ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2016 January 27; 8(1): 1-105

Published by Baishideng Publishing Group Inc

WJGS

World Journal of Gastrointestinal Surgery

A peer-reviewed, online, open-access journal of gastrointestinal surgery

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2012-2016

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World Journal of Gastrointestinal Surgery

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Monthly Volume 8 Number 1 January 27, 2016

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

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World Journal of Gastrointestinal Surgery is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

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NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
January 27, 2016

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-9366/g_info_20100305152206.htm

ONLINE SUBMISSION
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WJGS World Journal of Gastrointestinal Surgery

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4240/wjgs.v8.i1.1

World J Gastrointest Surg 2016 January 27; 8(1): 1-4
ISSN 1948-9366 (online)

EDITORIAL

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

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Author contributions: Giamundo P had performed the literature research and written the manuscript.

Conflict-of-interest statement: Giamundo P is a surgical trainer for Biolitec Italia, Milan, Italia. No fees were received to write this editorial.

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Received: August 21, 2015
Peer-review started: August 24, 2015
First decision: September 30, 2015
Revised: October 9, 2015
Accepted: November 24, 2015
Article in press: November 25, 2015
Published online: January 27, 2016

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

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 dearteria-lization in the treatment of symptomatic hemorrhoids. *World J*

Gastrointest Surg 2016; 8(1): 1-4 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/1.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.1

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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P- Reviewer: Christodoulidis G, Crea N, El-Tawil AM, Riss S
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

WJGS World Journal of Gastrointestinal Surgery

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4240/wjgs.v8.i1.5

World J Gastrointest Surg 2016 January 27; 8(1): 5-26
ISSN 1948-9366 (online)

TOPIC HIGHLIGHT

2016 Laparoscopic Surgery: Global view

Laparoscopic liver resection: Experience based guidelines

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Conflict-of-interest statement: All authors have no conflict of interest related to the manuscript.

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Received: April 28, 2015
Peer-review started: May 7, 2015
First decision: August 4, 2015
Revised: September 7, 2015
Accepted: November 24, 2015
Article in press: November 25, 2015
Published online: January 27, 2016

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

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 it's current role and expected achievements.

Coelho FF, Kruger JAP, Fonseca GM, Araújo RLC, Jeismann VB, Perini MV, Lupinacci RM, Cecconello I, Herman P. Laparoscopic liver resection: Experience based guidelines. *World J Gastrointest Surg* 2016; 8(1): 5-26 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/5.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.5

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*[1] and Descottes *et al*[2] 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 (CO_2) 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: $\leqslant$ 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 (%) PLLR	HALS	Hybrid	Major resections (%)	Conversion (%)	Operative time (median/mean, min)	Blood loss (median/mean, mL)	Transfusion (%)	LOS (median/mean, d)	Complication (%)	Mortality (%)
Koffron *et al*[13]	300	34	80.3	10.6	9	39	7.3	99	102	0.6	1.9	9.3	0
Buell *et al*[165]	306	42	NR	NR	NR	45	2.4	162	222	7	2.9	16	1.6
Bryant *et al*[163]	166	60	95.2	4.8	0	18.6	9.6	180	329	5.4	6	15.1	0
Long *et al*[164]	173	100 (HCC)	100	0	0	8.3	2.3	112	194	NR	6.5	2.4	0
Cai *et al*[81]	365	27.1	100	0	0	22.2	17.2	150	370	NR	9.2	12.2	0
Gobardhan *et al*[93]	476	79	NR	NR	NR	33.8	4.2	NA	NA	4.6	NR	21	0.8
Troisi *et al*[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

PLLR: 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[84,98]. 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 *et al*[28]	12[1]	Retrospective	0	8.3	0	0	0
Descottes *et al*[12]	87	Retrospective multicenter	3.4	10	6	5	0
Ardito *et al*[29]	50	Retrospective	16	8	2	10	0
Troisi *et al*[30]	20	Comparative (LLR × OLR)	2.5	10	10	20	0
Abu Hilal *et al*[32]	50	Retrospective	28	2	2	7	0
Abu Hilal *et al*[31]	13 HA only	Retrospective	62	0	7.7	7.7	0
Herman *et al*[17]	31 HA only	Retrospective	16.7	0	0	6.5	0
de'Angelis *et al*[197]	36 HA only	Comparative (LLR × OLR)	25	8.3	0	8.3	0
Dokmak *et al*[33]	31 LLS only	Comparative LLS (LLR × OLR)	0	6.5	NR	9.7	0
Ding *et al*[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

[1]Included 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	*P* value	LLR	OLR	*P* value		LLR	OLR	*P* value	LLR	OLR	*P* value	LLR	OLR	*P* value	LLR	OLR	*P* value
Belli *et al*[34]	54	125	297	580	< 0.01	11	25.6	0.03	7	19	36	0.02	2	4	NS	67[1]	-	NS	52[1]	-	NS
Tranchart *et al*[35]	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]	54.3[1]	NS
Truant *et al*[36]	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	33.6	NS
Lee *et al*[37]	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	55.9	NS
Hu *et al*[110]	30	30	520 g	480 g	NS	NA	NA	-	0	13.3	10	NS	0	0	NS	50	50.3	NS	NR	NR	-
Ker *et al*[38]	116	208	139	1147	< 0.001	6.9	50.9	< 0.001	5.2	6	30.2	< 0.001	0	2.9	NS	62.2	71.8	NS	NR	NR	-
Cheung *et al*[39]	32	64	150	300	0.001	0	4.7	NS	NR	6.3	18.8	NS	0	1.6	NS	76.6	57	NS	54.5	44.3	NS
Ai *et al*[40]	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]	67[1]	NS
Memeo *et al*[41]	45	45	200	200	NS	0	0	NS	NR	20	45	0.01	2	13	0.04	59	44	NS	19	23	NS
Kim *et al*[42]	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	NS
Kim *et al*[198]	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	NS
Ahn *et al*[43]	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	NS
Yamashita *et al*[44]	63	99	455	436	NS	6	2	NS	NA	10	26	0.046	0	0	NS	69	77	NS	33	41	NS
Yoon *et al*[45]	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]	NS
Martin *et al*[46]	100	254	336	755	< 0.001	1.2	2.4	0.043	NR	44	57	NS	6	8	NS	60.7[1]	41.8[1]	NS	20[1]	26[1]	NS
Lee *et al*[47]	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	NS
Han *et al*[48]	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	NS
Xiao *et al*[49]	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]	NS

[1]Data computed for 3-yr survival; [2]Data 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	*P* value	LLR	OLR	*P* value		LLR	OLR	*P* value	LLR	OLR	*P* value	LLR	OLR	*P* value	LLR	OLR	*P* value
Castaing *et al*[50]	60	60	NR	NR	-	15	36	0.007	10	27	28	NS	1.7	1.7	NS	64	56	NS	30	20	NS
Abu Hilal *et al*[51]	55	119	363	500	NR	3.6	NR	NR	12	15	20.2	NR	0	2	NR	NR	NR	NR	NR	NR	-
Cannon *et al*[52]	35	140	202	392	< 0.001	17	25	NS	NR	23	50	0.004	0	1.4	NS	36	42	NS	15	22	NS
Qiu *et al*[53]	30	140	215	390	< 0.001	10	25	< 0.05	6.6	26.2	55	< 0.001	0	0	NS	NR	NR	-	NR	NR	-
Guerron *et al*[54]	40	40	376	753	0.041	5	20	0.04	5	15	20	NS	0	0	NS	NR	NR	NS	NR	NR	NS
Kubota *et al*[55]	43	62	287.3	579.3	< 0.001	2.4	21	0.004	NR	2.4	9.7	NS	0	0	NS	88.4[1]	74.2[1]	NS[1]	NR	NR	-
Montalti *et al*[56]	57	57	454.2	691.5	0.003	NR	NR	-	15.8	15.8	31.6	0.03	0	0	NS	60	65	NS	29	38	NS
de'Angelis *et al*[57]	52	52	200	300	0.001	5.8	21.2	NS	5.8	17.3	22	NS	0	3.8	NS	73.1	62.5	NS	21.1	21.1	NS
Hasegawa *et al*[58]	102	69	127	620	0.000	NR	NR	NR	1	8.8	24.6	0.005	0.98	1.4	NS	56.8	48.8	NS	39.7	28.6	NS

[1]Data 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[136]. 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 × LLR	Conversion rate	Favors ORL	Favors LLR	Equal OLR × LLR
Simillis *et al*[151]	8 1998-2005	Observational Nonrandomized Comparative Benign and malignant disease	Short-term outcomes	244 (59.7%) × 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
Croome *et al*[150]	26 1998-2009	Observational Nonrandomized Comparative Benign and malignant disease	Short and long-term outcomes	1019 (53.9%) × 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	Blood transfusion rate Operative time Incidence of portal triad clamping Oncologic clearance Recurrence risk
Mirnezami *et al*[149]	26 1998-2009	Observational Nonrandomized Comparative Benign and malignant disease	Short and long-term outcomes	961 (57%) × 717 (43%)	7%	Operative time	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	Portal trial clamping time Margin size Hepatic tumor recurrence for HCC DFS for HCC
Zhou *et al*[118]	10 2001-2010	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	281 (56.9%) × 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
Mizuguchi *et al*[152]	11 2001-2008	Observational Nonrandomized Comparative Benign and malignant disease	Short-term outcomes	253 (52.2%) × 232 (47.8%)	NR	-	Operative blood loss Postoperative complications LOS	Operative time
Fancellu *et al*[111]	9 2001-2010	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	363 (61.5%) × 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
Rao *et al*[94]	7 2005-2009	Observational Nonrandomized Comparative only patients undergoing laparoscopic × open LLS	Short-term outcomes	111 (45.3%) × 134 (54.7%)	2.7%	-	Postoperative complications Operative time LOS	Operative blood loss Blood transfusion rate Rate of positive margins
Li *et al*[173]	10 2001-2011	Observational Nonrandomized Comparative HCC only	Short and long-term outcomes	383 (61%) × 244 (39%)	6.6%	-	Operative blood loss Blood transfusion rate Postoperative complications LOS	Operative time Surgical margin size Rate of positive margins Tumor recurrence
Rao *et al*[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	Overall and liver specific complications Operative mortality Margin width DFS OS Recurrence rate

Xiong *et al*[117]	15 2001-2011	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
Rao *et al*[172]	10 2002-2009	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	Operative time Ascitis Postoperative liver failure DFS OS Recurrence rate
Yin *et al*[174]	15 2001-2011	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	Surgical margins Operative time Negative margins rate Recurrence rate OS RFS
Zhou *et al*[129]	8 2002-2013	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 *et al*[168]	4 2009-2013	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	Operative time OS DFS
Parks *et al*[167]	15 2001-2011	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 *et al*[128]	7 2002-2013	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 time LOS OS DFS
Wei *et al*[127]	14 2002-2013	Observational Nonrandomized Comparative CRLM only [1]3 studies comparing simultaneous laparoscopic × open resections	Short and long-term outcomes	599 (61.4%) × 376 (38.6%)	NR	-	Operative blood loss Blood transfusion rate LOS Postoperative complications [1]Simultaneous resection LOS	Operative time Perioperative mortality OS DFS [1]Simultaneous resection Morbidity, operative time, operative blood loss

Schiffman *et al*[130]	8 2009-2013	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 *et al*[153]	46 2001-2013	Observational Nonrandomized Comparative Benign and malignant disease	Short-term outcomes	1741 (47.8%) × 1901 (52.2%)	5.68%	Cost	Operative blood loss Negative margin LOS Postoperative complications	Operative time 30-d mortality
Morise *et al*[169]	21 2001-2014	Observational Nonrandomized Comparative HCC only	Ascitis	602 (63.1%) × 352 (36.9%)	NR	-	Less ascites Less postoperative liver failure	-
			Postoperative liver failure	220 (54.6%) × 183 (45.7%)				

[1]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; LLS: 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. Vigano *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 CO_2 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 CO_2 embolism, this was not associated with any clinical deterioration[21,22,154]. Indeed, the occurrence of gas embolism in clinical practice is anecdotal[91]. CO_2 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 CO_2, 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 CO_2 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 futures 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 were 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 has 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, were 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

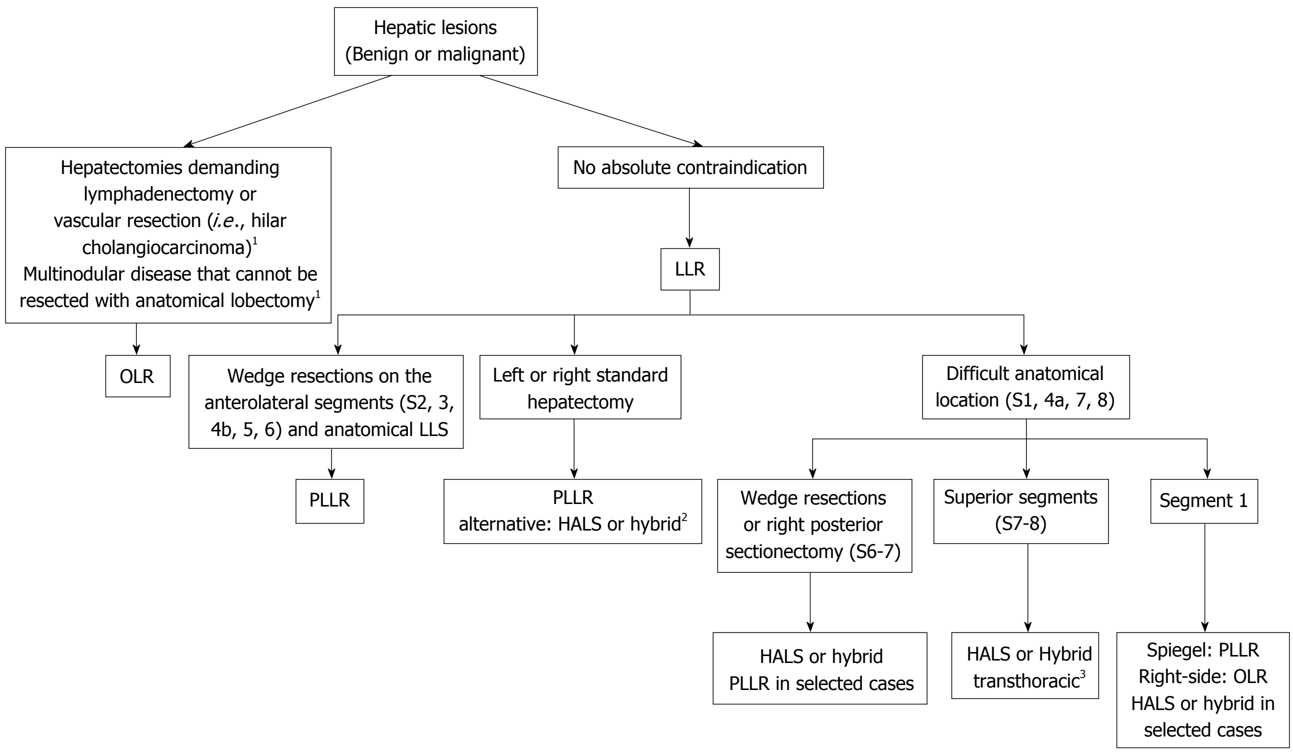

Figure 1 Flowchart demonstrating a suggested approach to the liver nodules using the minimally invasive approach (Liver Surgery Unit, University of São Paulo Medical School). [1]HALS or hybrid in selected cases; [2]When technical difficulties are anticipated/intraoperative difficulties; [3]When abdominal 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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P- Reviewer: Ker CG, Mizuguchi I **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

WJGS World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v8.i1.27

World J Gastrointest Surg 2016 January 27; 8(1): 27-40
ISSN 1948-9366 (online)

REVIEW

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

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Author contributions: Wagner D, DeMarco MM, Amini N and Pawlik TM study concept and design; Wagner D, DeMarco MM, Amini N, Buttner S, Gani F and Pawlik TM acquisited analysis or interpretation of data; all authors contributed to the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

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Received: June 24, 2015
Peer-review started: June 24, 2015
First decision: September 17, 2015
Revised: September 19, 2015
Accepted: October 20, 2015
Article in press: October 27, 2015
Published online: January 27, 2016

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

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-pancreatico-biliary surgery, Tables 1-3)[26-33]. Sixteen studies were conducted retrospectively on an unmatched cohort (2 gastroesophageal, 4 colorectal, and 10 hepato-

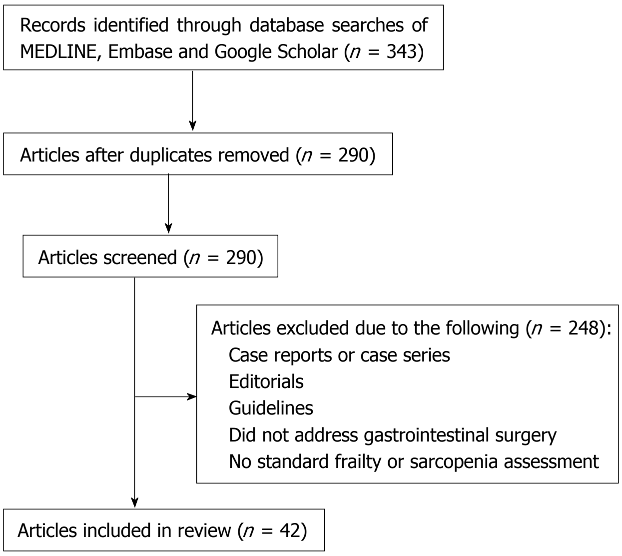

Figure 1 Flow chart depicting the review process for the inclusion of publications.

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 homogenously 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 Complies 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 *et al*[34]	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 *et al*[35]	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 *et al*[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 *et al*[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 *et al*[49]	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 Complies 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 *et al*[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 *et al*[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 *et al*[37]	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 *et al*[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 *et al*[29]	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 *et al*[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 *et al*[38]	United States	5	R	302	68	52	Colorectal resection	Psoas area; Psoas density	58	34	NR	NR	NR	NR	No outcome analysis	NR
Lieffers *et al*[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 *et al*[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 *et al*[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

[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.

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 Complies the characteristics of all trials which evaluated frailty in patients undergoing hepato-pancreatico-biliary 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 *et al*[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: 0.84-093, P = 0.002
van Vledder *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[76]	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 *et al*[32]	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 *et al*[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 *et al*[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 *et al*[33]	United States	9	P	76	67	55	Pancreaticoduo-denectomy	Fried's criteria, Short Physical Performance Battery, Vulnerable Elderly Survey	80	1	4	21	NR	NR	Postoperative complications	OR = 4.06, P = 0.01
Joglekar *et al*[48]	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 *et al*[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

[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.

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 20th 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 20th 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 20th 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 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,

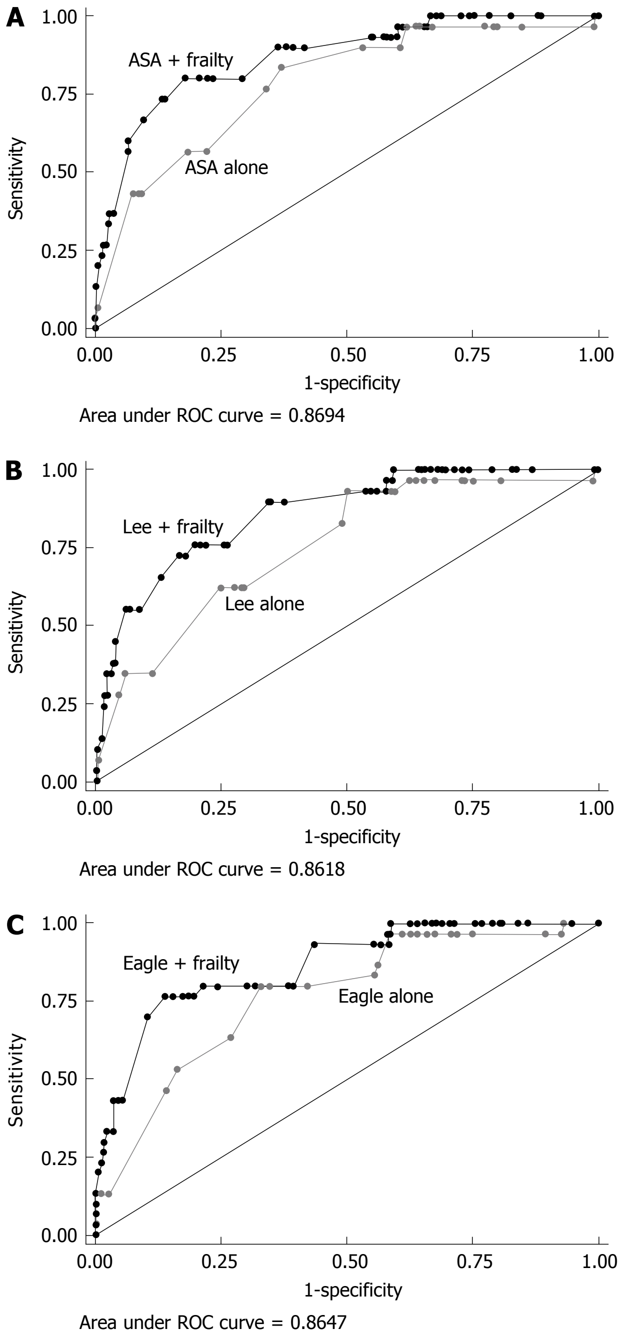

Figure 2 Power of frailty to predict worse outcomes was much higher than traditional peri-operative assessments. A: American Society of Anesthesiologists (ASA); B: Lee; C: Eagle risk indices. Each panel shows the area under the receiver operator characteristics (ROC) curve to demonstrate the ability 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.

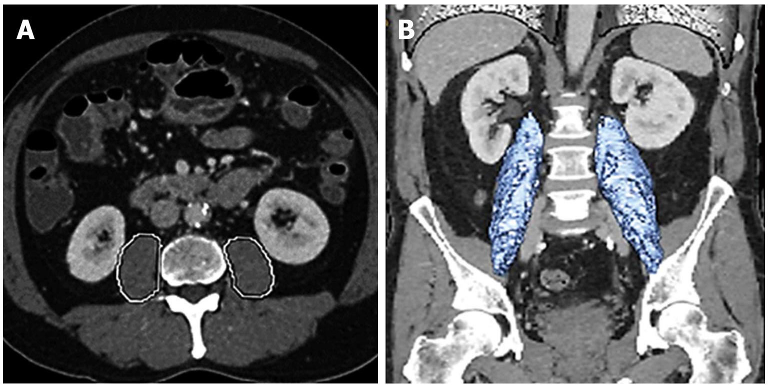

Figure 3 Define sarcopenia rather than a single axial image. A: Total psoas area is measured by circling both psoas muscles at the level of the patients computed tomography where both iliac crests are visible; B: Total psoas volume is measured at the full length of the psoas muscles and normalized for 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 peri-operative 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 $\geqslant$ 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 peri-operative 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 (HBP) 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 pancreatico-duodenectomy 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

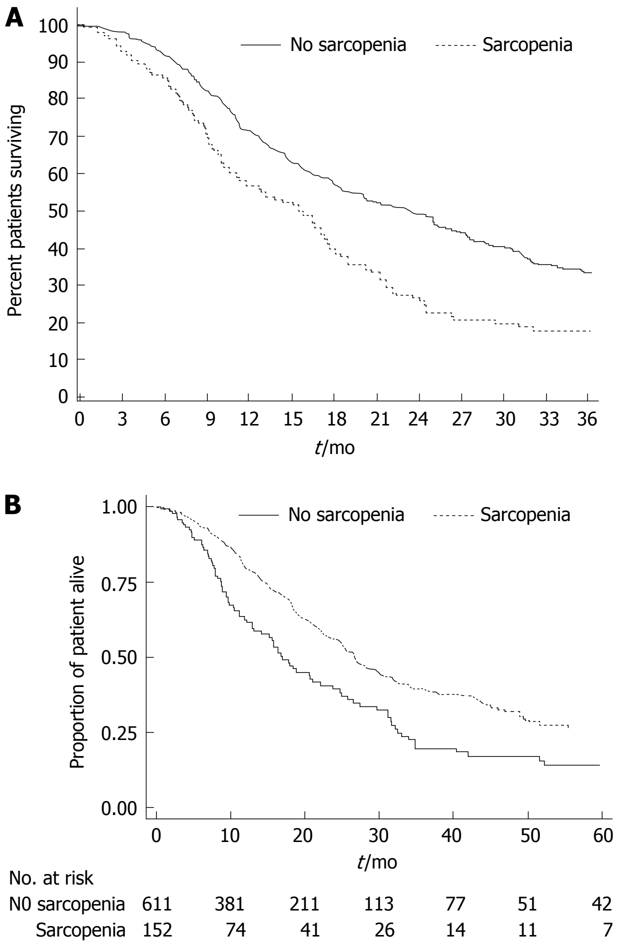

Figure 4 Sarcopenia was associated with an increased three year mortality. A: The presence of sarcopenia was also associated with the risk of death (no sarcopenia, 18.0 mo; 40.0% *vs* sarcopenia, 13.7 mo; 23.0% *vs* median, 3-yr survival, respectively; P = 0.01) in patients undergoing pancreatic surgery. 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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P- Reviewer: Bramhall S, Pera M **S- Editor**: Qi Y
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DOI: 10.4240/wjgs.v8.i1.41

World J Gastrointest Surg 2016 January 27; 8(1): 41-51
ISSN 1948-9366 (online)

REVIEW

Anal cancer and intraepithelial neoplasia screening: A review

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Author contributions: Leeds IL and Fang SH contributed to conception and design; Leeds IL contributed to data collection and analysis, and drafting manuscript; Fang SH contributed to critical revision.

Conflict-of-interest statement: Dr. Leeds reports no financial disclosures or funding sources; Dr. Fang reports receiving anal cancer research funding from the Maryland Department of Health and Hygiene Cigarette Restitution Fund; however this grant does not monetarily support this paper.

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Received: June 25, 2015
Peer-review started: June 27, 2015
First decision: September 17, 2015
Revised: October 2, 2015
Accepted: November 10, 2015
Article in press: November 11, 2015
Published online: January 27, 2016

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

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.

Leeds IL, Fang SH. Anal cancer and intraepithelial neoplasia screening: A review. *World J Gastrointest Surg* 2016; 8(1): 41-51 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/41.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.41

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]. Immunosuppression 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 European Society of Surgical Oncology European Society for Therapeutic Radiation and Oncology[102]	No recommendation	No recommendation	Surveillance only	Digital anorectal exam, standard anoscopy, computed tomography, magnetic resonance imaging
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/mm^3 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

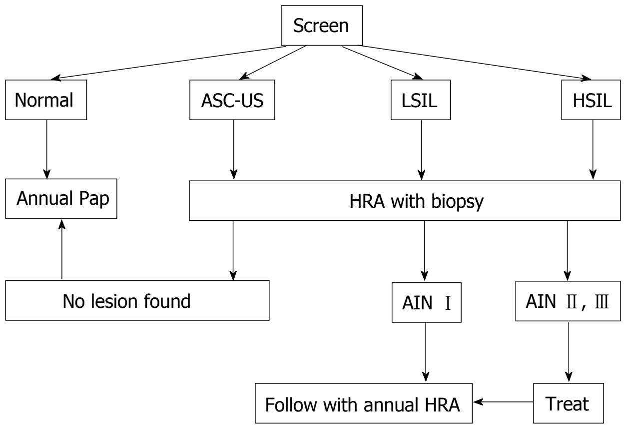

Figure 1 San Francisco algorithm for anal cancer screening of high-risk patients. ASC-US: Atypical squamous cells of undetermined significance; LSIL: Low-grade squamous intraepithelial lesions; HSIL: High-grade squamous intraepithelial lesions; Pap: Papanicolaou; HRA: High-resolution anoscopy; AIN: Anal 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

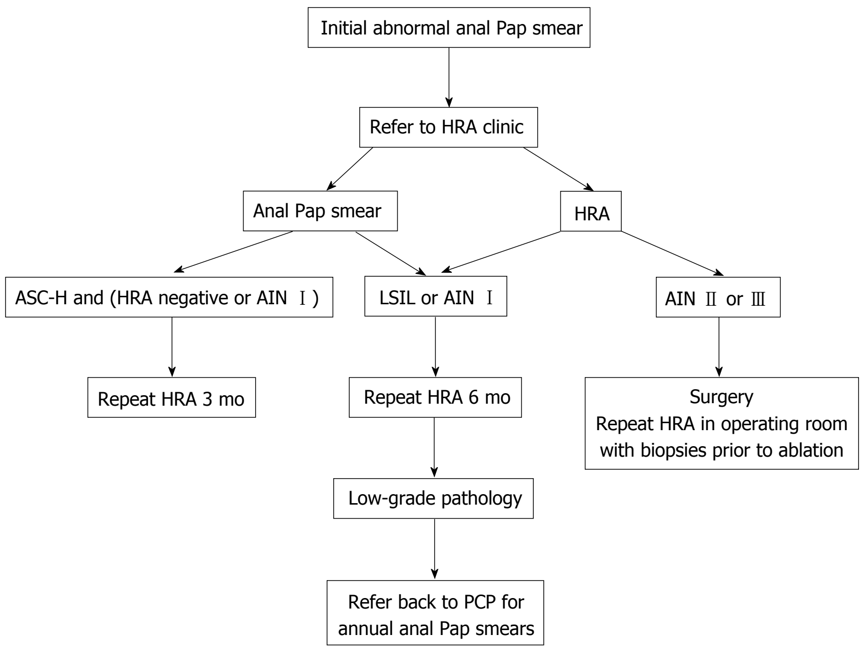

Figure 2 Johns Hopkins Hospital algorithm for anal cancer screening of high-risk patients. Pap: Papanicolaou; HRA: High-resolution anoscopy; ASC-H: Atypical squamous cells of undetermined significance, cannot rule-out high-grade dysplasia; AIN Ⅰ: Anal intraepithelial neoplasia Ⅰ; PCP: Primary care physician; 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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P- Reviewer: Grundmann RT, Murata A **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Liu SQ

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DOI: 10.4240/wjgs.v8.i1.52

World J Gastrointest Surg 2016 January 27; 8(1): 52-64
ISSN 1948-9366 (online)

REVIEW

Esophageal surgery in minimally invasive era

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Author contributions: All the authors contributed equally to this work; Bencini L conceived the idea and designed the research; Moraldi L, Bartolini I and Coratti A performed the research and contributed to the final draft of the paper.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Received: April 24, 2015
Peer-review started: April 26, 2015
First decision: September 8, 2015
Revised: November 28, 2015
Accepted: December 4, 2015
Article in press: December 8, 2015
Published online: January 27, 2016

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

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.

Bencini L, Moraldi L, Bartolini I, Coratti A. Esophageal surgery in minimally invasive era. *World J Gastrointest Surg* 2016; 8(1): 52-64 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/52.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.52

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 ± 6041 *vs* United States $12766 ± 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 ± 6969 *vs* United States $10644 ± 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 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 cricopharingeal 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 pharyngeo-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 ab-ingestis 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-thoracotomic 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 postoperative 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 occurs 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 consider 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

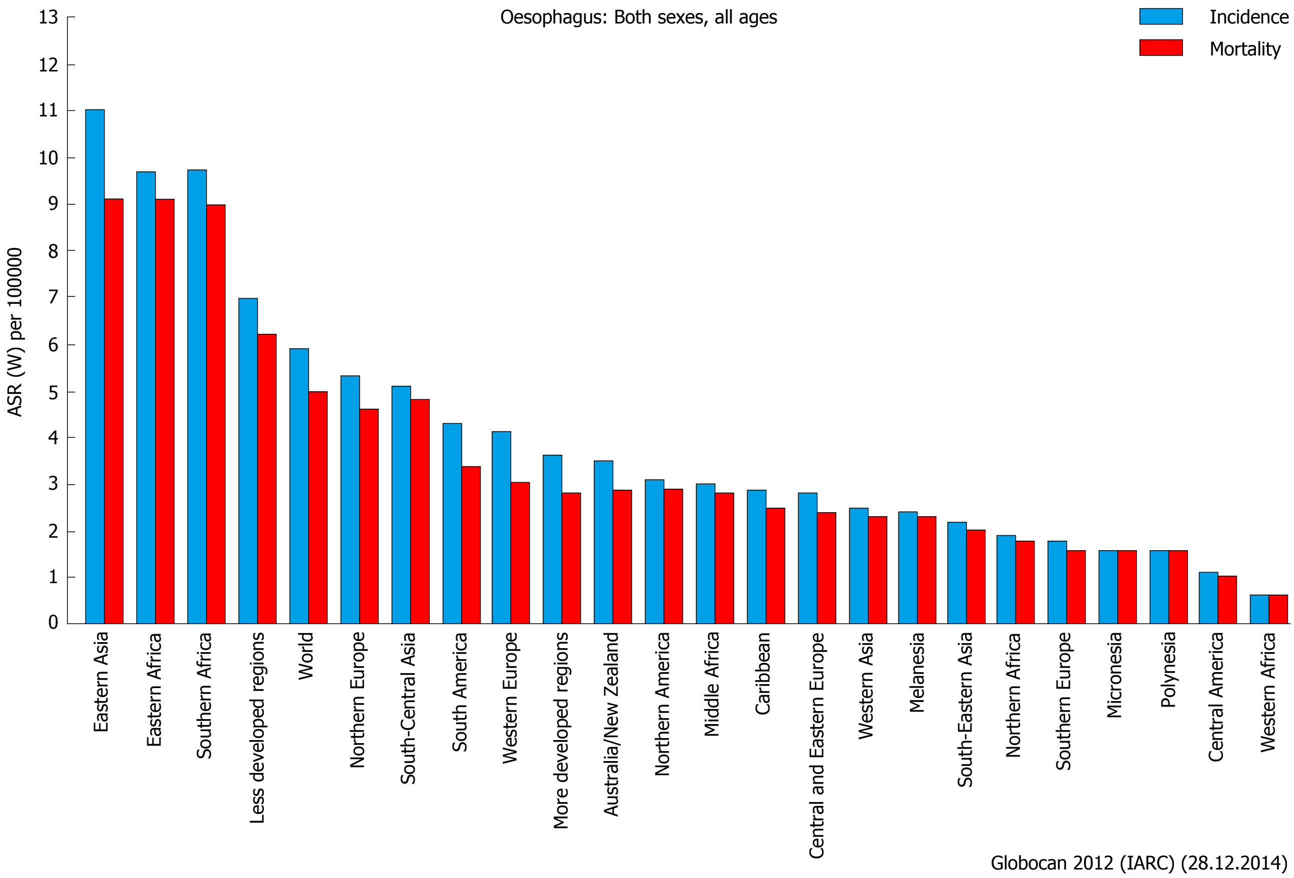

Figure 1 Incidence and mortality rates of esophageal cancer worldwide[114].

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, Khalaileh *et al*[113] reported favorable results of robotic approaches compared to the corresponding open or traditional laparo-scopic/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 100000 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 regiments 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 conducing 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-terms 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

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

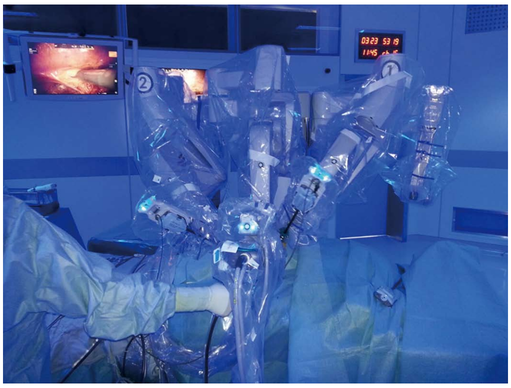

Figure 2 da Vinci® docking during the thoracic step of a completely robotic esophagectomy at the Division of Oncologic Surgery and Robotics, Careggi Hospital.

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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P- Reviewer: Kumagai K, Zampieri N **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Liu SQ

World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v8.i1.65

World J Gastrointest Surg 2016 January 27; 8(1): 65-76
ISSN 1948-9366 (online)

REVIEW

Gallstone ileus, clinical presentation, diagnostic and treatment approach

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Author contributions: Nuño-Guzmán CM and Marín-Contreras ME contributed to the conception and design of the paper, the writing of the paper and the final revision; Nuño-Guzmán CM, Marín-Contreras ME, Figueroa-Sánchez M and Corona JL contributed to the literature search, the writing of the paper and the final revision of the paper.

Conflict-of-interest statement: There are no disclosures.

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Received: July 4, 2015
Peer-review started: July 9, 2015
First decision: September 22, 2015
Revised: November 11, 2015
Accepted: December 7, 2015
Article in press: December 8, 2015
Published online: January 27, 2016

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

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.

Nuño-Guzmán CM, Marín-Contreras ME, Figueroa-Sánchez M, Corona JL. Gallstone ileus, clinical presentation, diagnostic and treatment approach. *World J Gastrointest Surg* 2016; 8(1): 65-76 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/65.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.65

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 papila 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].

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].

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].

Isquemia 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 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

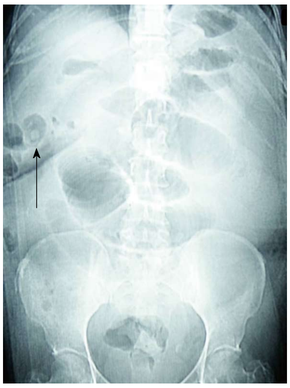

Figure 1 Plain abdominal radiograph showing dilated small bowel loops and a high density endoluminal image suggestive of a gallstone (arrow). No pneumobilia is visualized.

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,

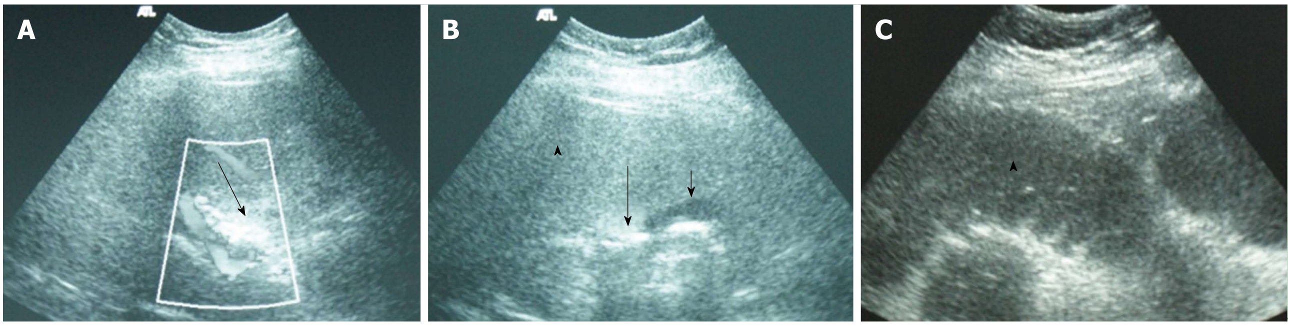

Figure 2 Ultrasound findings in a patient with gallstone ileus. A: Hyperechoic images without acoustic shadow in a non-dilated common bile duct, suggestive of air in the bile duct (arrow). Right portal vein was identified by Doppler US; B: US showing hyperechoic images without acoustic shadow in a collapsed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

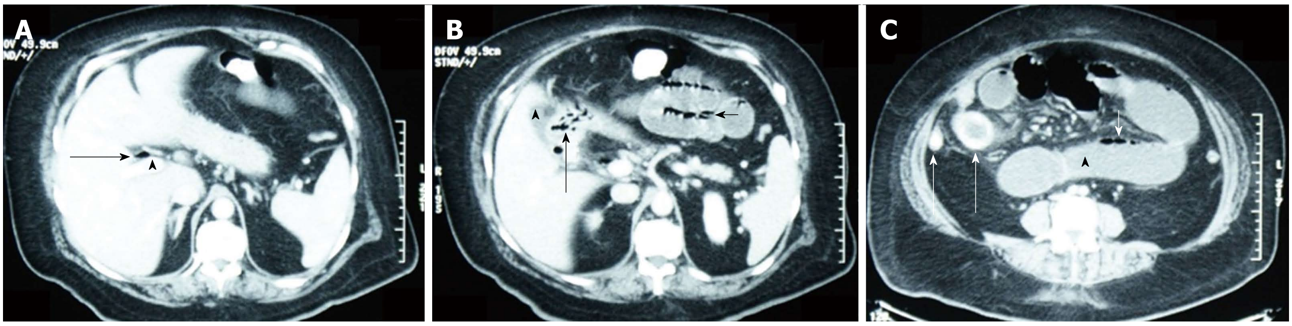

Figure 3 Contrast-enhanced computed tomography findings in a patient with gallstone ileus. A: Portal phase Ⅳ-contrast enhanced computed tomography section reveals air in the hepatic duct (arrow), anterior to a permeable right portal vein (arrowhead); B: Communication between a non-distended gallbladder (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).

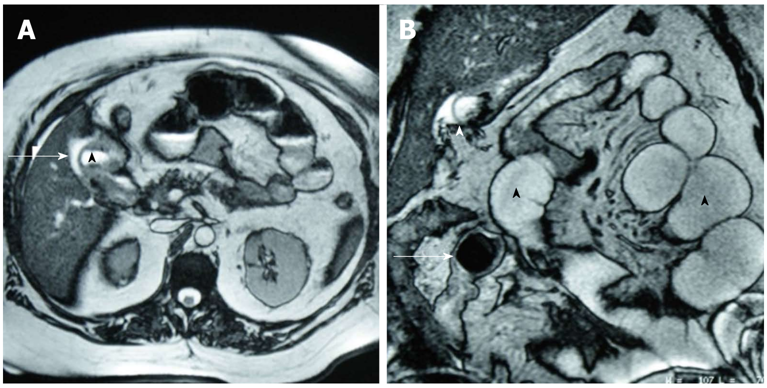

Figure 4 Magnetic resonance cholangiopancreatography findings in a patient with gallstone ileus. A: On T2-MRI, a hyperintense image is identified in the gallbladder bed (arrow), with communication with the duodenal second portion (arrowhead), suggestive of a cholecystoduodenal fistula; B: MRI coronal 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.

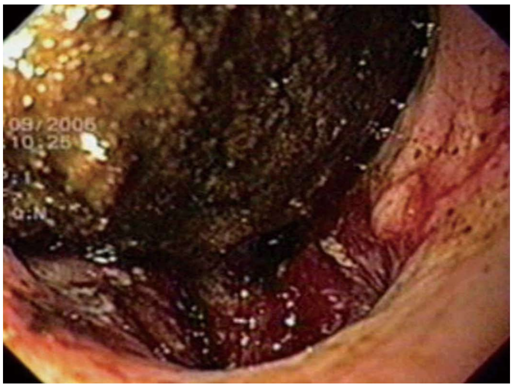

Figure 5 Esophagogastroduodenoscopy in a patient with Bouveret's syndrome revealed a gallstone in the duodenal bulb and the fistulous sinus. Courtesy of Gabriela Quintero-Tejeda, MD, Department of Gastrointestinal Endoscopy, Unidad Médica de Alta Especialidad, Hospital de Especialidades del Centro Médico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

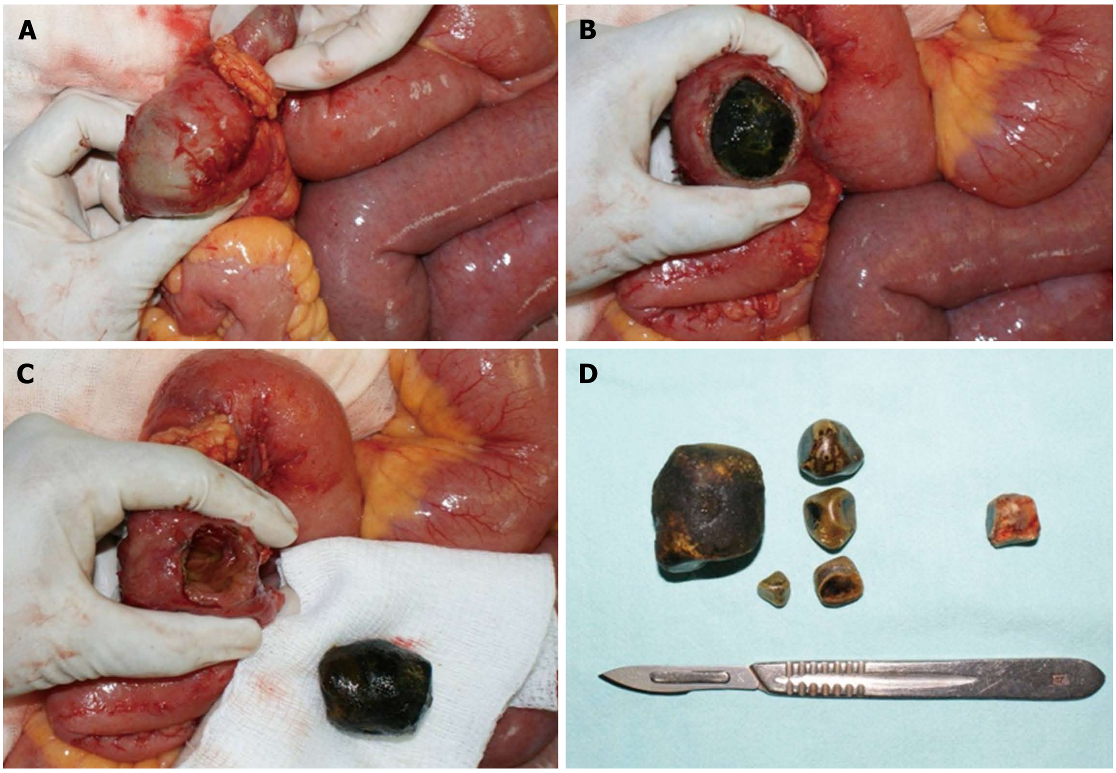

Figure 6 Surgical findings in a patient with gallstone ileus. A: An impacted gallstone was found in distal jejunum. A smaller gallstone proximal to the impacted one is observed; B: Enterotomy over the site of the impacted gallstone; C: Intestinal wall compromise due to gallstone impaction can be observed; 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, Warshaw *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]. Warshaw *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 hemodinamically-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 though 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[8]. 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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P- Reviewer: Mirnezami AH, Surlin V **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v8.i1.77

World J Gastrointest Surg 2016 January 27; 8(1): 77-83
ISSN 1948-9366 (online)

MINIREVIEWS

Gastroesophageal reflux disease: A review of surgical decision making

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Author contributions: Moore M was the first author of the paper and performed the majority of the writing, prepared the figure; Afaneh C and Zarnegar R helped with research and editing; Benhuri D, Antonacci C and Abelson J helped with research.

Conflict-of-interest statement: No conflict of interest.

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Received: July 28, 2015
Peer-review started: August 1, 2015
First decision: October 13, 2015
Revised: October 27, 2015
Accepted: November 24, 2015
Article in press: November 25, 2015
Published online: January 27, 2016

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 gastro-esophageal 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

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.

Moore M, Afaneh C, Benhuri D, Antonacci C, Abelson J, Zarnegar R. Gastroesophageal reflux disease: A review of surgical decision making. *World J Gastrointest Surg* 2016; 8(1): 77-83 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/77.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.77

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 TLSR 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 preoperatively, 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. Impedence 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 dysmolity. 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 impendance 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 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 fundoplications

	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 esophagus 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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P- Reviewer: Santos-Antunes J, Shimoyama S **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

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DOI: 10.4240/wjgs.v8.i1.84

World J Gastrointest Surg 2016 January 27; 8(1): 84-89
ISSN 1948-9366 (online)

MINIREVIEWS

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

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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Received: June 30, 2015
Peer-review started: July 5, 2015
First decision: October 13, 2015
Revised: November 6, 2015
Accepted: December 1, 2015
Article in press: December 2, 2015
Published online: January 27, 2016

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, particulary in reducing ostomy rates, allowing quicker return to oral diet, minimising extended post-operative recovery as well as some quality of life benefits. The uncertainity in managing patients with malignant colonic obstructions has lead 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

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.

Zahid A, Young CJ. How to decide on stent insertion or surgery in colorectal obstruction? *World J Gastrointest Surg* 2016; 8(1): 84-89 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/84.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.84

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, particulary 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 uncertainity in managing patients with malignant colonic obstructions has lead 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 trails 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 *et al*[9]	Single centre, palliation	11/11	0	1/11 (9%)	0	0	100%
Xinopoulos *et al*[7]	Single centre, palliation	15/15	0	0	0	0	93%
van Hooft *et al*[11]	Multicentre, palliation	11/10	11/11 (100%)	5/10 (50%)	3/11 (27%)	0	82%
Sankararajah *et al*[10]	Single centre	9/9	2/9 (22%)	6/9 (67%)	1/9 (11%)	1/9 (11%)	78%
Cheung *et al*[23]	Single centre, bridge to surgery	24/24	2/24 (8%)	17/24 (71%)	0	0	83%
van Hooft *et al*[24]	Multicentre, bridge to surgery	47/51	25/47 (53%)	23/51 (41%)	9/47 (19%)	9/51 (18%)	70%
Ho *et al*[15]	Single centre, bridge to surgery	20/19	7/20 (35%)	11/19 (35%)	0	3/19 (16%)	70%
Young *et al*[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 frought 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*[10] 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 senting technology is one that has traditionally being frought 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 paramenters 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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P- Reviewer: Cai KL, Fiori E **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Gastrointestinal Surgery

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4240/wjgs.v8.i1.90

World J Gastrointest Surg 2016 January 27; 8(1): 90-94
ISSN 1948-9366 (online)

MINIREVIEWS

Lymphatic spreading and lymphadenectomy for esophageal carcinoma

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Author contributions: Cai J and Chen Y performed the literature search; Chen LQ suggested the theme to be reviewed, designed the text structure and made several critical corrections; Ji X performed the literature search, wrote the text and made revisions until the submitted version was achieved.

Conflict-of-interest statement: The above-mentioned authors of this manuscript hereby declare that they do not have any conflict of interest (including but not limited to commercial, personal, political, intellectual or religious interests) related to this work.

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Received: June 29, 2015
Peer-review started: July 3, 2015
First decision: August 25, 2015
Revised: October 6, 2015
Accepted: December 1, 2015
Article in press: December 2, 2015
Published online: January 27, 2016

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

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.

Ji X, Cai J, Chen Y, Chen LQ. Lymphatic spreading and lymphadenectomy for esophageal carcinoma. *World J Gastrointest Surg* 2016; 8(1): 90-94 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i1/90.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i1.90

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 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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P- Reviewer: Shiryajev YN, Yan SL **S- Editor**: Ji FF
L- Editor: Roemmele A **E- Editor**: Liu SQ

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DOI: 10.4240/wjgs.v8.i11.95

World J Gastrointest Surg 2016 January 27; 8(1): 95-100
ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

Single-incision laparoscopic surgery for colorectal cancer

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Author contributions: Hirano Y designed and wrote the review for the Topic Highlight; all authors contributed to this manuscript.

Conflict-of-interest statement: Drs. Yasumitsu Hirano, Masakazu Hattori, Kenji Douden, Yasuhiro Ishiyama, and Yasuo Hashizume have no conflicts of interest or financial ties to disclose.

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Received: April 29, 2015
Peer-review started: May 6, 2015
First decision: June 3, 2015
Revised: July 6, 2015
Accepted: October 12, 2015
Article in press: October 15, 2015
Published online: January 27, 2016

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

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 cased-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/m²)		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.

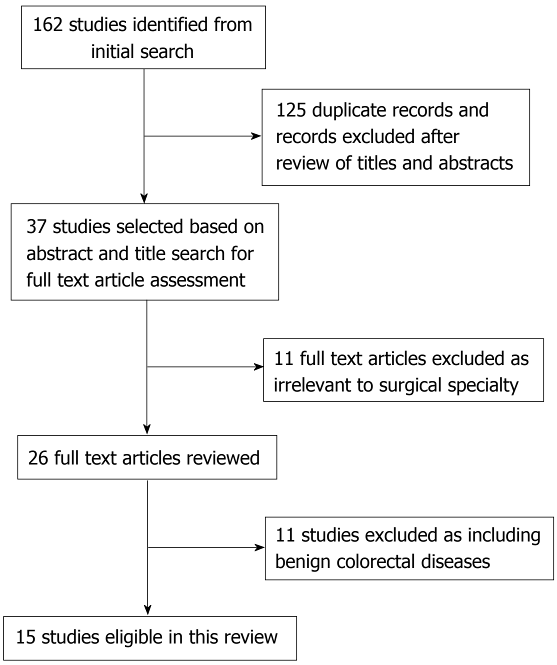

Figure 1 Flow chart of the selection process for studies included in the systematic review.

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	CLC	SILC	CLC	SILC	CLC	SILC
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 following 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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P- Reviewer: Lee SC, Weiss HG **S- Editor**: Yu J
L- Editor: A **E- Editor**: Liu SQ

WJGS World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v8.i1.101

World J Gastrointest Surg 2016 January 27; 8(1): 101-105
ISSN 1948-9366 (online)

CASE REPORT

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

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Author contributions: Garcia-Roca R data collection and writing of the manuscript; Tzvetanov IG writing of the manuscript; Hetterman E data collection and analysis; Jeon H revisions and corrections of the manuscript; Oberholzer J revisions and corrections of the manuscript; Benedetti E data supervision, original idea, and creation of guidelines for the manuscript, revision and correction of the manuscript.

Institutional review board statement: The Institutional review board does not require a protocol for reporting cases reports. Retrospective review of data pertaining intestinal transplant recipients is covered under protocol 2008-0070.

Informed consent statement: Recipients and donor consented for the procedures. The institutional review board protocol 2008-0070 refers to retrospective and prospective data collection and consent waived according to the study protocol.

Conflict-of-interest statement: No conflict of interest is declared by any of the authors.

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Received: May 23, 2015
Peer-review started: May 23, 2015
First decision: August 14, 2015
Revised: August 18, 2015
Accepted: September 10, 2015
Article in press: September 16, 2015
Published online: January 27, 2016

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

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 administrated 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 pseudopapillary 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 lymphoprolipherative disorder (PTLD) involving lymph nodes in both sides of the diaphragm. He was successfully treated with reduction of immunosuppression, antiviral therapy, Rituximab (375 mg/m^2) weekly for total of 6 doses and Cytoxan (600 mg/m^2) 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/m^2.

Her daughter, a healthy 36-year-old female ABO compatible, with a BMI of 24 kg/m^2, 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 lymphoprolipherative 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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P- Reviewer: Ramos E, Talmon GA, Ueno T, Uwe K
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Liu SQ

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