tolerability [mean change in the VAS at 2 h was 6.2 ± 3.6 cm for the ketorolac group, compared with 6.7 ± 3.6 cm for the meperidine group ($P = 0.25$)] but revealed higher incidences of nausea and dizziness in the Meperidine group ($n = 149$). The study goes on to conclude that Ketorolac ($n = 175$) is a well-tolerated and effective analgesia for biliary colic and the fact that it showed similar efficacy as Meperidine with decreased adverse effects makes it a better alternative.

This was a prospective, randomized and a double-blinded study which included a significant sample of patients. The inclusion and exclusion criteria were strictly

monitored. The limitation of this study was that out of a sizeable number of patients initially enrolled ($n = 534$), more than 220 patients were lost for a variety of reasons such as loss of data and inappropriately filled forms. Also the employment of convenience sampling makes the study prone to potential bias. However, the presence of power calculations makes this a robust and acceptable study. There is certainly evidence collected in this study which could potentially change practice; more patients with biliary pathology could be treated with Ketorolac for effective analgesia.

Antevil *et al*^[1] undertook a trial to determine the efficacy of intravenous glycopyrrolate for the relief of pain associated with the biliary tract. At the onset 312 patients were assessed for the study but eventually only 39 were actually included in the study. The rest either declined to participate or did not meet the inclusion criteria. The initial aim of the study was to include 54 patients but due to difficulty in patient enrollment, analysis was done on only 39 patients who completed the study protocol. The initial sample size was based on power calculations to give the study a representative character, which was later lost due to the fallouts. The results of the study failed to demonstrate any significant differences in the pain relief between patients receiving glycopyrrolate and those receiving a placebo. The statistical difference in visual analogue scale for pain between the former and the latter was 3 mm vs 8 mm respectively. It was proposed that a further, larger study would be needed to underline the supremacy (if any) of glycopyrrolate in treating patients with biliary colic.

This was a randomized, prospective and a double-blind study. The randomization was computer generated and the inclusion criteria were set up keeping in view the final size of the sample based on eligibility criteria. Factors such as the selection of patients and the methods used to sample by the enrolling physicians made the study weaker and the results less relevant. The patients enrolled for the study did not all necessarily have cholelithiasis, thus making them less suitable for treatment with an anticholinergic agent like glycopyrrolate. This was highly likely to give false negative results. This study failed to achieve its aim and left a lot to be desired in terms of patient selection and the inclusion criteria.

Kumar *et al*^[2] undertook a study to compare the effects of intramuscular diclofenac with intramuscular Hyoscine-N-butyl bromide in the treatment of acute biliary colic and also to study their role in the prevention of gallstone-related complications. The study was conducted on 72 consecutive patients with biliary colic. One group ($n = 36$) received 75 mg of intramuscular diclofenac and the other group ($n = 36$) received 20 mg of intramuscular hyoscine. Pain severity was later measured on a visual analog scale at different time intervals of 30 min, 1 h, 2 h, and 4 h after the administration of the drug. Patients were followed for 72 h for signs of relapse or development of complications. It was found that diclofenac provided much

Table 1 Comparison of studies with their design and outcomes

Ref.	Design of study	Sample size	Duration of treatment	Results
Akriviadis <i>et al</i> ^[4]	Randomized controlled trial	<i>n</i> = 53 Group I (<i>n</i> = 26) (NSAID) Group II (<i>n</i> = 27) (Placebo)	3 d	Superior results from Diclofenac usage
Tomida <i>et al</i> ^[5]	Non-randomized controlled trial	<i>n</i> = 527		Ursodeoxycholic acid a safe option in symptomatic but high surgical risk patients
Dula <i>et al</i> ^[6]	Randomized controlled trial	<i>n</i> = 30 Group I (<i>n</i> = 15) (NSAID) Group II (<i>n</i> = 15) (Meperidine)	1 d	Comparable efficacy but lesser side-effects from Ketorolac
Henderson <i>et al</i> ^[7]	Randomized controlled trial	<i>n</i> = 324 Group I (<i>n</i> = 175) (NSAID) Group I (<i>n</i> = 149) (Meperidine)		Comparable efficacy but lesser side-effects from Ketorolac
Kumar <i>et al</i> ^[2]	Randomized controlled trial	<i>n</i> = 72 Group I (<i>n</i> = 36) (NSAID) Group II (<i>n</i> = 36) (Hyoscine)	3 d	Rapid symptom relief with Diclofenac and lower rate of sequelae
Antevil <i>et al</i> ^[11]	Randomized controlled trial	<i>n</i> = 39 Group I (Glycopyrrolate) Group II (Placebo)		No significant difference in analgesia between glycopyrrolate and placebo
Olsen <i>et al</i> ^[9]	Randomized controlled trial	<i>n</i> = 46 Group I (<i>n</i> = 23) (Ketorolac) Group II (<i>n</i> = 23) (Butorphanol)	1 d	Both agents provided reasonable relief of symptoms
Basurto Oña <i>et al</i> ^[10]	Meta-analysis			NSAIDs drugs of choice for symptom control and improvement of prognosis

NSAIDs: Non-steroidal anti-inflammatory drugs.

more rapid pain relief, as shown by the fact that 91.7% of such patients recorded no symptoms at the 4-h interval. Furthermore, it was noted that progression to sequelae of cholelithiasis was significantly lower in this group of patients compared with the patients treated with hyoscine.

This was a prospective, randomized, and double-blinded study with a significant sample size. There were no dropouts in terms of follow-up and the focus of the study remained unaltered. The results of this study are precise and corroborate well with the past experiences of other researchers like Todd and Sorkin^[8] in 1988. The study has, in the authors' opinion, the potential to influence practice if backed by robust statistical analysis.

Olsen *et al*^[9] carried out a prospective randomized controlled trial comparing the efficacy of ketorolac vs butorphanol for patients with suspected biliary colic in the emergency department. This was a compact study with a definite aim (though limited by a small sample size) which concluded that both agents can be considered reasonable options in patients presenting with biliary colic, especially those with a need for further investigations.

Basurto Oña *et al*^[10] conducted a systematic review and meta-analysis of randomized controlled trials involving the management of biliary colic with anti-inflammatory agents. A systematic and manual search was conducted in the literature. The authors selected 7 RCTs of 349 patients. The inclusion criteria were all the RCTs which compared the effects of NSAIDs with other interventions that were employed for treating uncomplicated biliary colic in an acute setting. The outcome measures were set up as rescue analgesia, rapidity of analgesic effect, adverse reactions and progression to complications.

The results were well analyzed and statistically significant. These were expressed in terms of confidence intervals and odds ratios, making the analysis more rigorous. The results showed a clear advantage in favour of NSAIDs because there was lower need for rescue analgesia (OR = 0.32; 95%CI, 0.16-0.61) and progression to complications (OR = 0.19; 95%CI: 0.08-0.44). This is a very robust study and can be assigned as level-I evidence. The results cannot, however, be extrapolated to the general population simply because 349 patients cannot be

representative of a pathology which affects such a large part of the adult population. In these types of studies there is a danger of publication bias in terms of selecting only the favourable trials for the analysis.

The findings of this study are also well supported by observations of Macintyre *et al.*^[11], who have termed NSAIDs as effective analgesics for the management of acute pain (level- I evidence).

DISCUSSION

The review of the above studies clearly suggests that there are no set protocols for the administration of specific analgesic agents to the patients with biliary colic (Table 1). It follows that there is strong evidence demonstrating the therapeutic and preventive potency of NSAIDs in the management of biliary colic, not only in terms of symptom control but in disease progression as well^[12]. Apart from studies on diclofenac^[4] and ketorolac^[2], there are studies^[13,14] which have shown that intravenous tenoxicam and injectable flurbiprofen (both NSAIDs) respectively are equally effective in managing biliary colic. The efficacy of NSAIDs has been proven to be superior in comparison to agents such as meperidine and hyoscine. Initial analgesic requirements may be substantial, and treatment with NSAIDs or acetaminophen (also called paracetamol) should be initiated^[15]. NSAIDs also demonstrated pharmacological superiority in terms of smaller number of doses and side effects with longer duration of action in comparison to other analgesic agents^[4]. Therefore enough qualitative evidence is available to influence practice.

A multi-centric study needs to be undertaken, aimed at identifying the reasons leading to variation in practice between the various centers after these patients are identified as having biliary colic. The evidence provided (level- I)^[10] is significant and similar studies would go a long way toward laying down strict guidelines for prescribing analgesia to patients with biliary colic.

COMMENTS

Background

Cholelithiasis is a common surgical presentation in developed countries, present in 10% of the adult population and 20% of those aged over 65 years. Biliary colic is a presenting symptom in 75%-80% of those with symptomatic cholelithiasis. Despite this, there are currently no set protocols for the pain management in biliary colic.

Research frontiers

This paper reviews extensive literature from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane. Six randomized control trials, 1 non-randomized trial and 1 meta-analysis were analysed from the past 15 years.

Innovations and breakthroughs

The aim in this paper was to collate evidence for non-steroidal anti-inflammatory

drugs (NSAIDs) use in biliary colic as both pain relief and with a view to preventing further complications.

Applications

This review shows NSAIDs to be both safe and effective for biliary colic pain management as well as reducing the incidence of complications arising from cholelithiasis. Practically this could have implications for increased use of NSAIDs for biliary colic as well as encouraging further study in this area to investigate the role of NSAIDs in improving complication rates.

Peer-review

The article is complete and interesting.

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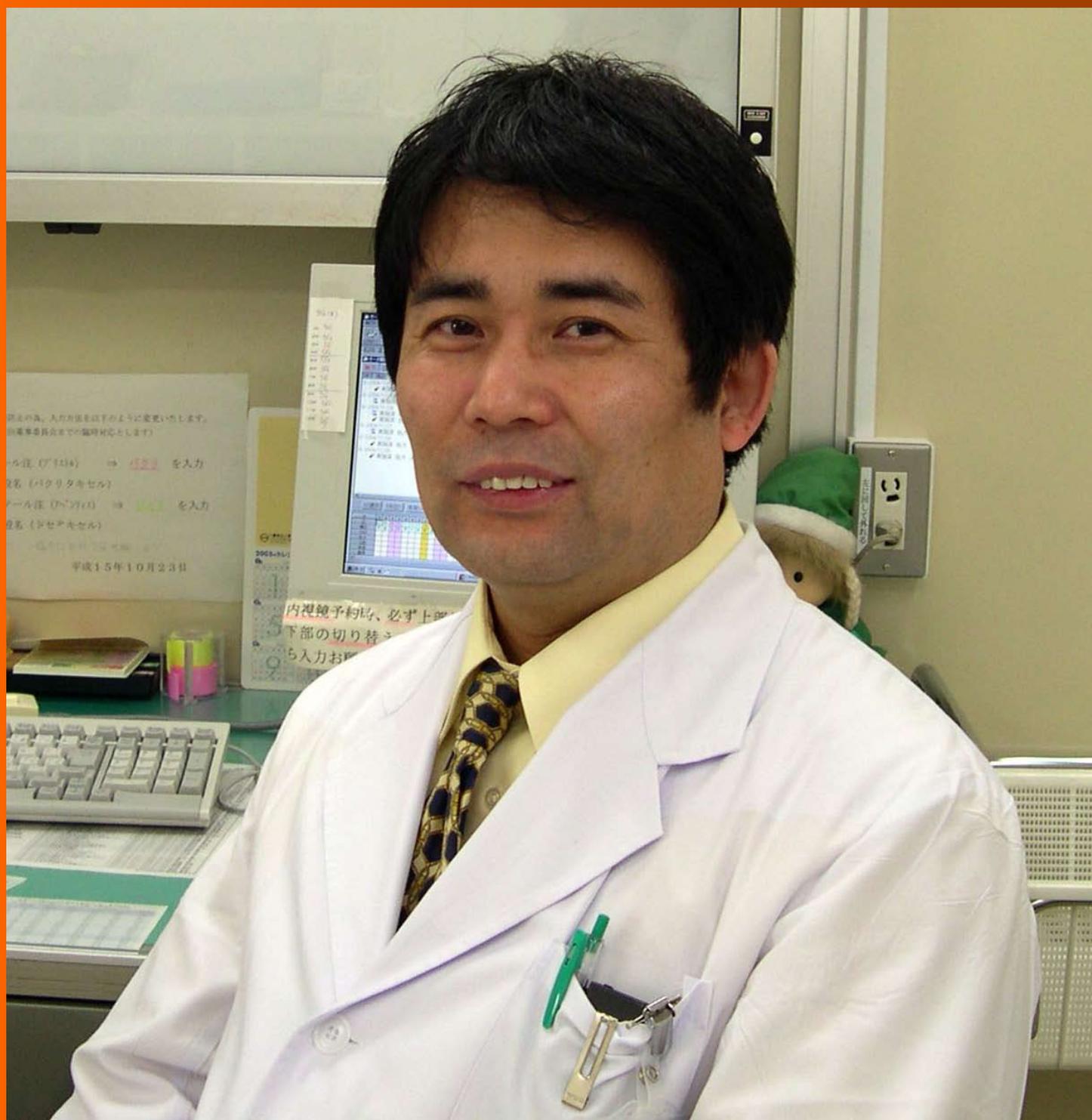
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Pre-operative clinical and instrumental factors as antireflux surgery outcome predictors

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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

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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.

Tolone S, Gualtieri G, Savarino E, Frazzoni M, de Bortoli N, Furnari M, Casalino G, Parisi S, Savarino V, Docimo L. Pre-operative clinical and instrumental factors as antireflux surgery outcome predictors. *World J Gastrointest Surg* 2016; 8(11): 719-728 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i11/719.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i11.719>

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 fact antireflux 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 dysfunction^[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 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 comorbidities, 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 relief in 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 ineffective 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 reoperative antireflux 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 endoscopic 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, Oelschlagel *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 be 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 symptomatic improvement 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 correct 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.

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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

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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 Kingdom 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 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

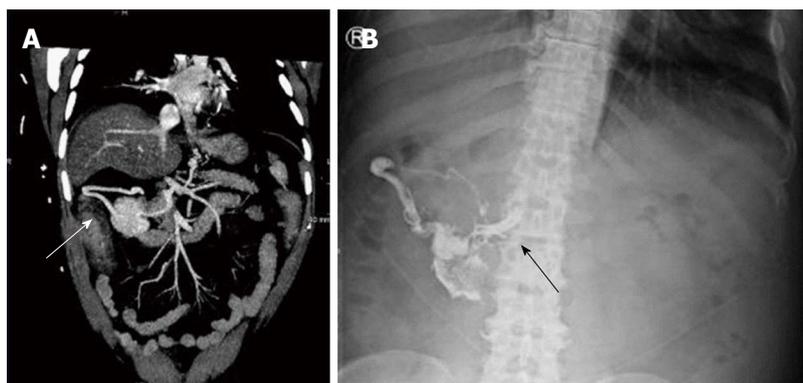


Figure 2 Duodenal varix on computed tomography and plain radiograph before and after glue injection. A: Computed tomography angiogram showing a large abdominal varix meeting the duodenum (white arrow); B: After glue injection a plain radiograph showed lipiodol/glue in the same vessel, with extension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

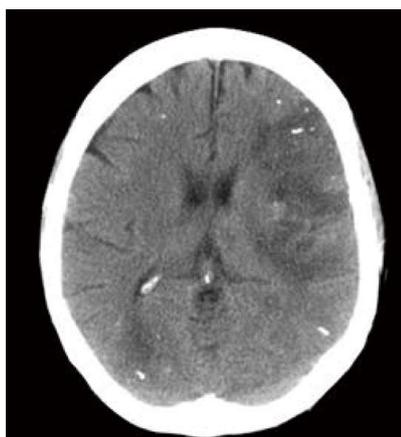


Figure 3 Computed tomogram of brain following glue/lipiodol injection. There are high signal deposits peripherally following embolisation of glue.

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 histoacryl 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 difficulty 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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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

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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.

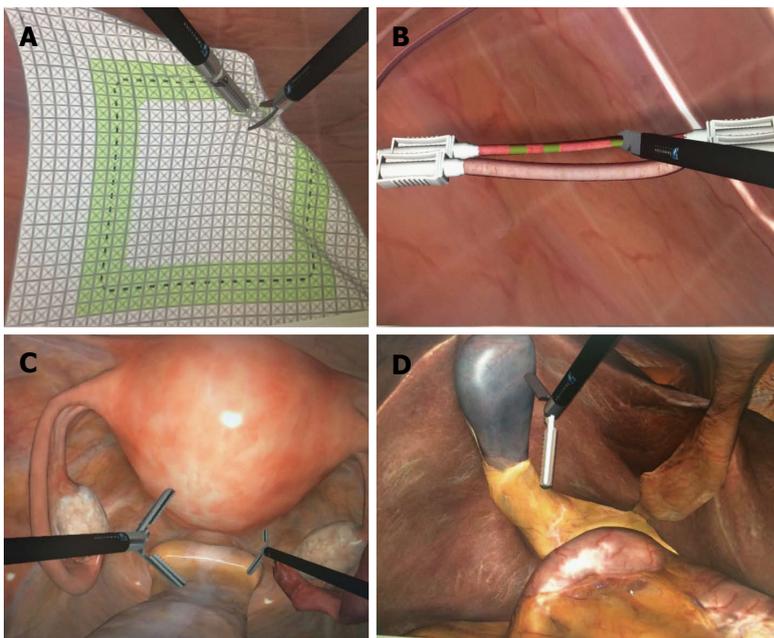


Figure 2 Virtual reality simulator. A: Cutting task; B: Clipping task; C: Hysterectomy; D: Cholecystectomy.

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. Okraanee *et al*^[37] in a 3-d course described the impact of the "fundamentals 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 significant 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.

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

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Abstract

AIM

To analyse 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

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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

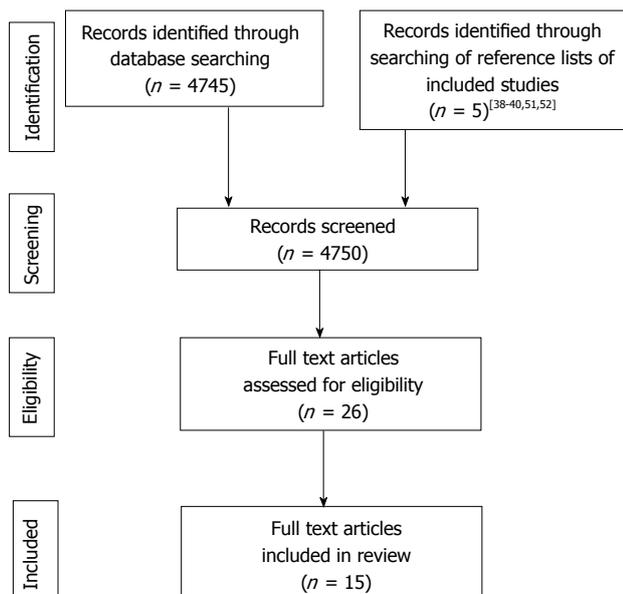


Figure 1 Selection process flow diagram.

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 assess 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 <i>et al</i> ^[34]	United States	Retrospective	No control group	39	No
Patriti <i>et al</i> ^[40]	Italy	RCT	Robot <i>vs</i> lap	29 rob <i>vs</i> 37 lap	No
Luca <i>et al</i> ^[6]	Italy	Prospective	No control group	74	Yes
Kim <i>et al</i> ^[31]	South Korea	Prospective	Robot <i>vs</i> lap	30 rob <i>vs</i> 39 lap	Yes
Park <i>et al</i> ^[39]	United States	Prospective	No control group	30	No
Leung <i>et al</i> ^[5]	Hong Kong	Prospective	No control group	33	Yes
Park <i>et al</i> ^[32]	South Korea	Retrospective	Robot <i>vs</i> lap	14 rob <i>vs</i> 15 lap	No
D'Annibale <i>et al</i> ^[33]	Italy	Retrospective	Robot <i>vs</i> lap	30 <i>vs</i> 30	No
Stănciulea <i>et al</i> ^[37]	Romania	Retrospective	No control group	78	No
Erguner <i>et al</i> ^[38]	Turkey	Prospective	Robot <i>vs</i> lap	27 rob <i>vs</i> 37 lap	No
Park <i>et al</i> ^[9]	South Korea	Retrospective	Robot <i>vs</i> lap	32 <i>vs</i> 32	Yes
Ozeki <i>et al</i> ^[18]	Japan	Prospective	Robot <i>vs</i> open	15 rob <i>vs</i> 22 open	Yes
Cho <i>et al</i> ^[35]	South Korea	Retrospective	Robot <i>vs</i> lap	278 <i>vs</i> 278	No
Alecu <i>et al</i> ^[36]	Romania	Retrospective	No control group	79	No
Morelli <i>et al</i> ^[30]	Italy	Retrospective	Robot <i>vs</i> lap	30 <i>vs</i> 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 <i>et al</i> ^[34]	Hybrid	No	Median f/u 13 mo	Not stated	+
Patriti <i>et al</i> ^[40]	Hybrid	No	Mean f/u 12 mo	Not stated	+
Luca <i>et al</i> ^[6]	Fully	Yes	1, 6, 12	2 surgeons	++
Kim <i>et al</i> ^[31]	Hybrid	Yes	1, 3, 6, 12	1 surgeon	++
Park <i>et al</i> ^[39]	Reverse hybrid	No	Not stated	Not stated	+
Leung <i>et al</i> ^[5]	Mixture	Yes	3	Not stated	++
Park <i>et al</i> ^[32]	Hybrid	Yes	3, 6, 12	1 surgeon	++
D'Annibale <i>et al</i> ^[33]	Fully	Yes	1, 12	1 surgeon	++
Stănciulea <i>et al</i> ^[37]	93% fully	Yes	Once b/n 6 and 12 mo	3 surgeons	+
Erguner <i>et al</i> ^[38]	Mixture	No	Not stated	Not stated	+
Park <i>et al</i> ^[9]	Hybrid	Yes	3, 6, 12	1 surgeon	++
Ozeki <i>et al</i> ^[18]	Fully	Yes	3, 6, 12	2 for robot cases	++
Cho <i>et al</i> ^[35]	Fully	No	1	3 surgeons did 97.1% cases	++
Alecu <i>et al</i> ^[36]	Hybrid	Yes	Not stated	Not stated	+
Morelli <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[18]	Yes	Yes	Robot vs open	15 rob vs 22 open	3, 6, 12	No statistical deterioration of IPSS scores in either group
Morelli <i>et al</i> ^[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 <i>et al</i> ^[5]	Yes	Yes	No control group	33	3	No significant male urological function deterioration
Luca <i>et al</i> ^[6]	Yes	Yes	No control group	38	1, 6, 12	No significant male urological function deterioration
Stănciulea <i>et al</i> ^[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 <i>et al</i> ^[34]	No	No	No control group	39	median F/U 13 mo	One patient (2.56%) developed bladder dysfunction post operatively
Park <i>et al</i> ^[39]	No	No	No control group	30	Not stated	No patients developed bladder dysfunction post operatively
Cho <i>et al</i> ^[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; (5) the follow up periods in months; and (6) 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 <i>et al</i> ^[30]	Yes	Yes	Robot vs lap	Not available	1, 6, 12	No difference between the pre- and post-operative scores in both groups
Luca <i>et al</i> ^[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 <i>et al</i> ^[31]	No	Yes	Robot vs lap	30 rob vs 39 lap	1, 3, 6, 12	As in Table 3
Stănciulea <i>et al</i> ^[37]	No	Yes	No control group	78	Once b/n 6 and 12	As in Table 3
Hellan <i>et al</i> ^[34]	No	No	No control group	39	Median f/u 13 mo	As in Table 3
Park <i>et al</i> ^[9]	No	No	No control group	30	Not stated	As in Table 3
Cho <i>et al</i> ^[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 <i>et al</i> ^[31]	Yes	Yes	Robot <i>vs</i> lap	18 rob <i>vs</i> 20 lap	1, 3, 6, 12	Quicker recovery of male sexual function in robotic group (6 mo <i>vs</i> 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 <i>et al</i> ^[9]	Yes	Yes	Robot <i>vs</i> lap	20 <i>vs</i> 20	3, 6, 12	Quicker recovery of male sexual function in robotic group (6 mo <i>vs</i> 12 mo) IIEF deterioration significantly higher in lap group at 6 mo ($P = 0.03$)
Park <i>et al</i> ^[32]	Yes	Yes	Robot <i>vs</i> lap	14 rob <i>vs</i> 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 <i>et al</i> ^[33]	Yes	Yes	Robot <i>vs</i> lap	18 rob <i>vs</i> 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 <i>et al</i> ^[18]	Yes	Yes	Robot <i>vs</i> open	15 rob <i>vs</i> 22 open	3, 6, 12	IIEF scores unchanged at 3, 6 and 12 mo in both groups
Morelli <i>et al</i> ^[30]	Yes	Yes	Robot <i>vs</i> lap	Not available	1, 6, 12	Quicker recovery of erectile and orgasmic function in robotic group (6 mo <i>vs</i> 12 mo) No difference in IIEF change from baseline between two groups at any stage
Leung <i>et al</i> ^[5]	Yes	Yes	No control group	15	3	No significant difference between post- and pre-operative IIEF scores
Luca <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[36]	No	Yes	No control group	79	Not stated	3 patients (3.79%) developed important sexual dysfunction. No mention of IIEF scores in results
Patriiti <i>et al</i> ^[40]	Yes	No	Robot <i>vs</i> lap	11 rob <i>vs</i> 12 lap	Mean f/u 12 mo	No difference in the incidence of sexual dysfunction between the 2 groups
Erguner <i>et al</i> ^[38]	No	No	Robot <i>vs</i> lap	27 rob <i>vs</i> 37 lap	Not stated	No difference in the incidence of sexual dysfunction between the 2 groups
Cho <i>et al</i> ^[35]	No	No	Robot <i>vs</i> lap	278 <i>vs</i> 278	1	No difference in the incidence of sexual dysfunction between the 2 groups
Park <i>et al</i> ^[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 <i>et al</i> ^[30]	Yes	Yes	Robot <i>vs</i> lap	not available	1, 6, 12	Female sexual function worse at 1 and 6 mo and restored by 12 mo, in both groups
Luca <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[36]	No	Yes	No control group	79 pts	Not stated	As in Table 5
Erguner <i>et al</i> ^[38]	No	No	Robot <i>vs</i> lap	27 rob <i>vs</i> 37 lap	Not stated	As in Table 5
Cho <i>et al</i> ^[35]	No	No	Robot <i>vs</i> lap	278 <i>vs</i> 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 end 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 of 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.

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

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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

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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,

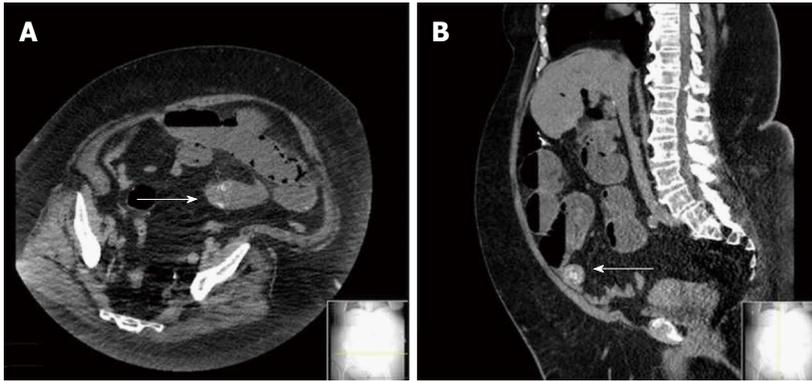


Figure 1 Computed tomography of abdomen pelvis without contrast. A: Axial section demonstrating 31.8 mm gallstone (arrow) in jejunum; B: Sagittal section demonstrating transition point and smaller gallstone (arrow) at proximal ileum.



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 intussusception 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 through 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

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 <i>et al</i> ^[15]	105	19%	7	
Reisner <i>et al</i> ^[5]	113	16.8%	801	11.7%	1001
Doko <i>et al</i> ^[26]	19	10.5%	11	9.1%	30
Tan <i>et al</i> ^[27]	12	0%	7	0%	19
Mallipeddi <i>et al</i> ^[23]	14	7.1%	113	5.3%	127
Halabi <i>et al</i> ^[21]	741	7.3%	2527	6.5%	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].

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 bowel 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.

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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

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Core tip: Sclerosing mesenteritis is a rare pathology including a benign acute or chronic inflammatory process affecting the adipose tissue of the mesentrium. 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



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).

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 (tazobactam/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

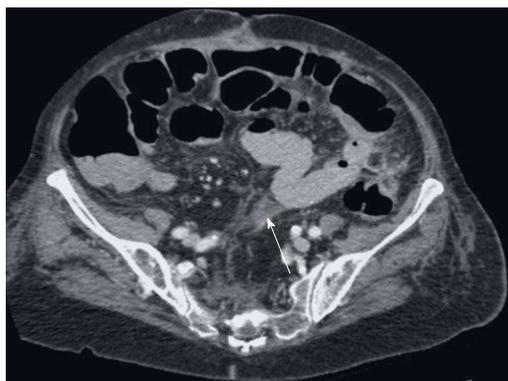


Figure 3 Transverse abdominal computed tomography scan as the gold standard with an inflammation of the mesentery at the height of the navel.

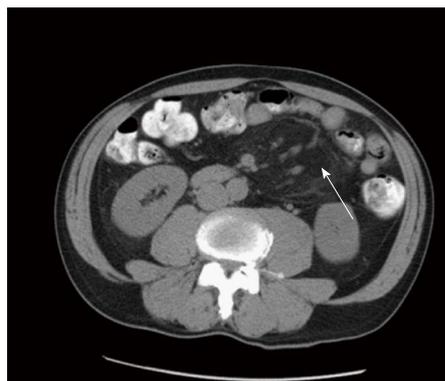


Figure 5 Inflammation of the small bowel adipose tissue formed as a pseudotumor in the left abdomen in the transverse abdominal computed tomography (white arrow).



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.

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Roux-en-Y augmented gastric advancement: An alternative technique for concurrent esophageal and pyloric stenosis secondary to corrosive intake

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Abstract

Select group of patients with concurrent esophageal

and gastric stricturing secondary to corrosive intake requires colonic or free jejunal transfer. These technically demanding reconstructions are associated with significant complications and have up to 18% ischemic conduit necrosis. Following corrosive intake, up to 30% of such patients have stricturing at the pyloro-duodenal canal area only and rest of the stomach is available for rather less complex and better perfused gastrointestinal reconstruction. Here we describe an alternative technique where we utilize stomach following distal gastric resection along with Roux-en-Y reconstruction instead of colonic or jejunal interposition. This neo-conduit is potentially superior in terms of perfusion, lower risk of gastro-esophageal anastomotic leakage and technical ease as opposed to colonic and jejunal counterparts. We have utilized the said technique in three patients with acceptable postoperative outcome. In addition this technique offers a feasible reconstruction plan in patients where colon is not available for reconstruction due to concomitant pathology. Utility of this technique may also merit consideration for gastroesophageal junction tumors.

Key words: Corrosive strictures; Roux-en-Y augmented gastric advancement; Colonic interposition

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Core tip: Selected patients with concurrent esophageal and gastric stricturing secondary to corrosive intake require colonic or free jejunal transfer. These technically demanding reconstructions are associated with significant conduit necrosis. An alternative technique we utilize stomach with Roux-en-Y reconstruction instead of colonic or jejunal interposition has been presented.

Waseem T, Azim A, Ashraf MH, Azim KM. Roux-en-Y augmented gastric advancement: An alternative technique for concurrent esophageal and pyloric stenosis secondary to corrosive intake.

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INTRODUCTION

Corrosive upper gastrointestinal (GI) strictures still remain challenging in surgical practice^[1]. Fortunately in majority of cases these either preferentially involve esophagus or stomach making surgical decision easier in favor of either esophagectomy or a form of gastric bypass^[1,2]. However in approximately 6%-50% of the cases it involves both esophagus and stomach making reconstruction a technically demanding task with inherent potential of multiple complications^[1-3].

Various surgical techniques with pros and cons have been advocated previously^[4-6]. Colonic and free jejunal conduits remain a standard for such difficult cases with favorable outcomes however with significant graft necrosis rates of 2.4%-18% and 14.1% respectively^[6-8]. Although proponents of colonic conduit have significant reasons in favor of its use however majority of the surgeons doing transhiatal resections of esophagus would agree that stomach is the most favorable conduit in terms of quality of blood supply and hence anastomotic leak rate^[9]. In a study by Mansour *et al*^[10], bowel interposition was associated with significant complications including 14.8% anastomosis leakage rate and 3% ischemic colitis rate. Similarly, Davis *et al*^[6] and Moorehead *et al*^[11] have previously shown that stomach is better in terms of postoperative ischemia than the colon. Stomach had lowest conduit ischemia rate of 0.5%-1% while jejunum had colon had ischemia up to 11.3% and 13.3% respectively^[6-11]. Patients having colonic interposition however, have low rates of GERD postoperatively^[12,13].

In a group of selected patients where the stomach has mere concentric pyloric stenosis along with esophageal involvement, many practicing surgeons would have questioned themselves per-operatively: "Can we employ this dilated well vascularized stomach instead of less vascular and technically more demanding colon or free jejunal transfer?" Here we describe alternative reconstruction plan which we have successfully employed in three of our patients with reasonable outcome.

OPERATIVE TECHNIQUE

A 33-year-old male patient presented with development of progressive dysphagia following history of caustic intake 3 years back. Endoscopy showed two significant strictures in upper GI tract, one 30 cm distal to cricopharynx and the second one in pyloric sphincter region. During last three years patient was managed by repeated dilatations of esophageal and pyloric strictures. Now he presented with strictures which were not dilatable due to extensive fibrosis in the said areas of the upper GI tract. A barium study showed esophageal stricture in the region of upper esophagus and the stomach was full

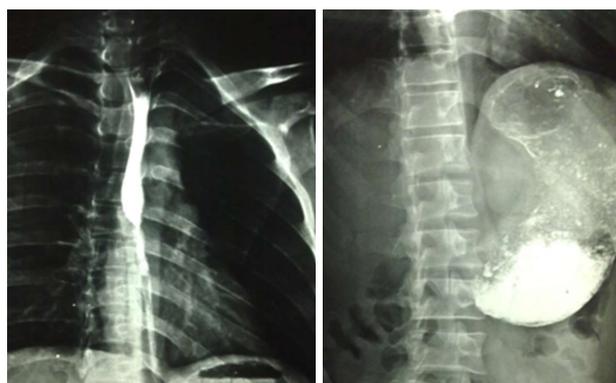


Figure 1 Barium study showing concurrent esophageal and gastric stenosis at pyloric canal level. Please note the distended stomach.

of the contrast material without any distal evacuation (Figure 1). Another dilatation of the upper esophageal stricture was possible in up to 5 mm at best. Considering the above surgical reconstruction was planned. Peroperatively the stomach was massively dilated with only distal stricturing at the pyloric region. Stomach was mobilized with preservation of right gastroepiploic vessels. Distal gastrectomy was done and distal end of stomach was closed along with closure of the duodenal stump. Transhiatal esophagectomy was done and jejunum was fashioned as a Roux-en-Y loop which was anastomosed to the distal end of the mobilized stomach. The stomach was delivered into the chest the way that the gastro-jejunal anastomosis of Roux-en-Y loop lays in hiatus. Neck dissection was done with predictable safety of recurrent laryngeal nerve. End to side triangulated gastroesophageal anastomosis was done with interrupted Prolene stitches (Figure 2). Postoperatively patient did well and was discharged on 18th postoperative day. We have employed the same technique in three of our patients, two males and one female. All three patients had technically viable reconstruction. We lost one of the three patients on 12nd postoperative day due to Acinobacter positive hospital acquired pneumonia. We did not find any evidence to suggest a procedural failure or anastomotic leakage in this particular case. We have followed up the cases over a period of 19 mo in one case and 5 mo in other case with only one with mild dumping symptoms.

CONCLUSION

Corrosive intake depending upon the chemical composition of ingested liquid, area and time of contact can cause mild to severe stricturing of the upper GI tract^[1-3]. Caustic soda preferentially affects the esophagus and the toilet cleaners in majority of cases affect the pyloric canal area^[3]. Endoscopic dilatation or surgical replacement is quite effective treatment in majority of the cases^[3]. In up to 50% percent of the cases there is concurrent involvement of esophagus and stomach leading to difficulty in reconstruction. In such cases, colonic interposition and free jejunal transfer still remain the gold standard conduits. Clearly such reconstructions are complex and

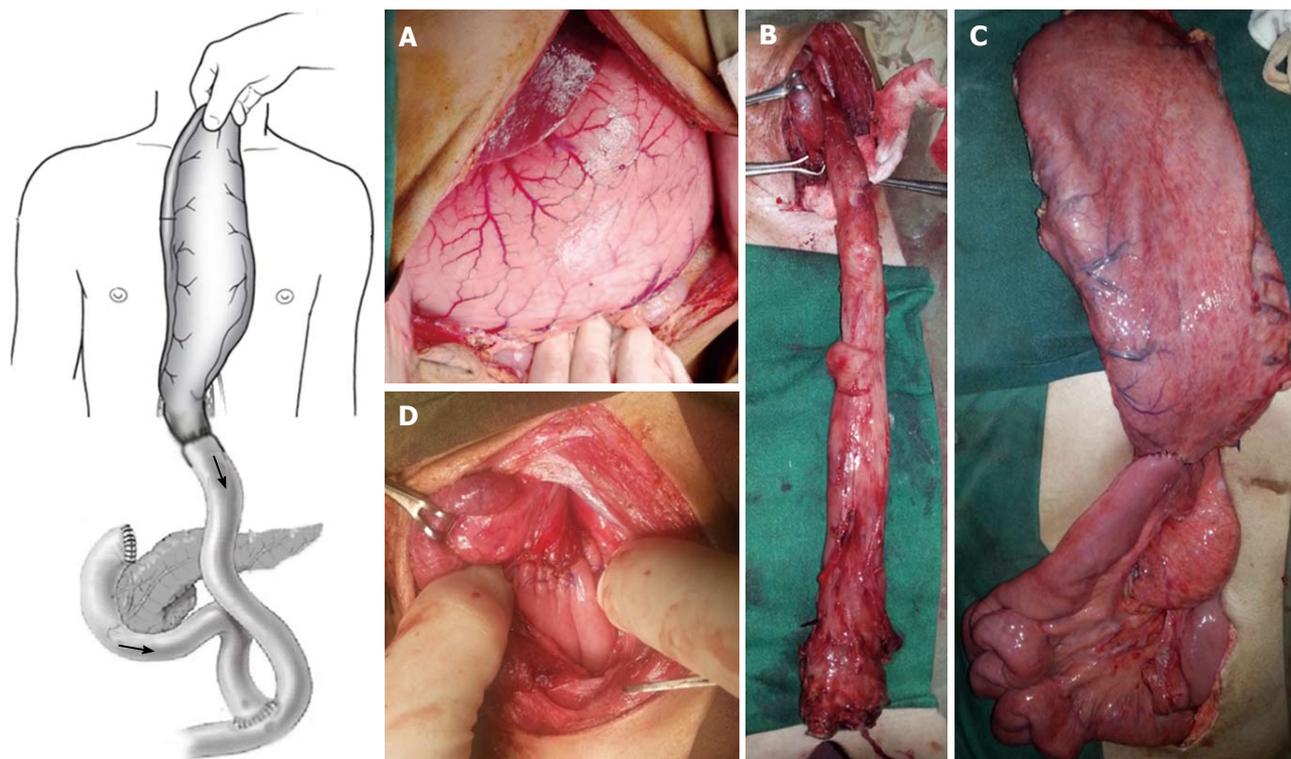


Figure 2 Roux-en-Y augmented gastric advancement with schematic reconstruction plan. A: Distended stomach; B: Esophageal specimen following standard transhiatal esophagectomy; C: Standard augmented gastric advancement reconstruction before esophageal anastomosis lying on the chest; D: Gastro-esophageal anastomosis in the neck.

are associated with higher morbidity and mortality^[4]. In words of T. DeMeester, these reconstructions should be flawless because the impact of complications is not additive but logarithmic^[14]. In experienced hands these reconstructions have favorable results however one of the frequently encountered problem is higher conduit necrosis rate in case of colon (2.8%-18%) and jejunum (14.1%) as opposed to stomach which has lower conduit necrosis rate (2.6%) and hence potentially lower leak rate^[6-8].

In select group of the patients with concurrent involvement of esophagus and stomach where stomach is merely affected at the pyloric sphincter area, surgeons have previously avoided using stomach in favor of colonic replacement. Here we have demonstrated that stomach tube along with Roux-en-Y reconstruction can be a feasible alternative to the colonic or jejunal interposition in this select group of patients.

The interposition of stomach tube potentially adds specific superiority of excellent vascular supply and potentially reduced conduit necrosis rate and low anastomotic leakage rate, which are subject of our upcoming randomized trial. The Roux-en-Y reconstruction adds to the complexity of the reconstruction however it has three distinct advantages: Firstly, it gives significant length to the conduit (about 30-40 cm), which normally would be attained by liberal kockerization of the duodenum in a standard case of the transhiatal esophagectomy; secondly, it would function as a pyloromyotomy which is frequently done by the surgeons during transhiatal

esophagectomy to prevent postoperative gastric stasis and thirdly, it potentially would reduce postoperative biliary reflux; and finally, this reconstruction plan can be of enormous value if the colon is not available for interposition due to some other concomitant reason like ulcerative colitis or Crohn's disease. Theoretically such reconstruction can also be beneficial in GE junction tumors, where we can achieve negative resection margins with limited resection of stomach.

RAGA like other constructions plans can be associated with potential complications. The preparation of the conduit requires special attention and preservation of blood supply as the conduit would be solely based on right gastroepiploic artery and its corresponding venous system as opposed to right gastroepiploic and right gastric arteries which are usually preserved during a standard transhiatal esophagectomy. This can potentially add to the probability of gastric erosions due to mucosal ischemia. Secondly the retention gastritis leading to postoperative gastric erosions are likely to be higher and hence patients may require use of proton pump inhibitors to prevent gastric erosions due to gastritis. One of our patient developed postoperative gastric erosions on 6th postoperative day owing to retention gastritis which was successfully treated with proton pump inhibitor infusion. A predicted comparison of the two said techniques has been tabulated in Table 1.

In select group of the patients of corrosive intake with concomitant involvement of esophagus and stomach where stomach is partially available for reconstruction, it

Table 1 Predicted potential comparison of the two techniques for esophageal replacement

	Colonic interposition	Roux-en-Y augmented gastric advancement
Vascular supply and conduit necrosis rates	Good; conduit necrosis rate 2.4%-18%	Potentially excellent; conduit necrosis rate 2%-5%
Mild mucosal ischemia	Ischemic colitis (3%)	Gastric erosions
Gastroesophageal and colo-esophageal reflux rates	Low (4%-5%)	Low
Conduit reservoir capacity	Acceptable	Better
Postprandial conduit fullness	Less	More
Probability of cervical esophageal anastomotic leakage rate	Low	Low
Probability of postoperative esophageal anastomotic stricture formation	Low	Higher
Potential complications	Higher probability of anastomotic leakage in colonic anastomosis	Higher probability of gastric erosions postoperatively due to retention gastritis

is feasible to utilize stomach for reconstruction in place of more complex colonic or jejunal transfer with favorable results. A randomized trial is warranted to compare this alternative reconstruction plan with gold standard colonic and jejunal transfer.

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Observational Study

Abdominosacral resection for locally recurring rectal cancer

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Abstract**AIM**

To investigate feasibility and outcome of abdominal-sacral resection for treatment of locally recurrent rectal adenocarcinoma.

METHODS

A population of patients who underwent an abdominal-sacral resection for posterior recurrent adenocarcinoma of the rectum at the National Cancer Institute of Milan, between 2005 and 2013, is considered. Retrospectively collected data includes patient characteristics, treatment and pathology details regarding the primary and the recurrent rectal tumor surgical resection. A clinical and instrumental follow-up was performed. Surgical and oncological outcome were investigated. Furthermore an analytical review of literature was conducted in order to compare our case series with other reported experiences.

RESULTS

At the time of abdomino-sacral resection, the mean age of patients was 55 (range, 38-64). The median operating time was 380 min (range, 270-480). Sacral resection was performed at S2/S3 level in 3 patients, S3/S4 in 3 patients and S4/S5 in 4 patients. The median operating time was 380 ± 58 min. Mean intraoperative blood loss was 1750 mL (range, 200-680). The median hospital stay was 22 d. Overall morbidity was 80%, mainly type II complication according to the Clavien-Dindo classification. Microscopically negative margins (R0) is obtained in all patients. Overall 5-year survival after first surgical procedure is 60%, with a median

survival from the first surgery of 88 ± 56 mo. The most common site of re-recurrence was intrapelvic.

CONCLUSION

Sacral resection represents a feasible approach to posterior rectal cancer recurrence without evidence of distant spreading. An accurate staging is essential for planning the best therapy.

Key words: Rectal cancer recurrence; Local recurrence; Sacral resection; Abdominosacral resection; Recurrent rectal cancer

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Core tip: During the last years, great efforts have been invested by many authors to contribute in treatment of rectal cancer recurrence without evidence of distant spreading. The most difficult surgical problem is to perform an affective radical R0 salvage resection. However, with the introduction of sacral resection, consistent improvements have been achieved in recent years, particularly when local tumor relapse occurs in the posterior part of the pelvis, from the presacral to the retrovesical spaces. However, abdominosacral resection is a complex surgical procedure affected by several postoperative complications. For this reason, these patients should be treated into dedicated and specialized institutions.

Belli F, Gronchi A, Corbellini C, Milione M, Leo E. Abdominosacral resection for locally recurring rectal cancer. *World J Gastrointest Surg* 2016; 8(12): 770-778 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i12/770.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i12.770>

INTRODUCTION

Local relapse of rectal cancer is still one of the most complex and challenging issue concerning surgical oncology of the last years. Indeed, nowadays, rectal cancer relapses during the first two years in the 7%-30% of patients after receiving surgical resection^[1-3]. In about half of these cases of relapse, the cancer remains confined in the pelvis without extraregional diffusion and most of the deceases associated to the disease are only due to local progression of it in the following periods.

The infiltration of the pelvic walls had represented up to recent years the main limitation to achieve a radical resection in the majority of relapsed rectal cancer cases. Nevertheless, the recent advancements in surgical techniques especially regarding posterior and anterior relapse resection, have widen up the spectrum of possibilities for effective curative treatment^[4-6].

With the aim of contribute in the field, we present the review of the literature and report the implications from the experience obtained at our hospital, the National

Cancer Institute of Milan, on abdomino-sacral resection (ASR) for pelvic posterior recurrences of rectal cancers expanding toward the sacral plane.

MATERIALS AND METHODS

Between 2005 and 2013 in our Unit 1324 patients affected with rectal cancer were treated with different surgical procedures. One hundred and sixty-two (12.2%) recurred in the pelvis in a period ranging from 10 to 38 mo after surgery. One hundred and fifty-four of these were considered candidates to a second surgical salvage approach. Different surgical procedures were applied accordingly with the extension, the site and the characteristic of the relapsing lesion.

In the same period, a population of ten patients underwent an ASR for recurrent adenocarcinoma of the rectum at the National Cancer Institute of Milano. These patients are included in the present study.

All the patients underwent, in the first place, a radical resection for the rectal cancer followed by at our Institution in combination with a total mesorectal excision (TME) and a local, nerve sparing, node dissection extended to the origin of low mesenteric vessels. Local recurrence is defined as the relapse of the tumour at the primary site confirmed by radiologically and/or histologically. In all cases the recurrence was mainly posterior and invading the presacral space or directly the sacral plane.

Indications for ASR exist when there is evidence of involvement of the sacrum detected by preoperative exams (Figure 1) or when there is a highly probability of it according with the pelvic local extension of local relapse.

Patients were staged preoperatively by a thoraco-abdominal computed tomography (CT)-scan, a pelvic magnetic resonance imaging (MRI), a positron emission tomography and, when possible, a colonoscopy. The study excluded patients whose recurrent rectal cancer was developed after a simple local excision or patients receiving a simple and limited coccyx resection.

Patients who had undergone resection of liver metastasis at initial surgery or before the diagnosis of local relapse were also considered suitable for ASR, given an adequately long distant metastasis-free survival period. All data are retrospectively collected and registered prospectively into an electronic database. Collected data includes patient characteristics, treatment and pathology of the primary rectal cancer, neoadjuvant therapy and operative details for recurrent tumor, pathology of recurrent tumor, length of hospital stay, peri-operative complications, blood transfusion needed and oncological outcome.

The macroscopic and microscopic assessments of the pathology specimens were done by a single pathologist at our Hospital. Pathological examination included histological type, number of lymph nodes harvested, number of metastatic lymph nodes, analysis of specimen resection margins and evaluation of sacral involvement. An R0

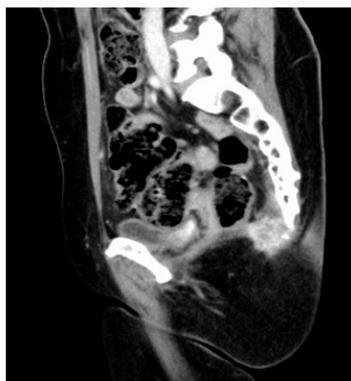


Figure 1 Radiological aspect of a local relapse infiltrating the coccyx and lower sacral bone.



Figure 2 Preparation of skin flaps allows a complete exposure of maximus gluteus muscles.

resection is defined when no tumour cells are shown in the surgical resection margin. Pathologic stage information was assessed using the 7th edition of the American Joint Committee on Cancer TNM system.

Surgical complications and overall morbidity complications are defined as adverse events that occurred within a 30 d period after surgery. Surgical complications are staged according to the Clavien Dindo Classification.

After ASR, clinical and instrumental evaluations were performed every 6 mo for the first three years and one a year for the following years. Computed axial CT-scan and MRI surveillance, as well as carcinoembryonic antigen levels, were the exams performed to assess patient outcome.

Surgical procedure

The surgical procedure is divided in three following steps: Abdominal, perineal and sacral.

Under general anesthesia the patient was placed in Lloyd-Davies position (lithotomic position with flexed and abducted thighs). After placement of ureteral stents (4 cases) in order to identify the ureters, a midline laparotomy was performed. The dissection of common and external iliac vessels is started from the promontorium. The anterior area from the aortic bifurcation to the sacral promontory is exposed to have access to the anterior surface of the sacrum. The dissection is made down to the distal sacrum paying the upmost attention to avoid bleeding from the presacral space that in some case could be really important. The area from the common iliac artery to the bifurcation between the internal and external iliac arteries is exposed. The dissection is then made toward the presacral space along the parietal pelvic fascia, outside the original plane of dissection. During this phase the endopelvic fascia and pubo-prostatic ligaments can be identified bilaterally and divided using electric cautery to expose the levator ani muscle. Some Authors propose preventive ligation of internal iliac vessels along the sacral plane, in order to control the risk of bleeding during surgical dissection. However, this procedure was not routinely performed in our series because we believe that this approach is needed only in upper sacral

resection due to a higher risk of local bleeding. The perineal phase corresponds to the typical procedure adopted in an abdomino-perineal resection performed for a primary rectal or anal carcinoma but avoiding to remove the surgical specimen through the perineal wound because the rectum and the other tissues will be removed "en bloc" with the sacrum during the following surgical steps. After formation of a terminal colostomy and closure of abdominal wound, the patient is placed in a prone position, with flexed and abducted thighs. Then, a posterior midline incision including the perineal lesion is made. The gluteus maximus muscles are dissected and detached from the sacrum in order to obtain a full exposure (Figure 2). The next step of this phase involves detaching the gluteal muscles, the sacrotuberous and sacrospinous ligaments and the piriform muscle from the sacrum to, subsequently, access the pelvic cavity. The surgeon inserts an index finger into the pelvic cavity from the lower edge of the sacroiliac joint and checks the dissected level of the anterior surface of the sacrum to determine the level of sacral amputation. The posterior wall of the sacrum is then osteotomized using a proper chisel and hammer at a stretch (Figure 3) scalpel and en-bloc resection of the tumor with the sacrum and the surrounding organs is accomplished (Figure 4). The canal is sealed with bone wax and fibrin sealant. A prolene mesh is placed anterior to the sacrum in order to close the perineal defect. A primary wound closure is usually performed. In some cases (two patients of the present series), perineal reconstruction is achieved with a pedicled musculocutaneous flap (Figure 5).

RESULTS

All ten patients included in this study (4 males and 6 females) underwent an anterior rectal resection as first operation at our hospital. Patients characteristics are reported in Table 1.

All the tumors were adenocarcinomas. Median distance from anal verge was 6 cm (range, 3-11). No patient received a pre-surgical neo-adjuvant therapy. In the pT3 cases this was mainly due to the bad clinical

Table 1 Patient characteristics and final outcome

Case	Age	Sex	First surgery	Pathological stage	DFS (mo)	OS ¹ (mo)	OS ² (mo)	Status
1	63	F	ARR	pT3 pN0 M0	103	216	111	DOD (local and lung recurrences)
2	60	F	ARR	pT2 pN0 M0	89	135	41	NED
3	62	F	ARR	pT2 pN0 M0	114	154	34	NED
4	53	F	ARR	pT2 pN1 M0	76	93	22	DOD (local recurrence)
5	46	M	ARR	pT3 pN1 M0 (R1)	12	54	41	DOD (local and lung recurrences)
6	64	F	ARR	pT2 pN0 M0	22	83	57	NED
7	57	F	ARR	pT3 pN2 M0	16	38	13	DOD (liver recurrence)
8	47	M	ARR and liver metastasectomy	pT3 pN1 M1 (liver)	29	47	14	DOD (local recurrence)
9	38	M	ARR	pT2 pN0 M0	49	110	57	NED
10	57	M	ARR	pT2 pN0 M0	17	56	29	NED

¹OS from first surgery to last follow-up or death; ²OS from ASR to last follow-up or death. NED: Non evidence disease; DOD: Dead of disease; DFS: Disease free survival; F: Female; M: Male; ARR: Anterior rectal resection; OS: Overall survival.



Figure 3 After the level of sacral transection is identified the sacrum is osteotomized using normally a proper hammer and scalpel.

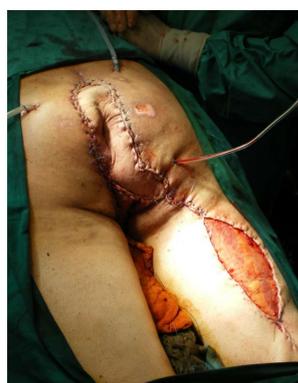


Figure 5 Example of a complex plastic reconstruction of the sacral area by a pedicled musculocutaneous flap and a thigh thin graft.



Figure 4 The figure shows a section of sacral specimen after S2 osteotomy.

status of the patients at the moment of diagnosis (occluding or bleeding lesions). All patients with histological nodal involvement or diffusion of disease into the perirectal fat received a post-operative CT-RT treatment in accordance to standardized schedules. The results of the pathological staging according to TNM are as follows: Stage I (5 cases), stage IIa (1 case), stage IIIa (1 case), stage IIIb (2 case) and stage IVa (1 case). In our case series, all stage I reported were high grade tumors with associated vascular and perineural invasion. Radicality was achieved during first surgery in all cases excepting one (R1, case 5).

At the time of ASR, the mean age of patients was 55 ± 9 years old, ranging from 38 to 64 years old. One out of ten patients was asymptomatic at presentation while 9 patients had increasing lower sacrococcygeal region pain. All patients were free of distant metastases at ASR and were considered eligible for a radical resection. In 6 patients surgery was performed 4 to 6 wk after the completion of a new chemo-radiation therapy. All patients underwent ASR according to the technique reported in the previous section. The median operating time was 380 ± 58 min (range, 270-480 min). In one case, a posterior colpectomy was needed due to a direct infiltration of posterior vaginal wall (Table 2). Sacral resection was performed at S2/S3 level in 3 patients, S3/S4 in 3 patients and S4/S5 in 4 patients.

In our case series, overall morbidity was 80%, *i.e.*, 5 presented postoperative type II complications, 2 had type IIIb and one 1 a type IIIa complication according to the Clavien-Dindo classification, whereas the most frequent complication (7 patients) was sacral wound skin infection and dehiscence. List of main complications are reported in Table 2. No differences in complication rates between higher and lower sacral resection are detected. Mean intraoperative blood loss was 1750 mL (range, 200-6800 mL). Blood transfusion was administered to 5 patients (median 1 unit; range, 0-8 units) during the surgical procedure and to 5 patients (median 2 units,

Table 2 Treatments for recurrence and complications

	Pre-ASR CT-RT	Surgical procedure	Level of sacrectomy	Procedure length (min)	In-hospital stay (d)	Sacral involvement	Early complications (within 30 d)	Late complications (after 30 d)
1	Yes	ASR	S2-S3	380	11	Yes	Neurologic bladder dysfunction	Perineal wound infection and leakage
2	Yes	ASR	S4-S5	400	10	Yes	Pelvic abscess	Uterus/bladder prolapsus
3	Yes	ASR	S2-S3	420	24	Yes	Perineal wound leakage and Neurologic bladder	No
4	No	ASR	S4-S5	370	10	Yes	Perineal wound leakage	No
5	No	ASR	S3-S4	430	93	No	Uretral fistula, perineal flap necrosis and wound leakage	No
6	Yes	ASR	S3-S4	360	25	No	Perineal wound leakage	No
7	CT only	ASR and posterior colectomy	S3-S4	360	8	No	Perineal wound leakage	Pelvic abscess and ileal fistula
8	No	ASR	S4-S5	480	11	Yes	No	No
9	Yes	ASR	S2-S3	270	9	No	No	No
10	Yes	ASR	S4-S5	330	15	No	Perineal wound infection	No

ASR: Abdomino-sacral resection; CT: Computed tomography.

range, 0-8 units) during the postoperative period. No in-hospital mortality was observed. The median hospital stay was 22 d (range, 8-93 d). Adjuvant chemotherapy was performed in 2 patients under suggestion of medical oncologists due to local extension of disease. Microscopically negative margins (R0) is obtained in all patients. Previous diagnosis was confirmed by histopathological examination. Sacral bone invasion was detected in 50% of the cases. Postoperative lymph node harvested are 4 ± 3 (range, 0-10). No node localizations are identified.

Survival

Five of 10 patient (50%) died at a median time from ASR of 38 ± 29 mo.

Overall 5-year survival after first surgical procedure is 60%, with a median survival from the first surgery of 88 ± 56 mo. Median disease free interval from first surgery to local recurrence is 39 ± 39 mo (range 12-114 mo). The most common site of re-recurrence was intrapelvic in 4 patients and two of these presented also lung metastases. One patient had liver metastasis alone.

DISCUSSION

The adoption of TME, described by MacFarlane *et al*^[7] associated with preoperative radiation has improved surgical management of primary rectal cancer leading to a significant decrease of locoregional recurrence from 33% to less than 10%^[8,9].

Despite these recent advancements, the occurrence of local relapse of rectal cancer is still quite frequent and produces a particular cancer situation characterized by the persistence of the disease in the pelvis without extraregional diffusion to distant sites. The specific behavior of this recurring tumor calls for the need of an advanced surgical or combined therapy in order to obtain a R0 resection in the pelvis.

Regretfully, these locoregional recurrences are often

spread through the whole pelvis and a salvage surgery cannot be attempted. As a result many of them die in very bad conditions only for progression of the local relapse.

Several risk factors for the recurrence of rectal tumors have been studied. Some of them are related to tumor features, including tumor localization and pathological stage^[10]. However, the main risk factors are linked to which and how surgical technique is performed, *e.g.*, incomplete resection of mesorectal fatty tissue and R1/R2 resection^[11]. This explains why up to 90% of these relapses occur in an extra-bowel site and justify the difficulties of diagnosis and complexity of surgical resection for the adhesion-infiltration of these recurrences to the pelvic structures.

An accurate locoregional staging of a rectal relapsing tumor is essential for planning the best therapy^[12-14]. A careful radiological examination provides information about the local extension of the disease, which is critical for the treatment decision-making process. A attentive evaluation of both tumor extent and anatomic planes is needed to determine a correct line during resection that is usually altered by the previous surgery and radiotherapy. Pelvic MRI and CT-scanning of the thorax and abdomen are the most used imaging modalities technique in pre-operative staging to evaluate whether or not curative surgery is feasible, although some authors underline a low sensitivity in accurate assessment of side wall involvement^[15,16].

The definition of the site distribution of the relapse is crucial because, from a practical point of view, the factor that seems to play the upmost relevant role in evaluating the surgical resectability of these peculiar lesions is the anatomical sites of recurrences in the pelvis, irrespective in many cases, of the dimension and time of occurrence.

The relevance of the sites of recurrences is confirmed by the effort that has been dedicated to this issue in all the schemes of classifications proposed in the past recent

years^[17-21]. Guillem *et al.*^[19] in 1998 classified relapses into four groups: Axial, anterior, posterior and lateral. Furthermore, Guillem's classification was adopted by Moore *et al.*^[21] to show that the likelihood of achieving a R0 resection is strongly correlated to the type of recurrence, reporting an higher R0 resection rate in axial and anterior lesions than in lateral and posterior ones. Others studies confirm that central or anterior localization of a relapse produced less complex difficulties due to the possibility of removing pelvic organs such as uterus, vagina or bladder by means of well defined procedures^[22-24]. With respect to lateral and posterior relapses, a crucial role is played by the presence/absence of infiltration of structures such as iliac vessels, ureters, bony pelvis and great sciatic notch. Extensive infiltration of the pelvic sidewall is also a poor prognostic factor for the oncological outcome^[25,26].

There are, anyway, bone sections that can be removed through complex surgical procedures with relatively limited functional consequences. This concerns, specifically, the middle and distal portion of the sacrum. Facing this technical problem there are many points that should be considered.

The first one is defining the level of bone transection to be done that must be at least 1-2 cm above the upper edge of the visible tumor, when possible. As a matter of fact, the level of resection in almost all published series remains as the key factor, influencing the neurological and intraoperative complications rate^[27-29]. In all generality, there are not absolute limitation even to the resection of the whole sacrum from S1 to the coccyx, but this massive resection has been considered an alternative in rare situations, mainly due to the complexity of the procedure and to the functional consequences that may affect the patient against the expected limited benefit for the extension of the disease^[30,31]. Regularly, the section of neural roots at S3 level has no main sequelae and it is well accepted. Moving to S2 the cutting of the second root could produce important modification of bladder function up to a complete loss of bladder motility. Upper sections produce remarkable lower limb motor disability and plantar flexion weakness and the need of a walking aid. Commonly, the level considered as acceptable limit for this type of surgery is the space between S2 and S3; this allows classifying as "high sacrectomy" all resections extended from the space between S2 and S3 and, as "low sacrectomy", the procedures performed below this level^[18,26,32]. Other authors suggest a different classification indicating as "high sacrectomy" resection from the intervertebral disk between S1 and S2, "middle sacrectomy" resections between S2 and S3, and "low sacrectomy" all the others below^[33]. High sacrectomy are indeed followed by significant complications and morbidity. Bhangu *et al.*^[23] reports a 60% incidence of major complications for S1-S2 resection in comparison to a 27%-29% rate for S3 and S4-S5 sacrectomy. These data have been strongly confirmed in the recent years by many others studies^[1,6,34-38].

A other relevant technical aspect concerns the intraoperative complications related to this difficult surgical

procedure with special regards to the occurrence of sacral bleeding. Furthermore, in this case, the level of transaction is directly correlated to the incidence and severity of venous blood loss that, in some cases, could be not easily controlled, even become life threatening. Intraoperative bleeding during this surgery can be sudden and severe, and more often in patients who underwent preoperative radiotherapy, as frequently observed in these cases^[39-42].

The postoperative period could also be compromised by different and complex problems. As indicated in several studies, perioperative complication rate is high, especially in upper sacral resections. Morbidity and mortality rate at three months after radical ASR for recurrence are reported to be 30% and 8%, respectively^[1,6,34-36]. The most common complications occurring after sacropelvic resection are wound infections and dehiscences, pelvic abscesses and clinical complication, like as pneumonia, urinary tract infections and sepsis^[6]. Between the 15%-58% local complication rate (wound dehiscence, pelvic sepsis, flap necrosis, etc.) are justified by a modified and affected wound healing processes of the perineal and sacral zone. This event is often due to a heavy and prolonged radiotherapy treatment applied to the perineum and to the sacral area following rectal resection^[6,23,29,36]. All these occurrences explain as well the need to perform, in many of these cases, different and elaborated plastic reconstructions (mio-cutaneous or fascial-cutaneous flaps, rotation flaps or others) or more specific procedures when the site of the disease request further and more extended demolitions, *e.g.*, the vaginal or bladder areas^[37].

Up to few years ago, the diagnosis of a local recurrence was strongly correlated to a poor prognosis with a mean 5 years overall survival not greater than 10%^[26]. However, despite all these technical difficulties, the application of correct, enlarged and radical procedures have achieved positive and consistent clinical results in terms of local control of disease and improvements in the final outcome of these patients.

Recently, many authors have contributed to this topic, most of them confirming the safety of these surgical approaches when performed by dedicate and experienced groups of physicians. Several studies have demonstrated a 5-year global survival rates in local relapses surgery ranging between 25% and 60%^[1,6,30-36], rate confirmed by our study in which out of 10 operated patients, all submitted a middle-distal resection of sacral body, 50% are currently alive with a 38 mo mean follow-up from ASR.

In order to increase radicality rate and have a better local control, neoadjuvant treatment may be useful, excepting patients who had previously received high dose radiotherapy for primary cancer or other diseases^[43-45]. The role of intraoperative radiotherapy in the treatment of patients with pelvic relapses is still under discussion, notwithstanding several studies have shown the benefits in survival, especially in recurrent unresectable rectal tumors due to bone involvement. Some authors have

reported an increase survival rate of 15% when this modality of radiotherapy is performed^[43].

Despite all these particular aspects, the key issue to be addressed when managing this kind of disease is the appropriate selection of treatment by the patient in order to achieve symptom control and even a curative treatment with acceptable morbidity. When presenting a surgical alternative to the patient, the specialist should take into account several prognostic factors including: The age and comorbidities of the patient, disease free interval and features of the recurrence of tumor presented earlier.

The most recent studies, as well as the one presented here, are highlighting that partial sacrectomy can be considered a safe and feasible approach for recurrent rectal cancer but also that such a complex surgical resection must only be considered if a radical resection is technically possible^[37,46-53] on the basis of a multidisciplinary team evaluation only into dedicated and specialized institutions.

The results obtained in our series are consistent with what reported in other studies and suggest that, currently, a 5 years survival up to 60% is achieved with an acceptable morbidity and minor functional failure, when partial sacrectomy, below S2 level, is performed.

COMMENTS

Background

Local relapses of rectal cancer remain one of the most complex and challenging aspects of surgical oncology of the last years.

Research frontiers

Recently, a consistent improvement has been achieved with the introduction of sacral resection for the patients with posterior pelvic extension of the recurrent tumor. Although abdominosacral resection could improve outcome in patients affected by rectal cancer recurrence, it is been reported to be a complex surgical procedure affected by several postoperative complications.

Innovations and breakthroughs

Reporting their experience, the authors would like to give a better comprehension of a challenging disease with some suggestions about its surgical management.

Applications

The results of this study support the previously published evidences, underling the indication to performed a carefully selection of patient to treat. Further researches are needed to improve surgical technique and patient selection.

Peer-review

This is an interesting article on a limited series of a surgical procedure which is not often performed for treatment of local recurrent rectal cancer. Authors report data from their own experience and also make a review of the literature on this subject.

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Prospective Study

Complete rectal prolapse in young Egyptian males: Is schistosomiasis really condemned?

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Abstract**AIM**

To investigate the assumption that schistosomiasis is the main cause of rectal prolapse in young Egyptian males.

METHODS

Twenty-one male patients between ages of 18 and 50 years with complete rectal prolapse were included in the study out of a total 29 patients with rectal prolapse admitted for surgery at Colorectal Surgery Unit, Ain Shams University hospitals between the period of January 2011 and April 2014. Patients were asked to fill out a specifically designed questionnaire about duration of the prolapse, different bowel symptoms and any past or present history of schistosomiasis. Patients also underwent flexible sigmoidoscopy and four quadrant mid-rectal biopsies documenting any gross or microscopic rectal pathology. Data from questionnaire and pathology results were analyzed and patients were categorized according to their socioeconomic class.

RESULTS

Twelve patients (57%) never contracted schistosomiasis and were never susceptible to the disease, nine patients (43%) had history of the disease but were properly treated. None of the patients had gross rectal polyps

and none of the patients had active schistosomiasis on histopathological examination. Fifteen patients (71%) had early onset prolapse that started in childhood, majority before the age of 5 years. Thirteen patients (62%) were habitual strainers, and four of them (19%) had straining dating since early childhood. Four patients (19%) stated that prolapse followed a period of straining that ranged between 8 mo and 2 years. Nine patients (43%) in the present study came from the low social class, 10 patients (48%) came from the working class and 2 patients (9%) came from the low middle social class.

CONCLUSION

Schistosomiasis should not be considered the main cause of rectal prolapse among young Egyptian males. Childhood prolapse that continues through adult life is likely involved. Childhood prolapse probably results from malnutrition, recurrent parasitic infections and diarrhea that induce straining and prolapse, all are common in lower socioeconomic classes.

Key words: Rectal prolapse; Schistosomiasis; Young Egyptian males; Low socioeconomic status; Chronic straining

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Core tip: Rectal prolapse in Western countries is mainly a disease of old women but in Egypt, the incidence of complete rectal prolapse was found to be highest among young males. Previous studies have attributed this to proctosigmoiditis caused by schistosomiasis, which is endemic in many rural areas of Egypt, and to which young males are more susceptible. In this study we disprove this assumption and shed light on other factors related to socioeconomic status that are more likely to be the cause of this disease distribution in the population.

Abou-Zeid AA, ElAbbassy IH, Kamal AM, Somaie DA. Complete rectal prolapse in young Egyptian males: Is schistosomiasis really condemned? *World J Gastrointest Surg* 2016; 8(12): 779-783 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i12/779.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i12.779>

INTRODUCTION

Complete rectal prolapse is not uncommon. Unlike Western countries, the disease in Egypt predominantly affects young males. This has been attributed to intestinal schistosomiasis^[1-3], a parasitic endemic disease in Egypt that predominantly affects young males causing periportal hepatic fibrosis, portal hypertension, and proctosigmoiditis. The latter is associated with thickening, edema and inflammation of the bowel wall as well as rectal inflammatory polyps, fibrosis and strictures. It has been postulated that the heavy weight of the rectum caused by rectal wall edema and polyps, the chronic

dysentery and straining during defecation caused by rectal wall inflammation, and the pelvic floor myopathy caused by the general malnutrition that is frequently seen in schistosomiasis patients are the cause of complete rectal prolapse in this young Egyptian age group^[1-3]. Despite those plausible explanations, it is not clear why complete rectal prolapse in Egypt is so infrequent when compared to other diseases associated with schistosomiasis such as liver cell failure, ascites, splenomegaly and hematemesis^[4]. It is also not clear why other inflammatory and polypoidal diseases such as ulcerative colitis, Crohn's colitis and familial adenomatous polyposis are not known to be associated with complete rectal prolapse. Finally, it is not clear why the significant reduction in the incidence of schistosomiasis in Egypt that resulted from the aggressive national program for eradication of the disease was not reflected in a similar decrease in the incidence or change in the pattern of rectal prolapse in this country^[5,6]. The present study is trying to answer the question: Is schistosomiasis really condemned as a cause of complete rectal prolapse in young Egyptian males.

MATERIALS AND METHODS

Patient recruitment

This prospective study included all male patients with complete rectal prolapse in the age group 18-50 years ($n = 21$, median age 23 years, range 18-45 years) who were admitted for surgery for their disease to the Unit of Colorectal Surgery, Ain Shams University Hospitals, Cairo, Egypt in the period between January 2011 and April 2014. Female patients in the same age group ($n = 3$), patients younger than 18 years ($n = 2$) or older than 50 years ($n = 4$) were excluded from the study.

Assessment methods

All patients were requested to fill out a questionnaire about duration of the prolapse, different bowel symptoms and any past or present history of schistosomiasis. All patients had flexible sigmoidoscopy and four quadrant mid-rectal biopsies documenting any gross or microscopic rectal pathology. Patients were categorized according to their socioeconomic class (Table 1)^[7].

Ethical considerations

The nature and importance of the study were explained to all patients who were consented to participate in the study. The study was reviewed and approved by the IRB.

RESULTS

Twelve patients (57%) never contracted schistosomiasis and neither lived in a rural area nor worked in a job where they can come in contact with infested Nile water to contract the disease. Nine patients (43%) contracted the disease in the past and received timely proper treatment. None of the patients had gross polyps on sigmoidoscopy and none of the patients had evidence of

Table 1 Description of different socioeconomic classes

Class	Description
The lower class	Typified by poverty, homelessness, and unemployment Few individuals in this class finish their high school education
The working class	They suffer from lack of medical care, adequate housing and food, decent clothing, safety, and vocational training Minimally educated people who engage in "manual labor" with little or no prestige Unskilled workers in the class-dishwashers, cashiers, maids, and waitresses-usually are underpaid and have no opportunity for career advancement Skilled workers in this class-carpenters, plumbers, and electricians-may make more money than workers in the middle class, however, their jobs are usually more physically taxing, and in some cases quite dangerous
The middle class	Have more money than those below them on the "social ladder," but less than those above them The lower middle class is often made up of less educated people with lower incomes, such as managers, small business owners, teachers, and secretaries The upper middle class is often made up of highly educated business and professional people with high incomes, such as doctors, lawyers, stockbrokers, and CEOs
The upper class	The lower-upper class includes those with "new money," or money made from investments, business ventures, and so forth The upper-upper class includes those aristocratic and "high-society" families with "old money" who have been rich for generations. The upper-upper class is more prestigious than the lower-upper class Both segments of the upper class are exceptionally rich. They live in exclusive neighborhoods, gather at expensive social clubs, and send their children to the finest schools. As might be expected, they also exercise a great deal of influence and power both nationally and globally

CEOs: Chief executives.

Table 2 Distribution of gross appearance by sigmoidoscopy

Gross pathology	n (%)
Normal mucosa	10 (48)
Mucosal edema	8 (38)
Fine mucosal granularity + small superficial ulcers	3 (14)

Data are number of patients (and percentage of total).

Table 3 Distribution of histopathology of sigmoidoscopic biopsies

Histopathology	n (%)
Normal mucosa	8 (38)
Submucosal infiltration with chronic non-specific inflammatory cells	8 (38)
Features of solitary rectal ulcer	5 (24)

Data are number of patients (and percentage of total).

active schistosomiasis on histopathology. The detailed gross and histopathology results are shown in Tables 2 and 3.

Fifteen patients (71%) had early onset prolapse that started in early childhood (age < 5 years) in 11, or in late childhood or early teen ages (age between 5 and 15 years) in 4. The duration of prolapse in those patients ranged between 3 and 40 years (median duration 15 years). The median age of presentation in this group was 21 years (range 18-42 years). Six patients had late onset prolapse that started to appear in late teen ages or adulthood. The duration of prolapse in those patients ranged between 6 mo and 10 years (median duration 2 years). The median age of presentation was 34 years (range 21-41 years) (Figure 1).

Thirteen patients (62%) were habitual strainers (9 patients with long duration prolapse and 4 patients with short duration prolapse). Four patients (19%) reported straining since early childhood and four (19%) stated that prolapse followed a period of straining that ranged between 8 mo and 2 years. Two chronic strainers had stool incontinence after long period of straining; one of them was a habitual strainer since early childhood. Seven patients had recurrent prolapse when they first presented to our institution. Five of those patients were habitual strainers and all did not stop straining after their previous non-resection surgery. Three patients stated that the prolapse followed an anal operation (haemorrhoidectomy

in 2 patients and lateral sphincterotomy in one patient). Two of those patients were habitual strainers.

Nine patients (43%) in the present study came from the low social class, 10 patients (48%) came from the working class and 2 patients (9%) came from the low middle social class.

DISCUSSION

Complete rectal prolapse in Western countries occurs most commonly in elderly females, the disease being attributed to damage to the pudendal nerves during childbirth, prolonged straining at stool, and/or anatomical considerations such as a wider pelvis^[8]. The majority of complete rectal prolapse in Egypt occurs in young males. Previous studies from this country attributed this young male preponderance to intestinal schistosomiasis with its associated proctosigmoiditis, the disease being prevalent in 30% to 81% of prolapse patients in those studies^[1-3]. Unlike previous results, none of the patients in the present study had symptoms of active schistosomiasis at the time of presentation, none had gross polyps or dysentery and none had histologic evidence of schistosomiasis on rectal biopsies. Despite this, the majority of patients with rectal prolapse that we see in our institution are young males, implying that predisposing factors other than schistosomiasis must be

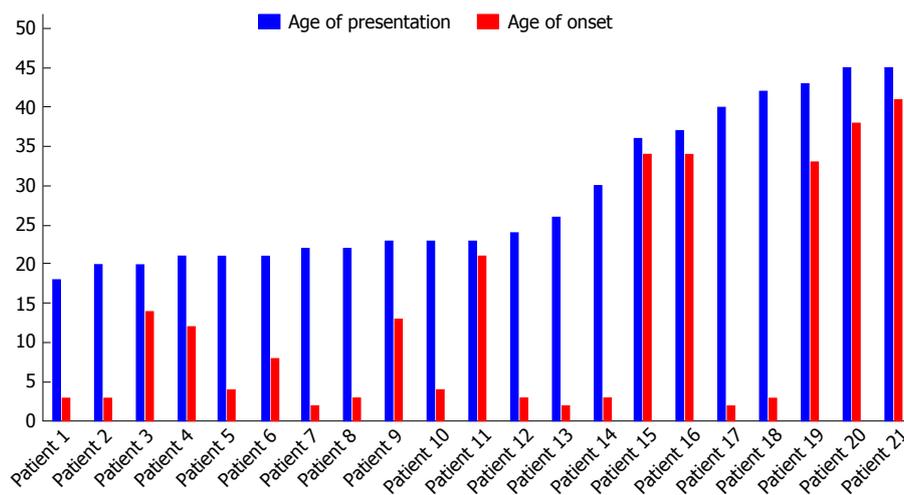


Figure 1 Age of presentation and age of onset of rectal prolapse in study subjects.

involved.

In the present study, 71% of patients had childhood or early teen age prolapse that continued through adulthood, 81% were chronic strainers at stools, and 19% started straining in their early childhood. It is therefore likely that early childhood prolapse that continues through adulthood together with chronic straining during defecation are important factors that predispose to occurrence of rectal prolapse in young Egyptian males.

Childhood rectal prolapse is uncommon in Western countries. The disease is seen more frequently in poor and developing countries where it is predisposed to by malnutrition and inadequate food hygiene^[9]. Malnutrition aggravates the natural laxity of the rectal pelvic supports that is present in infants and children, and inadequate food hygiene is associated with parasitic infections of the gastrointestinal tract and chronic diarrhea that induces excessive straining during defecation and rectal prolapse^[10]. Enterobiasis, Amoebiasis, Shigellosis, Giardiasis and infection with *Hymenolepis nana* are all common parasitic diseases that have been reported to cause diarrhea and complete rectal prolapse in children in developing countries^[11-13].

Even in developing countries, a group of countries in which Egypt is categorized, malnutrition and parasitic infections are diseases that mainly affect the lower socioeconomic classes^[14,15]. Population coming from lower socioeconomic classes suffer from poverty, unemployment, lack of high school education, lack of medical care and lack of adequate housing and food (Table 1). Ninety one percent of patients in the present study came from the low and working socioeconomic classes. Those patients are thus likely brought up in an environment in which they were malnourished and had recurrent infectious diarrhea that caused straining and complete rectal prolapse which continued to their adult life. Indeed, complete rectal prolapse is almost never seen in this age group in upper middle and high social classes in Egypt. The importance of malnutrition, diarrhea and straining in causing complete rectal prolapse in children was clearly demonstrated during the 1994 crisis in Rwanda when

a high incidence of full-thickness rectal prolapse was noted among the refugee children in the south-west of the country, the prolapses arose as a result of acute diarrheal illness superimposed on malnutrition and worm infestation^[16].

Other factors that might contribute to occurrence of complete rectal prolapse in the lower social classes are the lack of medical care for the children and the lack of high school education of the parents, the former indicates that infectious diarrhea that affects the children is unlikely to be properly treated and the latter can be reflected in bad potty training that has been shown in many studies to predispose to straining during defecation and complete rectal prolapse^[11,17].

Three patients in the present study had their prolapse after different anal operations. Probably the anal complaint in those patients was a result of straining and that they also had occult prolapse when they had their surgeries, the anal procedure just unveiled the occult prolapse. Indeed, two of those patients were chronic strainers.

Finally, we believe the high incidence of schistosomiasis in prolapse patients in previous studies from Egypt was a mere coincidence because those studies came from centers which drain rural northern delta regions where schistosomiasis is prevalent. Human infection with *Schistosoma* requires continuous contact with fresh Nile water where cercaria, a stage of *Schistosoma* life cycle, live and can infect man by penetrating his skin. This scenario essentially occurs in farmers living in rural Nile delta regions where they contact Nile water all the time during irrigation of their fields. The center in which the present study was performed is located in Cairo and it drains urban regions where schistosomiasis is non-existent. This can explain the low incidence of schistosomiasis in the present study.

Schistosomiasis should no longer be considered the main culprit for the unconventional distribution of rectal prolapse among young Egyptian males. Other factors related to socioeconomic status such as malnutrition, recurrent infectious diarrhea and bad toilet training result

in habitual straining and hence increase incidence of childhood prolapse, which when combined with neglect of treatment result in continuance of the problem through adult life. We believe this to be the cause of the currently observed distribution of complete rectal prolapse in the population.

COMMENTS

Background

In Egypt, there is an abnormal distribution of rectal prolapse among young men although in Western countries the disease is usually more common in old women. Previous literature from the area has attributed this to the spread of schistosomiasis in rural areas of Egypt which causes proctosigmoiditis and hence according to the literature - rectal prolapse.

Research frontiers

There were several findings that brought doubt to this assumption; eradication programs that caused great reduction in schistosomiasis infection, didn't similarly reduce the incidence of rectal prolapse and many of the patients with prolapse had no history of contracting schistosomiasis or even living in rural areas. This raised questions about the actual etiology for this distribution in Egypt.

Innovations and breakthroughs

Through analysis of history given by patients with rectal prolapse and assessment of possible risk factors, the authors found that socioeconomic status plays a great role in the epidemiological distribution of rectal prolapse among young males. Low socioeconomic status was associated with malnutrition, infectious diarrhea, bad toilet habits and neglect of proper treatment all of which contribute to the preponderance of rectal prolapse in this unusual subset of the population.

Applications

Identification of the actual factors causing rectal prolapse in young males is the first step in addressing the problem and directing efforts to improve conditions of lower social classes regarding sanitation, nutrition and proper treatment of various diarrheal illnesses. The authors have tried to shed some light on what the authors believe are the main causes of prolapse in young population and further studies are required in this area as proper management of etiological factors will reduce the incidence of the disease and its economic burden since young males are the main earners and source of income in many areas of Egypt.

Terminology

Authors believe there is no unusual terminology that requires further description.

Peer-review

Nice paper, well written. Very "small subject" but relevant and well analysed and discussed.

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Contemporary review of minimally invasive pancreaticoduodenectomy

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Abstract

AIM

To assess the current literature describing various minimally invasive techniques for and to review short-term outcomes after minimally invasive pancreaticoduodenectomy (PD).

METHODS

PD remains the only potentially curative treatment for periampullary malignancies, including, most commonly, pancreatic adenocarcinoma. Minimally invasive approaches to this complex operation have begun to be increasingly reported in the literature and are purported by some to reduce the historically high morbidity of PD associated with the open technique. In this systematic review, we have searched the literature for high-quality publications describing minimally invasive techniques for PD-including laparoscopic, robotic, and laparoscopic-assisted robotic approaches (hybrid approach). We have identified publications with the largest operative experiences from well-known centers of excellence for this complex procedure. We report primarily short term operative and perioperative results and some short term oncologic endpoints.

RESULTS

Minimally invasive techniques include laparoscopic, robotic and hybrid approaches and each of these techniques has strong advocates. Consistently, across all minimally invasive modalities, these techniques are associated less intraoperative blood loss than traditional open PD (OPD), but in exchange for longer operating times. These techniques are relatively equivalent in terms of perioperative morbidity and short term oncologic outcomes. Importantly, pancreatic fistula rate appears to be comparable in most minimally invasive series compared to open technique. Impact of minimally invasive technique on length of stay is mixed compared to some traditional open series. A few series have suggested

that initiation of and time to adjuvant therapy may be improved with minimally invasive techniques, however this assertion remains controversial. In terms of short-term costs, minimally invasive PD is significantly higher than that of OPD.

CONCLUSION

Minimally invasive approaches to PD show great promise as a strategy to improve short-term outcomes in patients undergoing PD, but the best results remain isolated to high-volume centers of excellence.

Key words: Pancreatic adenocarcinoma; Periampullary malignancy; Pancreaticoduodenectomy; Minimally invasive surgery; Whipple

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Core tip: In this contemporary review, we systematically review current literature regarding minimally invasive techniques and outcomes for pancreaticoduodenectomy. This review will be highly educational to providers-surgical and nonsurgical alike-who care for patients with resectable periampullary malignancies.

Dai R, Turley RS, Blazer DG. Contemporary review of minimally invasive pancreaticoduodenectomy. *World J Gastrointest Surg* 2016; 8(12): 784-791 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i12/784.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i12.784>

INTRODUCTION

Pancreaticoduodenectomy (PD) remains the only potentially curative therapy for periampullary malignancies, including, most commonly, pancreatic adenocarcinoma. Despite advances in minimally invasive techniques over the last 2 decades, the vast majority of PDs are still performed with the standard open technique that has evolved from the original Whipple procedure described in 1935^[1]. Even with modern improvements in perioperative care, contemporary complication rates after open PD (OPD) range from 25% to 65%, and thus highlight the need for surgical innovation aimed at reducing perioperative morbidity^[2-9].

In general, minimally invasive techniques have been shown to provide shorter postoperative length of stay, decreased postoperative pain, fewer wound complications, and quicker return to daily activities. Despite this evidence for the benefit of minimally invasive surgery across a broad array of surgical procedures, minimally invasive approaches to PD have not been widely adopted and remain confined to large tertiary referral centers with highly experienced surgeons^[10,11]. PD is a highly complex operation with a steep learning curve. This complexity has led some to question whether the advantages of minimally invasive approaches, seen in other general surgical procedures, translate to PD. In this review, we evaluate

the published literature to date on contemporary approaches to minimally invasive PD-including laparoscopic, robotic, and hybrid approaches-in regards to perioperative morbidity and short-term outcomes.

MATERIALS AND METHODS

Appropriate articles were identified by manually searching through PubMed and Google Scholar databases between January 1st, 2005 to January 1st, 2015, using "laparoscopic" or "robotic" or "minimally invasive" AND "pancreaticoduodenectomy" or "Whipple". Subsequent full-text papers were screened, and only the most recent publications from individual groups were used. We only included manuscripts that distinguished among or singularly published data from laparoscopic, robotic or hybrid PDs. Similarly, we only focused on studies which included greater than 5 patients, in order to assure the surgeon's experience with the technique. We only included studies which distinguished among laparoscopic, robotic or robotic assisted laparoscopic PDs (RALPDs).

Study variables included: (1) minimally invasive technique (laparoscopic, robotic, or hybrid approach); (2) number of patients; (3) age range; (4) body mass index (BMI) range; (5) American Society of Anesthesiologist physical status classification^[12]; (6) estimated blood loss; (7) operative time; (8) length of stay; (9) pancreatic fistula rate; and (10) postoperative mortality. The data are represented as average \pm SD, unless otherwise indicated in the text or table.

Average American Society of Anesthesiologist physical status classification (ASA) is used as a surrogate for an independent evaluation of how well the patient presents prior to the procedure^[13]. The higher the score, the more complicated the patient, where ASA I is defined as a normal healthy patient, and ASA III is someone with severe systemic disease. Overall complication is defined, if available, as the number of patients with post-operative complications with a graded Clavien-Dindo classification (\geq grade I)^[14]. Postoperative mortality is defined as surgical-related deaths within 30 d of procedure.

Surgical techniques

This manuscript focuses on primarily three minimally invasive surgical techniques for PD. The first is laparoscopic PD (LPD), which uses laparoscopic instrumentation to dissect, extract, and reconstruct intestinal continuity^[15]. Robotic PD (RPD) uses a robotic system (da Vinci Surgical System) in lieu of handheld laparoscopic instruments (Intuitive Surgical, Inc., Sunnyvale, CA)^[16]. Finally, hybrid RALPDs uses both laparoscopic and robotic techniques for various steps in the PD, most commonly laparoscopic dissection and specimen extraction followed by robotic reconstruction^[17].

RESULTS

LPD

Since its introduction by Gagner *et al*^[18] in 1994, widespread adoption of LPD has been limited by a steep

Table 1 Laparoscopic procedures

Ref.	Year	Robotic, open, Lap, or RAL	No. of patients	Age of patients	BMI of patients	ASA classification	EBL (mL)	Transfusion (#)	Op time (min)	Conversion (#)	Overall complications (# of patients)	Panc fistula	Length of stay	Postop death
Asbun <i>et al</i> ^[19]	2012	Lap	53	62.9 ± 14.14	27.64 ± 7.16	2.73	195 ¹ ± 136	9 ¹	541 ¹ ± 88	Counted as open	13	7	8 ¹ ± 3.2	3
Dulucq <i>et al</i> ^[21]	2006	Lap	25	62 ± 14	NR	1.39 ± 0.5	107 ± 48	3	287 ¹ ± 44	3	7	1	16.2 ± 2.7	1
Kendrick <i>et al</i> ^[22]	2010	Lap	62	66 ± 12	26	3	240	NR	368	3	11	NR	7	1
Palanivelu <i>et al</i> ^[23]	2007	Lap	42	61	NR	Only I and II	65	NR	370	0	8	3	10.2	1
Pugliese <i>et al</i> ^[20]	2008	Lap	19	64 ± 12	< 35	2.3	180 ± 55	0	461 ± 90	6	6	3	18 ± 7	0
Zureikat <i>et al</i> ^[16]	2011	Lap	14	69.8 ± 10.2	28.5	2.64	300	4	456 ¹	2	9	5	8	1

¹Indicates statistically significant compared to open procedures. RAL: Robotic assisted laparoscopy; BMI: Body mass index; ASA: American Society of Anaesthesiologists physical status classification; EBL: Estimated blood loss; NR: Not reported.

learning curve confounded by modest case volumes seen in most centers. Despite these challenges, LPD has clearly been shown to be technically feasible and is purported to have tremendous potential in improving patient outcomes. Six LPD studies without robotic components were analyzed, two of which directly compare laparoscopic with open techniques^[16,19-23]. There were no distinct differences in the patient populations (Table 1).

In the two studies which compared LPD outcomes to matched open cases at the same institution, the authors reported advantages of LPD over OPD^[16,19]. Asbun *et al*^[19] noted that LPD had significantly less intraoperative blood loss ($P < 0.001$), reduced rate of transfusion ($P < 0.001$), length of hospital stay ($P < 0.001$), and length of intensive care unit stay ($P < 0.001$). Both Asbun *et al*^[19] and Zureikat *et al*^[16] noted that operative time was significantly higher for LPD, but there were no differences in overall complications, pancreatic fistula rate, or delayed gastric emptying.

There were no significant differences in oncologic outcomes in these two studies. Asbun *et al*^[19] found that LPD had higher number of lymph nodes retrieved ($P = 0.007$), more favorable lymph node ratio ($P < 0.001$), less estimated blood loss, transfusions, and length of stay for laparoscopic procedures, while Zureikat *et al*^[24] found no significant difference in R0 resection rate, lymph node harvest, and estimated blood loss, transfusions, and length of stay.

Of the four studies that examined only LPD, all found that LPD was safe and feasible^[18,21-23]. Kendrick *et al*^[22] reported that only 3 of the 65 patients enrolled in the study converted to OPD, and of the 62 patients who underwent LPD, 26 experienced post-operative morbidity, including pancreatic fistula ($n = 11$), delayed gastric emptying ($n = 9$), bleeding ($n = 5$), and deep vein thrombosis ($n = 2$). There was one postoperative mortality within 30-d of operation. Median operating time reported was 368 min (range 258-608) and median length of hospital stay was 7 d (range 4-69 d)^[22].

Dulucq *et al*^[21] reported three of the 25 patients enrolled in the study converted to OPD, and of the 22 patients who underwent unconverted LPD, seven patients experienced postoperative complications and one patient died of a cardiac event three days after an uncomplicated surgery. A mean of 18 ± 5 lymph nodes were retrieved for malignant lesions, and all resected margins were free. Only two patients with metastatic disease received adjuvant therapy. The mean hospital stay was 16.2 ± 2.7 d. Mean operating time was 287 ± 39 min^[21].

Palanivelu *et al*^[23] also reported 5-year survival rates for the 42 patients enrolled in the study. They found that after 5-years, 32% survival over all malignancies, 30.7% with ampullary adenocarcinoma, 33.3% for pancreatic cystadenocarcinoma, 19.1% for pancreatic head adenocarcinoma, and 50% for common bile duct adenocarcinoma. The study presented with similar perioperative statistics with 8 patients with comorbidities, including gastrojejunostomy obstruction, postoperative pancreatic fistula, postoperative bile leak, pulmonary complications, intraabdominal abscess, and deep vein thrombosis. Mean operating time was 370 min, with 13 mean lymph nodes harvested, and 65 mL mean of estimated blood loss^[23].

Pugliese *et al*^[20] found that of the 19 patients undergoing LPD, 6 patients required conversion to laparotomy, 3 for bleeding and 3 for difficulties in dissection. The study recorded no mortality, but noted that 3 of the converted PDs resulted in complications including bile leakage, hemorrhage, and pulmonary embolism. The mean operating time was 461 ± 90 min, and hospital stay of 18 ± 7 d. An average of 13 ± 4 (range 4-22) lymph nodes were harvested^[18].

RPD

Robotic technology has many of the advantages ascribed to laparoscopic surgery by virtue of using laparoscopic ports and minimal incision size and was first reported by Giulianotti *et al*^[25] in 2003. Robotic instrumentation

Table 2 Robotic procedures

Ref.	Year	Robotic, open, Lap, or RAL	No. of patients	Age of Patients	BMI of patients	ASA classification	EBL (mL)	Transfusion (#)	Op time (min)	Conversion (#)	Overall complications (# of patients)	Panc fistula	Length of stay	Postop death
Boggi <i>et al</i> ^[28]	2013	Robotic	34	60	24.4	2.29	220	4	597	0	19	13	23	0
Buchs <i>et al</i> ^[29]	2011	Robotic	44	63 ± 14.5	27.7 ± 5.4	2.5 ± 0.5	387 ¹ ± 334	10 ¹	444 ¹ ± 93.5	2	16 ¹	8	13 ¹ ± 7.5	2
Chan <i>et al</i> ^[31]	2011	Robotic	8	71.5	NR	NR	200	NR	478	1	5	3	12	0
Zhou <i>et al</i> ^[30]	2011	Robotic	8	64.4 ± 9.1	NR	NR	153.8 ¹ ± 43.4	NR	718.8 ¹ ± 186.7	0	2 ¹	NR	16.38 ¹ ± 4.1	0

¹Indicates statistically significant compared to open procedures. RAL: Robotic assisted laparoscopy; BMI: Body mass index; ASA: American Society of Anaesthesiologists physical status classification; EBL: Estimated blood loss; NR: Not reported.

provides 3-dimensional visibility, increased degrees of freedom, and improved ergonomics though possibly less haptic advantage^[26,27]. Advocates of robotic surgery suggest that the advantages in robotics provide obvious benefits for complex procedures such as PD surgeries^[28]. However there is little comparative data available to support the routine use of robotics over laparoscopy for pancreatic resections (Table 2).

This review describes four robotics experiences, of which two incorporated comparison studies with OPD^[29-31]. Buchs *et al*^[29] found that despite the RPD group having statistically significant older (63 years old RPD vs 56 years old OPD; $P = 0.04$) and heavier patients (BMI 27.7 RPD vs 24.8 OPD; $P = 0.01$), with a higher American Society of Anesthesiologist score (RPD 2.5 vs OPD 2.15; $P = 0.01$), when compared to OPD group, there were no significant differences in complications, mortality rates, and length of hospital stays between the two groups^[29]. The study found that RPD surprisingly had shorter operative time (444 min vs 559 min; $P = 0.0001$), reduced blood loss (387 mL vs 827 mL; $P = 0.0001$), and higher number of lymph nodes harvested (16.8 vs 11; $P = 0.02$).

Similarly, Zhou *et al*^[30] found that RPD group had longer operative times than OPD (718 min RPD vs 420 min OPD; $P = 0.011$), but less intraoperative blood loss (153 mL RPD vs 210 mL OPD; $P = 0.04$), fewer complications (25% RPD vs 75% OPD, $P = 0.05$), and decreased hospital stay (27.5 h RPD vs 96 h, $P = 0.000$). There was no significant difference in R0 resection rate between the two groups.

Boggi *et al*^[28] reported for 34 patients undergoing RPD, the mean operating time was 597 min (range 420-960 min) and mean intraoperative blood loss was 220 mL (range 150-400 mL), with 4 patients requiring blood transfusions. Nineteen of the 34 patients in the study developed postoperative complications (utilizing the Clavien-Dindo classification), five of which had a classification of III or higher. The mean number of lymph nodes retrieved in the study was 32 (range 15-76). Thirty-day mortality was 0%^[28].

Chan *et al*^[31] reported 55 patients undergoing robotic hepatobiliary and pancreatic surgeries, of which eight were pancreaticoduodenectomies. Of the patients under-

going pancreatic resections, Chan *et al*^[31] found that the operating time had a median of 478 min, ranging from 270-692 min, with blood loss of 200 mL (range 30-300 mL). There were 4 complications resulting in pancreatic fistula and biliary fistula, but all were treated conservatively and healed without any significant sequelae. There was no mortality in the postoperative hospital stay of a median 12 d (range 6-21 d).

RALPD: Hybrid techniques (RALPD) include a combination of laparoscopic and robotic utilization for PD. We report five hybrid studies here, three of which are comparison studies to OPD^[32-36]. In all 3 comparison studies, RALPD demonstrated significantly lower intraoperative blood loss. In the first reported RALPD study, Chalikonda *et al*^[32] found that there was a significant increase in operative time (476.2 min RALPD vs 366.4 min OPD; $P = 0.005$), but decreased length of stay for RALPD (9.79 d RALPD vs 13.26 d OPD; $P = 0.043$)^[24]. The study found that there was no significant difference between the two techniques in postoperative morbidity (30% RALPD vs 44% OPD; $P = 0.14$), or reoperation (6% RALPD vs 24% OPD; $P = 0.17$). The study noted that there were 3 patients (12%) undergoing RALPD that were converted to OPD due to excessive bleeding (Table 3).

Similarly, Kuroki *et al*^[34] found decreased intraoperative blood loss with RALPD (376 mL RALPD vs 1509.5 mL OPD; $P < 0.01$), but there was also a significantly higher number of blood transfusions compared with OPD (0 blood transfusions in RALPD vs 13 in OPD; $P < 0.01$). The study found that there was no significant difference between the two techniques in operative time or postoperative complications.

Lai *et al*^[35] reported that RALPD had a significantly longer operative time (491.5 min RALPD vs 264.9 min; $P = 0.01$), decreased blood loss (247 mL RALPD vs 774.8 mL OPD; $P = 0.03$), and shorter hospital stay (13.7 d RALPD vs 25.8 d OPD; $P = 0.02$). Conversion rate from RALPD to OPD was 5%, and the study did not find a significant difference between the two groups in overall complication rates (50% RALPD vs 49.3%; $P = 0.95$), mortality rates (0% RALPD vs 3% OPD; $P = 0.43$), rate

Table 3 Robotic assisted procedures

Ref.	Year	Robotic, open, Lap, or RAL	No. of patients	Age of Patients	BMI of patients	ASA classification	EBL (mL)	Transfusion (#)	Op time (min)	Conversion (#)	Overall complications (# of patients)	Panc fistula	Length of stay	Postop death
Chalikonda <i>et al</i> ^[32]	2012	RAL	30	62	24.8	2.6	485	NR	476 ¹	3	9	2	9.79 ¹	1
Giulianotti <i>et al</i> ^[33]	2010	RAL	60	58	NR	NR	394	6	421	11	No PD only	19	22	2
Kuroki <i>et al</i> ^[34]	2012	RAL	20	71.2 ± 8.8	21.9	1.5 ± 0.6	376.6 ± 291.4 ¹	0 ¹	656.6 ± 191.4	NR	9	12	NR	NR
Lai <i>et al</i> ^[35]	2012	RAL	132	66.4 ± 11.9	NR	1.8	247 ¹	NR	491.5 ¹ ± 94	1	10	7	13.7 ¹ ± 6.1	0
Zeh <i>et al</i> ^[36]	2012	RAL	50	68 ± 16	27 ± 5	2.6	350 ¹	11	568 ¹	8	28	11	10 ¹	1

¹Indicates statistically significant compared to open procedures. RAL: Robotic assisted laparoscopy; BMI: Body mass index; ASA: American Society of Anaesthesiologists physical status classification; EBL: Estimated blood loss; NR: Not reported; PD: Pancreaticoduodenectomy.

of reoperation (2% or 10% RALPD vs 3% or 4.5% OPD; $P = 0.04$), R0 resection rate (11% or 73.3% RALPD vs 34% or 64.1% OPD; $P = 0.92$), and harvested lymph node numbers (10 ± 6 RALPD vs 10 ± 8 OPD; $P = 0.99$).

Of the 2 noncomparison studies, Giulianotti *et al*^[33] published the largest series of robotic pancreatic surgery to date with 134 patients, 60 of which were PD. This study reported similar outcomes to previous studies, including mean operative time with 331 min (range 75-660 min), mean length of hospital stay at 9.3 d (range 3-85 d), postoperative complication rate at 26%, and mortality rate of 2.23% (3 patients).

Zeh *et al*^[36] examined 50 patients undergoing RALPD, 8 of which required conversion to open procedure (16%). Overall, 28 patients (56%) experienced postoperative complications, 13 of which were Clavien I / II. Intraoperative blood loss had a median of 350 mL (interquartile range: 150-625), with 11 patients (22%) requiring transfusions. The median length of stay reported by the study was 10 d (IQR 8-13). The median number of lymph nodes collected was 18 (IQR 5) and Zeh *et al*^[36] report that 89% of the resections had negative margins.

Pancreatic fistula

Pancreatic leak at the pancreaticojejunostomy anastomosis is one of the most serious and common postoperative complications after PD, and can lead to erosion of adjacent tissues, bleeding from large vessels, severe pancreatitis, peritonitis, and sepsis. The complexity of this anastomosis has often been cited as the primary obstacle to widespread adoption of minimally invasive techniques for PD. Broadly, there did not appear to be significant differences in pancreatic fistula rates between minimally invasive and open techniques. Pancreatic leaks can be classified according to the International Study Group on Pancreatic Fistula criteria^[37]. In Asbun *et al*^[19], there were 29 (13.5%) pancreatic fistulas in the open group (Grade A = 14, B = 5, C = 10), and 7 (13.2%) in the laparoscopic group (Grade A = 3, B = 1, C = 3), with a nonsignificant P -value^[19]. Similarly, there is no significant difference in the pancreatic fistula rate between robotic

and open groups as demonstrated in Buchs *et al*^[29], where both open and robotic had 8 pancreatic fistulas at a rate 21% (Grade A = 5, B = 1, C = 2) and 18% (Grade A = 4, B = 3, C = 1) respectively, with a $P = 1$. The same could be seen between open and RAL groups, such as in Chalikonda *et al*^[32], where there were 5 (16.7%) in the open group (Grade B = 2, C = 5), and 2 (6.7%) in the RAL group (Grade B = 1, C = 1)^[32].

Cost analysis

In 2013, Mesleh *et al*^[38] published an analysis of a single institution analysis of the cost of LPD vs OPD. Using a similar dataset as Asbun *et al*^[19], Mesleh *et al*^[38] found that of 123 patients who underwent PD, with 48 OPD (39%) and 75 LPD (61%), there was no significant difference in overall cost of LPD compared to OPD, because of increased postoperative cost of OPD.

Consistent with other studies, Mesleh *et al*^[38] found that the intraoperative cost of LPD was significantly higher than that of OPD, due to increased equipment expense and mean operative time ($P < 0.0001$, OPD 355 min, range 199-681; LPD 551 min, range 390-819). Similarly, they determined that both OPD and LPD had similar rates of morbidity of 31% for both groups, with median hospital stay for OPD at 8 d (range 5-63), and 7 d (range 4-68) for LPD ($P = 0.5$). However in postoperative categories, OPD represented slightly higher cost per unit in anesthesia, critical care, pathology, pharmacy, nursing, and radiology. Because admission accounted for 65%-70% of the total cost, the increased postoperative cost of OPD balanced the excess intraoperative cost of LPD.

Similarly, Boggi *et al*^[28] reported a cost analysis of RPD compared to OPD, and found that RPD's intraoperative cost significant exceeds that of OPD by approximately 6193 euros, or \$5034.90 based on the currency exchange rate used in the study on 15 August 2012 (<http://www.x-rates.com/calculator.html>). In the United States, according to Chalikonda *et al*^[32], the cost of disposables of robotic and laparoscopic equipment can be as high as \$4000-5000 per case, plus the associated significant higher operative time.

Thus, in an era of limited health care dollars, cost

issues associated with minimally invasive techniques, especially robotic platforms, are important considerations as these techniques are adopted more broadly into less experienced centers.

With the emergence of newer technologies and improving minimally invasive techniques, it is important to understand the potential benefits of laparoscopic, robotic, and robotic assisted techniques. From this systematic review of the data presented, LPD, RPD, and RALPD in general appear to have less intraoperative blood loss than OPD, but in exchange for longer operating times. However, it is important to realize that all of these studies are subject to heavy selection bias, with the most difficult cases still typically being performed with open technique.

Most studies have failed to show any significant difference between the open and minimally invasive techniques in terms postoperative mortality and overall complications, though mortality may be higher with minimally invasive PD at less experienced centers^[39,40]. This issue is an extraordinarily important consideration for centers with lower surgeon volume and potentially less expertise with minimally invasive techniques. Regarding pancreatic fistula, there does not appear to be a significant difference between minimally invasive and open techniques. As the learning curve improves and technology improves, differences between techniques may begin to emerge. This issue has been most consistently touted by robotics advocates. Finally, minimally invasive techniques also appear to be equivalent in terms of short-term oncologic endpoints.

In the context of broader oncologic issues, Some studies suggest that more favorable short-term outcomes including decreased pain, quicker return to daily activities, and potentially fewer wound issues may favor increased utilization of and shorter time to adjuvant therapy^[41-44]. This issue too remains somewhat unproven but is an important consideration given the dismal outcomes with surgery alone for this disease^[23,45-47].

In summary, there remain many hurdles before the widespread use of laparoscopic and RPD take hold, the most significant of which is the steep learning curve associated with minimally invasive PD^[48,49]. Currently, minimally invasive PDs require extensive training and advanced equipment, and so are only performed by select surgeons for select patients at select tertiary centers^[50]. Robotic approaches may shorten the learning curve for minimally invasive PD but this has yet to be definitely proven^[51]. Even for OPD, the learning curve is steep, and a robust literature has shown tremendous variations in outcome for patients, depending on surgeon volume, hospital volume, and multidisciplinary collaboration. Thus, minimally invasive approaches to PD appear to be feasible and safe in the hands of highly experienced surgeons at centers of expertise, but widespread adoption remains a challenge given the steep learning curve, limitations of technology, and important cost considerations in an era of limited health care resources.

COMMENTS

Background

Pancreaticoduodenectomy (PD) remains the only potential curative therapy for periampullary malignancies, including, most commonly, pancreatic adenocarcinoma. Despite advances in minimally invasive techniques over the last 2 decades, the vast majority of PDs are still performed with a standard open technique (OPD) that has evolved from the original Whipple procedure described in 1935.

Research frontiers

Even with modern improvements in perioperative care, contemporary complication rates after OPD range from 25% to 65%, and thus highlight the need for surgical innovation aimed at reducing perioperative morbidity.

Innovations and breakthroughs

Despite a growing body of evidence supporting minimally invasive techniques to expedite post-operative recovery, decrease postoperative pain and reduce wound complications, minimally invasive approaches to PD have not been widely adopted and remain confined to large tertiary referral centers with highly experienced surgeons.

Applications

In general, minimally invasive techniques have been noted to provide shorter hospitalizations, fewer post-operative complications, and less time to adjuvant therapy. However, whether the advantages of minimally invasive approaches, seen in other general surgical oncologic procedures, translate to PD remains unclear. Here, the authors review current data regarding the applicability of minimally invasive approaches to PD.

Peer-review

This is an interesting and timely study.

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Bevacizumab and gastrointestinal bleeding in hereditary hemorrhagic telangiectasia

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Abstract

We report a case of severe, refractory gastrointestinal (GI) bleeding in a patient with hereditary hemorrhagic telangiectasia (HHT) whose massive transfusion dependence was lifted shortly after treatment with bevacizumab, an anti-vascular endothelial growth factor. The patient's bleeding had been refractory to repeated endoscopic interventions, tranexamic acid, and tamoxifen. However, following treatment with bevacizumab at 5 mg/kg every other week, nearly 300 units of packed red blood cell transfusions were avoided in one year's time. Despite its relatively high cost, bevacizumab may have a more active role in the management of severe GI bleeding in HHT if such remarkable response can be consistently demonstrated.

Key words: Bevacizumab; Vascular endothelial growth factor; Hereditary hemorrhagic telangiectasia; Bleeding; Osler-Weber-Rendu syndrome

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Core tip: Management of gastrointestinal (GI) bleeding in patients with hereditary hemorrhagic telangiectasia (HHT) can be challenging when the vascular lesions recur despite repeated endoscopic treatments. There is increasing evidence supporting the use of anti-angiogenesis agents in the management of bleeding in HHT patients. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been shown to reduce recurrent epistaxis. This case demonstrates the therapeutic potential of bevacizumab in patients with severe GI bleeding requiring massive transfusions.

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bleeding in hereditary hemorrhagic telangiectasia. *World J Gastrointest Surg* 2016; 8(12): 792-795 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i12/792.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i12.792>

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterized by vascular malformations that occur systemically, leading to manifestations such as recurrent epistaxis, gastrointestinal (GI) bleeding, and arteriovenous malformations (AVM) of the lung, liver, and brain. Since the discovery of elevated vascular endothelial growth factor (VEGF) expression in patients with HHT^[1], reports of bevacizumab, a monoclonal antibody against VEGF, in managing complications of HHT have emerged^[2-16], with most of the reported experience in recurrent epistaxis. We present a case of HHT with massive, refractory transfusion requirements secondary to severe GI bleeding that did not respond to conventional therapy, but subsequently achieved transfusion-independence with anti-VEGF mono-therapy.

CASE REPORT

A 58-year-old female with HHT and positive family history, involving her mother, sister, and daughter, presents with a 30-plus-year history of increasing transfusion dependency due to a combination of daily epistaxis, gastrointestinal bleeding, and intermittent gross hematuria. She did not have hemoptysis. Relevant medical history included hepatitis C infection secondary to transfusions, pulmonary hypertension from high-output cardiac failure secondary to chronic severe anemia, pulmonary AVMs with previous embolizations, and hysterectomy at the age of 26 for menorrhagia.

Her initial transfusion requirement was approximately one unit of packed red blood cells (pRBC) per month, but as of 2003 required > 40 units per year due to persistent epistaxis and increasing upper GI bleeding in the form of melena. Capsule endoscopies and upper endoscopies demonstrated innumerable AVMs in the esophagus, stomach, duodenum, and jejunum, with the bulk of the lesions located in the proximal small bowel where active bleeding was most frequently seen. Mesenteric angiography also demonstrated diffuse vascular abnormality/telangiectasia involving proximal small bowel but no focal AVM amenable to embolization. Biochemical investigations excluding other etiologies included normal renal function, thyroid stimulating hormone, haptoglobin, bilirubin, lactate dehydrogenase, direct agglutination testing, serum protein electrophoresis, serum free light chain, urine protein electrophoresis, and von Willebrand factor studies. Her hepatitis C viral load was low and abdominal ultrasound did not demonstrate cirrhosis.

Her transfusion requirement further escalated despite successful interventions including multiple septal

dermatoplasties and facial/nasal vessel angiography with embolization. At least seven upper endoscopies with argon plasma coagulation, two-month tamoxifen therapy, and tranexamic acid which led to upper extremity deep vein thrombosis, were used for ongoing bleeding from the duodenum/proximal jejunum. She received neither estrogen therapy nor thalidomide due to risk of hormone-sensitive malignancy and limited access/financial constraint, respectively. Additionally, her advanced cardiopulmonary comorbidities, which were complications of HHT, precluded surgical resection of the proximal small bowel (*i.e.*, Whipple procedure) containing the majority of the vascular lesions in order to reduce GI bleeding. Between 2008 and 2015, she received on average six units of pRBC weekly (*i.e.*, 312 unit per year) as well as monthly intravenous iron infusion.

In April 2015, she was started on bevacizumab, an anti-VEGF antibody, at 5 mg/kg every two weeks as a last resort. The patient's response to bevacizumab in terms of GI bleeding was immediate and dramatic: Her stools returned to normal color and consistency, and her transfusion requirement dropped to four units per month between May and September, and further down to only two units over the course of the following seven months with intravenous iron supplementation (Figure 1). She continued to experience minor epistaxis that was much less severe than previous, and ongoing microscopic hematuria without proteinuria or renal function impairment.

Over the past 12 mo, the administration of bevacizumab has resulted in a decrease of approximately 290 units of pRBC's and improved the patient's quality of life immensely. The patient has tolerated the infusions without any reported side-effects.

DISCUSSION

This case highlights the potential challenges in managing HHT with complicated, refractory GI bleeding. In our patient's case, she acquired hepatitis C infection due to repeated transfusions, and developed high-output cardiac failure and pulmonary hypertension due to severe chronic anemia. Her functional capacity was poor due to anemia and pulmonary hypertension, but the need for frequent transfusions three times a week (> 1400 units of pRBC in the five years prior to treatment) also posed a tremendous negative impact on her quality of life in addition to causing a significant burden on the health care system. Fortunately, the patient's response to bevacizumab exceeded our expectations. The greatest hurdle of obtaining the drug was in fact, obtaining approval from regulatory bodies for financial coverage of it. However, after one year, the overall cost to the health care system of avoiding most transfusions is staggering. Given the severity of her blood loss, which to our knowledge is one of the most severe cases reported, our initial goal had been to reduce her transfusion requirement by 40%-50%, but she essentially became transfusion-independent.

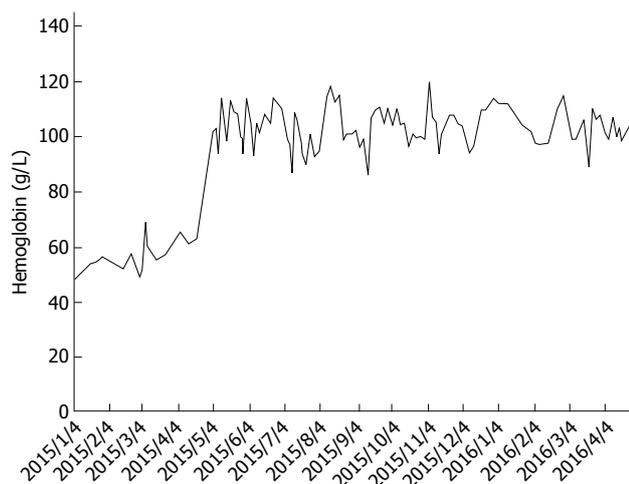


Figure 1 Hemoglobin trend. Hemoglobin trend before and after initiation of bevacizumab 5 mg/kg every other week starting in April 2015.

We opted to prescribe 5 mg/kg every other week, which is the typical dose for solid organ malignancies, since this is the regimen with the most clinical evidence to date for HHT^[17]. The optimal dosage and duration of bevacizumab for GI bleeding in HHT remains to be determined, and requires balancing the clinical benefits against potential adverse events of systemic treatment such as hypertension, nephrotic syndrome, poor wound healing, bowel perforation, and thromboembolic events^[18]. There have been reports successfully utilizing lower doses for GI bleeding, based on the drug's pharmacokinetics^[4,5,7,15], but some patients may require higher doses to maintain optimal response^[10]. Although the specific optimal dosage is not entirely clear at this time, the duration of treatment is likely indefinite as relapses upon discontinuation of therapy have been noted in previous reports, with the interval ranging from one to three months after the last dose^[4,7,8,15].

This case demonstrates a remarkable response in regards to GI bleeding to bevacizumab in the setting of HHT. Although not specifically examined yet in our patient, additional benefits such as partial reversal of liver failure and high-output cardiac failure have also been reported^[19-21]. Despite its high cost, earlier administration should be considered if benefit of this extent is regularly demonstrated in this group of patients as prevention of end organ complications (*i.e.*, cardiac/hepatic) theoretically might have been prevented with early administration. The issue of cost in many situations perhaps should not be paramount when aiming for ideal care in these patients with limited options.

Bevacizumab effectively controlled severe GI bleeding in this patient with complicated HHT.

COMMENTS

Case characteristics

A 58-year-old woman with hereditary hemorrhagic telangiectasia (HHT) presented with severe, chronic gastrointestinal (GI) bleeding refractory to multiple treatment modalities.

Clinical diagnosis

Endoscopies demonstrated numerous arteriovenous malformations in the esophagus, stomach, duodenum, and jejunum. The majority of the lesions were located in the proximal small bowel where active bleeding was frequently seen.

Differential diagnosis

Vascular lesions of GI tract: Angiodysplasia (sporadic, end-stage renal disease, aortic stenosis, von Willebrand disease, left ventricular assist device), systemic disease (CREST, HHT).

Laboratory diagnosis

Biochemical investigations included normal renal function, thyroid stimulating hormone, haptoglobin, bilirubin, lactate dehydrogenase, direct agglutination testing, serum protein electrophoresis, serum free light chain, urine protein electrophoresis, and von Willebrand factor studies. Pre-bevacizumab mean hemoglobin was 57.2 ± 5.8 g/dL. Post-bevacizumab hemoglobin was 103.4 ± 8.3 g/dL.

Imaging diagnosis

Mesenteric angiography did not identify suitable arteriovenous malformation that was amenable to treatment via embolization of the gastroduodenal artery.

Treatment

Bevacizumab 5 mg/kg infusion every other week.

Related reports

There is growing evidence in the literature on bevacizumab's efficacy in treating recurrent epistaxis due to HHT, but relatively few reports exist for the management of severe, chronic, refractory GI bleeding. This case highlights the potential utility of bevacizumab for such management.

Term explanation

HHT is an autosomal dominant condition characterized by vascular malformations that can occur anywhere in the body, leading to various presentations including epistaxis, GI bleeding, high-output cardiac failure, and hypoxemia.

Experiences and lessons

Earlier administration of bevacizumab should be considered in patients with severe, refractory GI bleeding despite its relatively high cost given the potential benefit.

Peer-review

This is a pretty straightforward case report.

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