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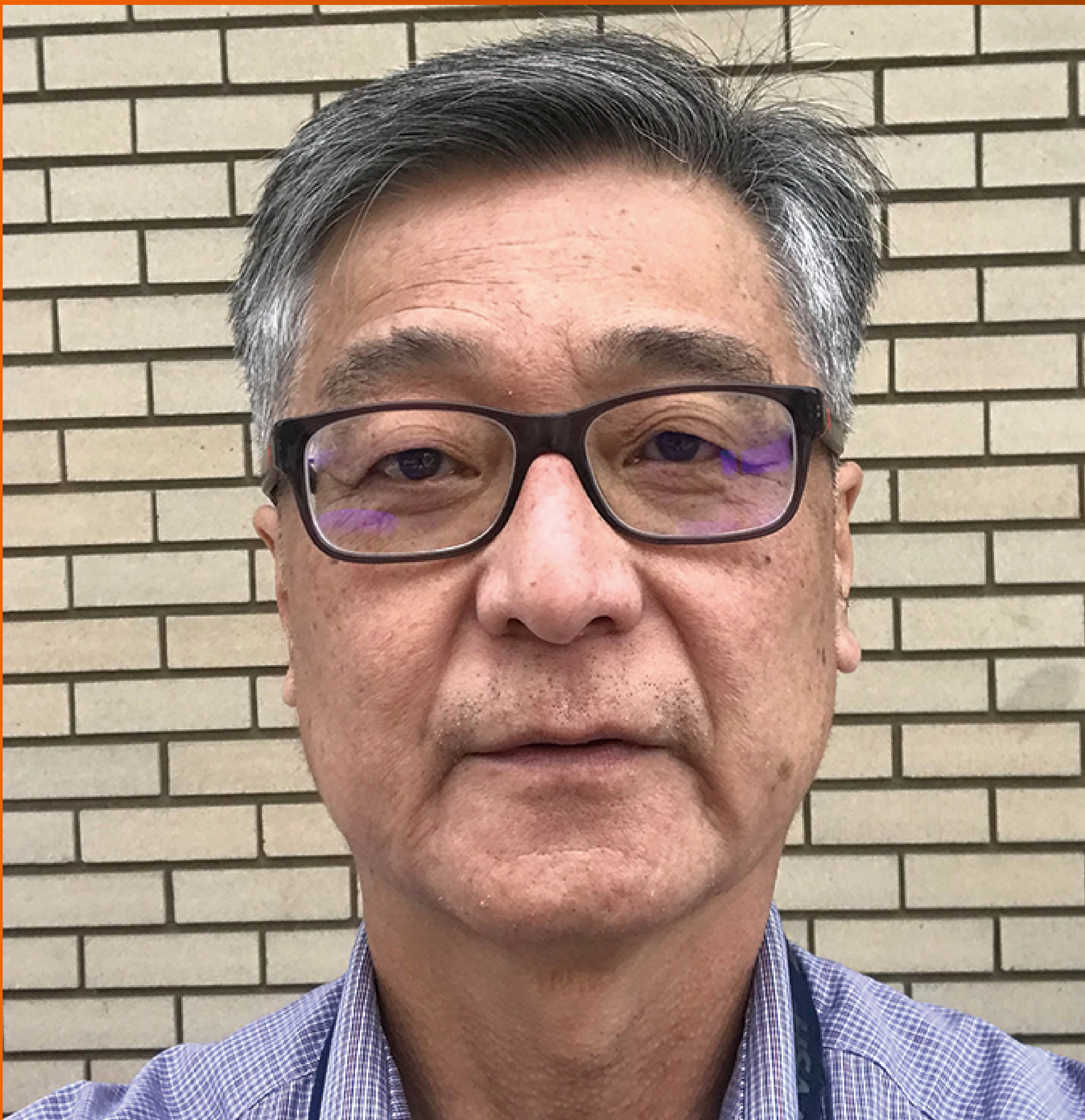

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DIAGNOSTIC AND THERAPEUTIC NORMS

Including video and novel parameter-height of penetration of external anal sphincter-in magnetic resonance imaging reporting of anal fistula

Pankaj Garg, Baljit Kaur, Vipul D Yagnik, Sushil Dawka

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Abstract

The main purpose of a radiologist's expertise in evaluation of anal fistula magnetic resonance imaging (MRI) is to benefit patients by decreasing the incontinence rate and increasing the healing rate. Any loss of vital information during the transfer of this data from the radiologist to the operating surgeon is unwarranted and is best prevented. In this regard, two methods are suggested. First, a short video to be attached with the standardized written report highlighting the vital parameters of the fistula. This would ensure minimum loss of information when it is conveyed from the radiologist to the operating surgeon. Second, inclusion of a new parameter, the amount of external sphincter involvement by the anal fistula. This parameter is usually not included in the MRI report. This can be evaluated as the height of penetration of the external anal sphincter (HOPE) by the fistula. The external anal sphincter plays a pivotal role in maintaining continence. This parameter (HOPE) is distinct from the 'height of internal opening' and assumes immense importance as its knowledge is paramount to prevent damage to the external anal sphincter by the surgeon during surgery.

Key Words: Magnetic resonance imaging; Anal fistula; External anal sphincter; Video reporting; Incontinence

Core Tip: There is loss of vital information when a fistula-in-ano magnetic resonance imaging (MRI) report from the radiologist is interpreted by the operating surgeon. To prevent this loss, a novel method is suggested: sending a small video highlighting vital fistula parameters along with the written MRI report. Also, another vital parameter is the amount of external sphincter involvement by the fistula. This parameter is not included in the MRI report and can be evaluated from the height of penetration of the external anal sphincter (HOPE) by the fistula. This parameter (HOPE) is distinct from the 'height of internal opening' and would help prevent damage to the external anal sphincter during surgery.

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INTRODUCTION

Anal fistulas are associated with a high rate of recurrence and risk to the anal continence mechanism. The operating surgeons need to understand the exact position of the anal fistula and its relation to the anatomical structures in order to achieve high cure rate especially in complex anal fistulas. Magnetic resonance imaging (MRI) is the gold standard investigation used for anal fistulas. Usually, the MRI is interpreted by the radiologists who then send a written report to the operating surgeon and the surgeon performs the surgery after reading the radiologist's report. Formats have been suggested for reporting the MRI in fistulas[1,2]. However, utility of MRI to the operating surgeon can be improved immensely if the two features discussed below (inclusion of an MRI video and addition of HOPE parameter) are added to MRI report (Table 1).

First, when only a written report is sent by the radiologist who has analyzed the MRI scans, then a lot of important information is lost. This happens because the three-dimensional picture created in the radiologist's mind by the detailed visual analysis of the MRI scans cannot be replicated in the surgeon's mind just by reading the text in the radiologist's report. This loss of three-dimensional visual data can be prevented by sending a small video highlighting all relevant parameters along with the written report. Second, as discussed, the two main concerns in anal fistulas are recurrence and incontinence[3]. It is a known fact that the recurrence risk of fistula is directly related to surgeon's knowledge about the precise location of fistula tract's internal opening (where the fistula opens into the anal canal)[4,5]. On the other hand, the accurate assessment of the amount of external anal sphincter (EAS) involvement is key to prevent sphincter damage (incontinence)[6]. The importance of reporting the location of the internal opening has now been established[7], but the other equally important parameter, HOPE (height of penetration of external anal sphincter by the fistula) parameter is not reported by the radiologists (Figure 1). The EAS is mainly responsible for anal continence. HOPE parameter conveys the extent of involvement of the EAS to the operating surgeon and is thus pivotal to avoid damaging the EAS. The studies have demonstrated that when the surgeon performing the surgery is unsure of the accurate extent of EAS involvement, then the fistulotomy procedure is generally avoided and remains largely underutilized, even in simple anal fistulas, due to fear of incontinence in the mind of surgeons[8]. Fistulotomy is the simplest procedure for low anal fistulas and is associated with the maximum cure rate (93%-99%) and no other procedure has been shown to have success rate comparable to fistulotomy [6,8]. Therefore, lack of knowledge of HOPE (EAS involvement) leads to a lower healing rate which can be prevented by proper MRI reporting.

As the origin of most fistulas is at the level of the dentate line, the location of the internal opening in most of them is at that level only. The location of the internal opening does not accurately correspond to the amount of involvement of the EAS as penetration of the EAS by the fistula is often at a different level (Figure 1 and Video 1). Therefore, HOPE is the parameter which should be reported separately for helping the operating surgeon to precisely assess the amount of involvement of the EAS.

The level of understanding of fistula anatomy is greatly enhanced in the surgeon's mind when a small video of MRI scan showing the fistula characteristics is send along with the written report (Video 1). The key points regarding the fistula characteristics can be highlighted by using a pointer in the video

Table 1 Format for the written magnetic resonance imaging report

Parameters	Example
Primary tract	The primary fistula tract
External opening	Is opening in perianal skin at 7 o'clock position
Course and location	It extends superiorly in right ischiorectal fossa from 7 to 8 o'clock position
Length	For a length of 6.35 cm
Location and height of penetration of EAS (HOPE)	and penetrates the EAS at 8 o'clock position involving approximately two-thirds of the EAS. It then bends inferiorly and
Intersphincteric tract	follows an intersphincteric route from 8 to 6 o'clock
Location and height Internal opening	and opens in the anal canal at the level of dentate line
Secondary extension- intersphincteric/ ischiorectal fossa/supralevator	There are no secondary extensions of primary tract
Secondary tract	There are no secondary tracts,
External opening	
Course and location	
Associated abscess	No associated abscess
Supralevator or suprasphincteric tract	And supralevator tract
Sphincter anatomy	The sphincters look normally preserved
Classification	Parks grade -II, SJUH[1] grade III

[1]SJUH- St James's University Hospital classification.

Report: The primary fistula tract is opening in perianal skin at 7 o'clock position. It extends superiorly in right ischiorectal fossa from 7 to 8 o'clock position for a length of 6.35 cm and penetrates the external anal sphincter (EAS) at 8 o'clock position involving approximately two-thirds of the EAS. It then bends inferiorly and follows an intersphincteric route from 8 to 6 o'clock and opens in the anal canal at the level of dentate line. There are no secondary extensions of primary tract. There are no secondary tracts, no associated abscess, and no supralevator tract. The sphincters look normally preserved. Impression- A right transsphincteric high fistula involving about two-thirds of the external anal sphincter, intersphincteric tract from 8 to 6 o'clock and internal opening at 6 o'clock at the level of dentate line. No secondary tract, abscess or supralevator extensions. Parks grade -II, SJUH grade III.

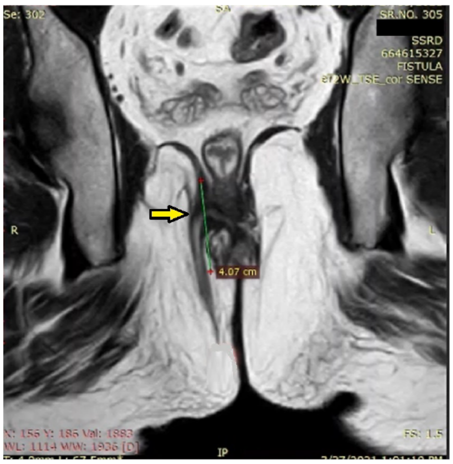

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Figure 1 Height of penetration of external sphincter parameter. Demonstration of height of penetration of external anal sphincter by the fistula tract in the patient included in accompanying video (Video 1). Approximately 2/3 of the external sphincter is involved by the fistula tract. The yellow arrow demonstrates the point of penetration of external anal sphincter by the fistula tract.

(Video 1). The fistula parameters which should be mentioned and highlighted in the video have been listed in Table 2. The MRI report should also be standardized as shown in Table 1. An example of a final written report (of the fistula shown in Video 1 has been included at the bottom of Table 1 to clarify the format).

As can be seen, the novel parameter reported in this study, HOPE (height of penetration of external anal sphincter by the fistula tract) has also been incorporated in the video (Video 1) as well as the report

Table 2 Format for reporting the fistula magnetic resonance imaging in the video

Axial Section T2-weighted
1 External opening- location
2 Define primary tracts
Location and course – Ischiorectal fossa/ Intersphincteric and clock-dial position
Location and 'height' of penetration of external anal sphincter (HOPE)- Point of penetration of external anal sphincter
Intersphincteric course
Location and height of internal opening- clock-dial position and whether it is at dentate line or higher
3 Secondary tracts
4 Associated abscesses
5 Supralevator extension
6 Additional internal opening
7 Sphincter anatomy
Axial section-STIR
1 Confirm findings of Axial-T2
2 Additional areas with inflammation
Coronal T2-weighted
1 Confirm findings of Axial-T2
2 Length of tract
3 Supralevator or suprasphincteric tract
4 Confirm the 'height' of penetration of external anal sphincter (HOPE) by the fistula tract – Indicates the amount of external sphincter involved
5 Confirm the 'height' of the site of internal opening
6 Extent of fistula tract in anterior fistulas- relation with urethra
7 Sphincter anatomy
Coronal section- STIR
1 Confirm findings of Coronal-T2
2 Good to detect thin Intersphincteric collections
Biplanar (Axial T-2 weighted + Coronal T-2 weighted)
1 Confirm the 'height' of the site of penetration of external sphincter by the fistula tract – Indicates the amount of external sphincter involved
2 Confirm the 'height' of the site of internal opening
Sagittal section
1 Extent of fistula tract in posterior fistulas- Relation with sacrococcygeal spine, presacral space
2 Extent of fistula tract in anterior fistulas- Relation with urethra

format (Table 1) (Figure 1). This parameter (HOPE) conveys the amount of EAS involved by the fistula tract (Figure 1).

The study concept was reviewed and approved by the Hospital-Institute Ethics Committee.

CONCLUSION

This paper describes two novel additions to the MRI reporting of anal fistulas. The first is inclusion of a video along with the standardized written report (Tables 1 and 2, Video 1). This would prevent loss of vital three-dimensional data about the disease when the information is being transferred from the radiologist to the operating surgeon and would significantly enhance the surgeon's understanding of the fistula anatomy. Second, when the HOPE parameter (height of penetration of external anal sphincter by the fistula) is incorporated in the video as well as written report, the risk of EAS damage would be drastically reduced and the success rate of the surgical procedure would also be enhanced. Therefore, HOPE should be reported as a separate parameter apart from the location of the internal opening. This format of MRI reporting (including a video) can also be stored on PACS (picture archiving and communication system)[9,10]. PACS provide storage and convenient access to medical images from where the clinician can see the report, images as well as the video as per their convenience[9,10].

FOOTNOTES

Author contributions: Garg P conceived and designed the study, collected, and analyzed the data, revised the data, finally approved and submitted the manuscript (Guarantor of the review); Kaur B and Yagnik VD collected, and analyzed the data, revised the data, finally approved and submitted the manuscript; Dawka S critically analyzed the data, reviewed and edited the manuscript, finally approved and submitted the manuscript

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MINIREVIEWS

Current status of surgical management of patients with gastroenteropancreatic neuroendocrine neoplasms

Rafał Stankiewicz, Michał Grąt

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Abstract

Neuroendocrine neoplasms (NENs) of the gastroenteropancreatic system are rare and heterogeneous tumours, yet with increasing prevalence. The most frequent primary sites are the small intestine, rectum, pancreas, and stomach. For a localized disease, surgical resection with local lymph nodes is usually curative with good overall and disease free survival. More complex situation is the treatment of locally advanced lesions, liver metastases, and, surprisingly, small asymptomatic tumours of the rectum and pancreas. In this review, we focus on the current role of surgical management of gastroenteropancreatic NENs. We present surgical approach for the most frequent primary sites. We highlight the role of endoscopic surgery and the watch-and-wait strategy for selected cases. As liver metastases pose an important clinical challenge, we present current indications and contraindications for liver resection and a role of liver transplantation for metastatic NENs.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Treatment; Management; Liver metastases; Liver transplantation; Surgery

Core Tip: Neuroendocrine neoplasms of the gastroenteropancreatic system are a rare and heterogeneous group of tumours. Due to the advancement of the diagnostic methods like new serum biomarkers and more accurate imaging modalities (including positron emission tomography), its incidence is rising. We present a review focused on up-to-date recommended surgical management of these tumours. We discuss key points of treatment for the most frequent primary sites and liver metastases. Finally, we point areas where univocal consensus is still being achieved by presenting recommendations of various Oncological and Surgical Societies.

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INTRODUCTION

Neuroendocrine neoplasms (NENs) arise from the diffuse neuroendocrine cell system and may occur at many different sites. NENs constitute a heterogeneous group of malignancies with neural phenotype and capacity to secrete amines and hormones. The gastroenteropancreatic (GEP) system and lungs are the most common primary tumour sites[1]. In this review, we focus on GEP-NENs.

Histological diagnosis is mandatory in all patients and can be carried out on resection specimen or core biopsies in an advanced disease. GEP-NENs should be classified based on morphology and proliferation into well-differentiated neuroendocrine tumours (NETs) (G1 to G3) and poorly-differentiated neuroendocrine cancers (NECs) (always G3) as shown in Table 1[2].

GEP-NENs are rare tumours with an annual incidence of 6.98 *per* 100000 persons in 2012 in the United States. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the rise in the annual number of cases can be observed in the last few decades with the most dramatic rise in patients older than 65 years (25.3 *per* 100000 persons). The order of frequency in NENs is the small intestine (1.05 *per* 100000), rectum (1.04 *per* 100000), and pancreas (0.48 *per* 100000)[3]. Hepatic metastases occur in 50%-75% of patients with NENs[4]. The most common primary sites in patients with NEN liver metastasis are the small intestine (56%), pancreas (10%), and colon (10%)[5]. The overall survival (OS) varies depending on primary site and grade. According to the SEER, the median OS for all patients is 9.3 years. NENs in the rectum and appendix had the best median OS, while NENs in the pancreas had the worst median OS. Localized, low grade (G1/G2) NETs have the best prognosis of long OS[3].

In this review, we focus on NENs of the GEP system and their step-by-step surgical management. We discuss tumours of the stomach, small intestine, rectum, and pancreas. Special emphasis is put on the treatment of hepatic metastases with the role of liver transplantation (LT).

NENs OF THE STOMACH

Gastric NENs are slow growing, indolent tumours but with potential for aggressiveness and metastases. They are very often incidental findings with tendency to being multi-focal. Registries show a rising frequency in diagnosis of gastric NEN[6]. The SEER estimates an incidence of gastric NENs at 0.5 *per* 100000 persons[3].

There are three types of gastric NETs. Type I (70%-80%) is characterized by rare metastases and excellent prognosis and evolves on the background of chronic atrophic gastritis. Type II (5%-10%) is a result of Zollinger-Ellison syndrome and metastases to lymph nodes and the liver can be expected. The prognosis in patients with type II is very good. Type III (15%-20%) is a sporadic tumour with a very high prevalence of metastases either to lymph nodes (50%-100%) or the liver (22%-75%), and the prognosis is similar to that of gastric adenocarcinoma[7].

Endoscopic assessment of the lesions is crucial for further treatment. In addition to taking biopsies, the number and size of tumours should also be noted. Large lesions (> 1-2 cm) should also be assessed by endoscopic ultrasound (EUS) in terms of invasion depth and positive lymph nodes[8].

Surgical management of gastric NETs depends on several factors, such as tumour subtype, degree of differentiation, and presence or absence of invasion.

Treatments for type I and II gastric NETs are: (1) < 1 cm–endoscopic removal or monitoring by close endoscopic surveillance; (2) 1-2 cm and lesions with submucosal invasion (EUS)–snare polypectomy or endoscopic mucosal resection (EMR); and (3) > 2 cm–individualized strategy, either endoscopic resection (if possible) or surgical resection.

Treatments for type III gastric NETs are: Partial gastrectomy and lymph node dissection; in selected cases with lesions < 1-2 cm in size, EMR or endoscopic submucosal dissection (ESD) should be considered[9].

A potential alternative for patients with small type I lesions who cannot be managed endoscopically is treatment with somatostatin analogues (SSA)[10,11]. Also, netazepide (gastrin/cholecystokinin receptor antagonist) seems a promising option for patients with type I gastric NETs[12]. The downside of this agent though, is that if this treatment is stopped, tumours will regrow.

Table 1 The 2019 World Health Organization classification for gastroenteropancreatic neuroendocrine neoplasms

Morphology	Grade	Mitotic count (2 mm^2)[1]	Ki-67 index (%)[2]
Well-differentiated NETs	G1	< 2	< 3
	G2	2-20	3-20
	G3	> 20	> 20
Poorly-differentiated NECs		> 20	> 20

[1]Of ten high power fields = 2 mm^2, at least 40 fields (at × 40 magnification) evaluated in areas of highest mitotic density.
[2]MIB1 antibody; percentage of 500-2000 tumour cells in areas with the highest nuclear labeling.
NET: Neuroendocrine tumour; NEC: Neuroendocrine cancer.

NENs OF THE SMALL INTESTINE

The small intestine is the most common primary site of NENs. The presence of carcinoid heart disease, mesenteric lymph node metastases, distal abdominal lymph node metastases, liver metastatic burden, extra-abdominal metastases, skeletal involvement, and peritoneal carcinomatosis are independent prognostic factors for OS[13].

Surgical strategy for any locoregional small intestine NENs (SI-NENs) should be *en bloc* resection with its lymphatic drainage field, including the mesentery[14]. The entire small and large intestines should be evaluated (pre- and intra-operatively), as up to 40% of SI-NENs may have more than one site of primary gastrointestinal tract malignancy. Therefore, open resection seems preferred over laparoscopic, unless the latter enables a thorough examination by palpation, *i.e.*, by small incision[15].

SI-NENs have a significant metastatic potential, and even for lesions < 1 cm, nodal and distant metastases can be found in 12% and 5% of cases, respectively[16]. The liver is the most common site of metastases. In the setting of resectable synchronous primary tumour and hepatic metastases, resection of the primary tumour and lymph nodes, with combination with liver metastases is warranted[14]. According to ESMO guidelines, patients qualified for synchronous resection must have a tumour with a Ki-67 index < 10% (or slow growing tumour) and metastases limited to the liver[17]. Those exceeding the above mentioned criteria should be qualified for medical therapy (Figure 1).

There are controversies over whether to resect or not the primary SI-NEN in the case of unresectable liver metastases. For symptomatic SI-NENs, resection with lymphadenectomy is advised[17]. ENETS guidelines acknowledge that the lack of prospective evidence does not permit a definite conclusion on any potential survival benefit in case of an asymptomatic disease–risk and benefit of the surgical intervention need to be considered individually[18]. In a systematic review, Capurso *et al*[19] presented benefit in survival (75-139 mo *vs* 50-88 mo) for patients who underwent primary site resection. This was based on six retrospective cohort studies which included a total number of 971 patients[19]. These findings were supported by the meta-analysis conducted by Almond *et al*[20]. They found an increase in median survival from 22 to 112 mo across six studies for patients who underwent primary site resection [20]. Conversely, a study by Daskalakis *et al*[21] based on the Swedish prospective database found no difference in terms of OS, morbidity, and 30-d mortality. Both groups of patients (161 underwent upfront locoregional surgery and 202 underwent delayed surgery) received systematic oncologic therapy for NENs (SSAs, interferon-alfa, liver-directed treatment, and peptide receptor radionuclide therapy) [21].

There is also some experience with intestinal transplantation for advanced local SI-NENs with unresectable mesenteric lymph node metastases[22]. This kind of therapy is still anecdotal and not accessible for all patients amenable for this treatment.

NENs OF THE RECTUM

Rectal NENs are subepithelial lesions that are diagnosed with an increasing frequency. They constitute about 1% of rectal lesions, and are often accidental findings in colonoscopy[23]. Rectal NENs are usually small (< 1 cm in diameter) single lesions located 5-10 cm from the dental line[24]. Due to its typical macroscopic appearance, 95.9% of cases can be diagnosed on endoscopy alone[25]. Therefore, biopsy should only be considered in doubtful cases (atypical features) and in tumours that are more than 2 cm in size. Methods of treatment are either EMR, ESD, transanal endoscopic microsurgery, or surgery, depending on tumour size, grade, and lymph node and distant metastases. EUS is indicated for lesions more than 5 mm in size, to identify muscular layer invasion[23].

There is an accordance across the guidelines that all tumours larger than 2 cm should be removed surgically, either by low anterior resection or abdominoperineal resection. Tumours < 1 cm (G1, G2, and G3) should be removed by TEM or endoscopy. There are differences in the treatment strategy

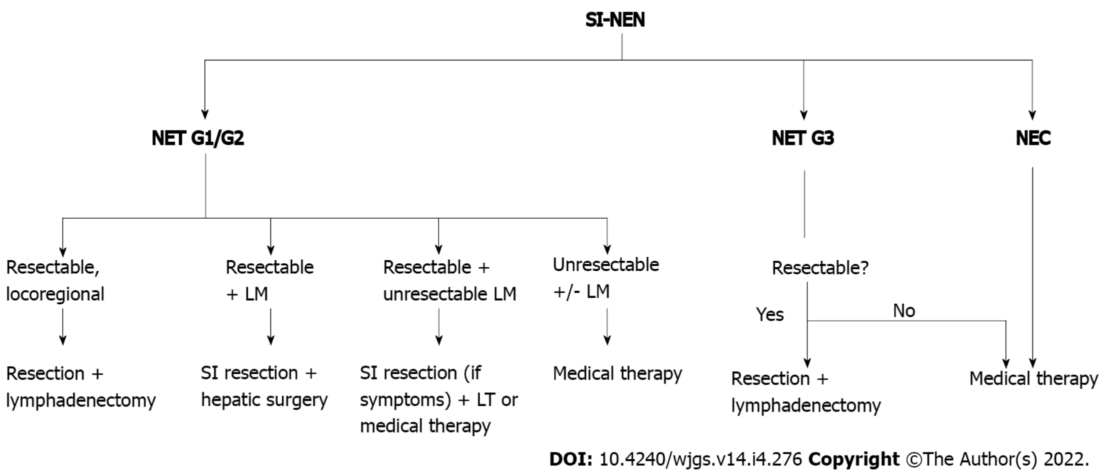

Figure 1 Therapeutic options for small intestinal neuroendocrine neoplasm. SI-NEN: Small intestine neuroendocrine neoplasm; NET: Neuroendocrine tumour; G: Grade; NEC: Neuroendocrine cancer; LM: Liver metastases; LT: Liver transplantation.

concerning lesions 1-2 cm in diameter. In general, those lesions with muscularis propria invasion should be resected surgically. Other lesions should be considered individually with tendency to TEM or endoscopy[14,23,26].

NENs OF THE PANCREAS

Pancreatic neuroendocrine neoplasms (PNENs) are a subgroup of NENs that have relatively distinct biological behavior and clinical management compared with pancreatic adenocarcinoma. Like other NENs, they have a capacity to produce amines and hormones. PNENs are believed to arise from islet cells precursors[27]. Tumours that overproduce hormones may be associated with various clinical syndromes and are referred to as functional. In contrast, those that do not secrete hormones or secrete peptides which do not result in an obvious syndrome are termed non-functional (70% of PNENs). The most common hormones produced by PNENs are: Insulin (insulinoma; 1-32 million *per* year), gastrin (gastrinoma; 0.5-21.5 million *per* year), vasoactive intestinal peptide (VIPoma; 0.05-.02 million *per* year), and glucagon (glucagonoma; 0.01-0.1 million *per* year)[28]. Most PNENs are malignant, and upwards of 60% of patients will have metastatic disease at the time of diagnosis[27]. Ten to twenty percent are associated with inherited cancer syndromes, such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome, and neurofibromatosis type 1 (NF-1)[29]. Detailed management of these syndromes is beyond the scope of this review.

Disease stage and tumour grade (Table 1) must be assessed along with hormonal activity (if symptoms occur). Computed tomography is the most commonly used modality for staging. It is quick and widely available, and provides excellent anatomic definition of the pancreas, and lymph node or liver metastases. Histological diagnosis is usually based on samples taken by fine-needle aspiration or biopsy under EUS guidance.

Patients with functional PNENs irrespective of their size, should be evaluated for surgery[30]. Typical resections (pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy) or tumour enucleation may be used. The latter should be considered primarily for small (< 2 cm), peripheral insulinomas[14]. The advantage of enucleation over standard resection is that the former is associated with a lower rate of postoperative pancreatic insufficiency, shorter operative time, and less operative blood loss[31]. In high-grade PNETs or PNECs, only oncologic resection (pancreaticoduodenectomy or distal pancreatectomy with lymphadenectomy) should be considered[9] (Figure 2).

Non-functional PNETs < 2 cm can be managed either surgically or by the wait-and-watch approach. In the meta-analysis conducted by Sallinen *et al*[32], small, sporadic PNETs in 344 patients were observed with satisfactory results[32]. In only 22% of cases, tumour growth was observed and no metastases were reported. Twelve percent of patients had surgery, and the most common indications were tumour growth (47%) and patients' preferences (31%). The same study showed more aggressive character of the small MEN-1 related PNETs. Over half of these patients had tumour growth during observation and in 9% of cases metastases were reported (distant and nodal). Opposite results come from the meta-analysis by Finkelstein *et al*[31]. Seven hundred and fourteen patients had tumours ≤ 2 cm, of which 587 underwent surgical resection and 127 were managed nonsurgically. Analysis showed an improved OS in the resection group at 1 year (P = 0.745), 3 years (P < 0.001), and 5 years (P < 0.001).

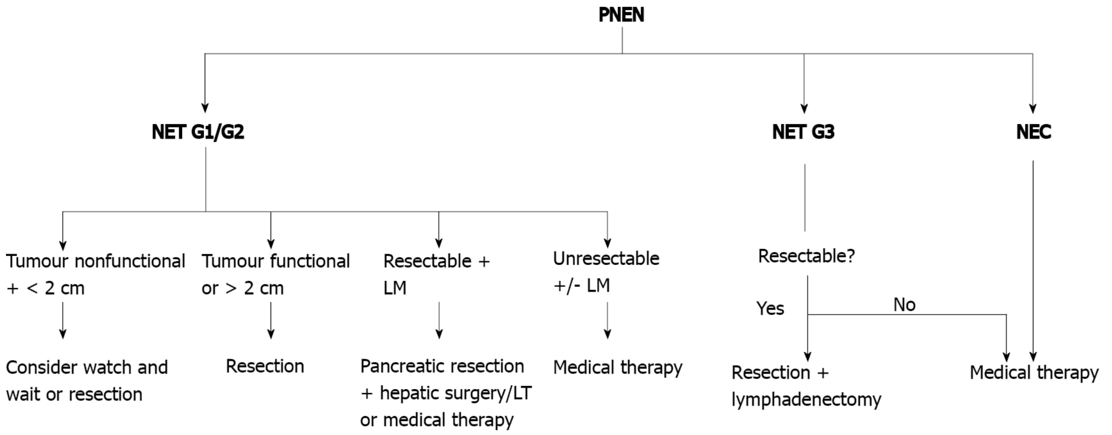

Figure 2 Therapeutic options for pancreatic neuroendocrine neoplasm. PNEN: Pancreatic neuroendocrine neoplasm; NET: Neuroendocrine tumour; G: Grade; NEC: Neuroendocrine cancer; LM: Liver metastases; LT: Liver transplantation.

In the management of small (< 2 cm in size) PNENs, the malignant potential of the tumour (rather small in most of the cases) and consequences of the aggressive pancreatic surgery (about a 30% complication rate and 1.7% mortality) must be taken under consideration[33]. Each patient should be individually assessed and when conservative approach is decided, close follow-up is recommended[14,17].

LIVER METASTASES

GEP-NENs at diagnosis are metastatic in 40%-95% of cases[4]. The most common metastatic sites are the liver, other intraperitoneal sites, bone, and the lung. Of all liver metastases, over half are from the small intestine. In about 10% of patients with liver NEN metastases, the primary site remains unknown[5]. Liver metastases represent the most crucial prognostic factor, irrespective of the primary NEN site. As G3 NETs and NECs present with aggressive behaviour (multifocal or bilobar growth, and anticipated high recurrence rate), systemic therapy is more commonly used than resection of the metastases.

Despite a high recurrence rate after resection (80%-95% within 5 years[34]), surgery remains the most favorable approach for selected (G1 and G2 NET) patients with liver metastases. Surgical treatment comprises resection and cytoreductive surgery for symptom management and improvement of survival. For a few decades, debulking threshold of resection was debated. In the first series presented in 1977, the authors achieved good symptom control with a threshold of 95% for debulking[35]. After being confirmed by other authors, such a threshold of approximately 90% for debulking was a goal to achieve [34,36]. Graff-Baker *et al*[37] found no difference in progression free survival between groups with > 70% debulking and > 90% debulking, and the OS for the study population was 88%[37]. Adoption of this lower debulking threshold of > 70%, along with the use of parenchymal-sparing techniques, allowed for more than 75% of patients to undergo hepatic cytoreduction. Also, when > 70% debulking is achieved, despite less than complete resection (R1/R0), comparable survival outcomes are observed as for R0 resection with > 70% cytoreduction[37]. In patients with carcinoid syndrome, it is important to control the hypersecretion of serotonin with SSA prior to surgery, in order to prevent carcinoid crisis [18].

When evaluating patients with NET liver metastases for surgical treatment, one must remember that current imaging modalities are limited in detecting small lesions. Accuracy of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging is calculated to be only 24%, 38%, and 49%, respectively. Lesions smaller than 2 mm are not visible in the preoperative assessment [38].

In patients who cannot be qualified for partial liver resection, LT is an option for a improved survival for selected patients[39]. LT for metastatic NETs provides a 5-year OS rate between 47% and 71%[40]. Each patient should be considered individually for prognostic factors that would impact post-LT outcomes. These prognostic factors are: (1) Histologic grade. LT is reserved for G1 and G2 NETs[39,41]. Le Treut *et al*[42] found a difference in survival between well and poorly differentiated NENs in the European Liver Transplant Registry (ELTR), reaching almost 30% in 5-year OS[42]. The histologic grade can be different between primary and metastatic tumours in the liver, and treatment is guided by the worst grade in the available specimen; (2) Tumour burden. The cut-off < 50% for this factor was arbitrarily set by Mazzaferro *et al*[39]. Data from the ELTR found that the 5-year OS rate after LT was 42% when the estimated tumoral invasion was over 50%, while it was 61% for tumours under 50%[42].

Some data challenge this threshold of 50% tumour burden, stating underestimation of tumour burden in the pre-LT workup in the early, ELTR-based studies[43]; (3) Primary tumour site. While Mazzaferro *et al* [39] allowed only NET liver metastases originating from portal venous drainage to be suitable for LT, further analysis of ELTR data did not support this idea[39,42]. Among the patients in the ELTR study, the 5-year survival rate of patients with bronchial tree origin NETs was comparable to that of patients with GEP NETs (53% and 40%-62%, respectively); and (4) Surgical control of the primary tumour. It is recommended to resect primary tumour before LT. This is to monitor biologic response of the liver metastases and to avoid surgical complications from simultaneous surgeries. Data from the ELTR showed an inferior 5-year OS rate in cases where primary tumour was resected during LT compared to those cases where tumour was resected before LT (22% and 56%, respectively). The same study found that in 13% to 14% of cases of NETs with liver metastases, the primary tumour is unknown. The 5-year survival of this cohort was 54%[42]. As such, patients without identifiable primary tumour are still good candidates for LT.

There are two major, widely accepted patients selection criteria for LT in NET metastases. The group from Milan proposed their criteria in 2007 and revised them in 2016[39,44]. The Milan-NET selection criteria are: (1) Histologic grade G1 or G2; (2) Portal drainage of the primary tumour; (3) Pre-transplant curative resection of all extrahepatic lesions; (4) Hepatic tumour invasion under 50%; (5) Duration of stable disease over 6 mo; and (6) Age under 60 year (relative).

The Milan group reported 5-year OS and disease-free survival rates of 97% and 89%, respectively. However, only 15% of patients referred to LT underwent LT[44].

In the United States, the current guidelines regarding LT for NET liver metastases are based on the Milan-NET criteria[45] with the following additional criteria: (1) Unresectable liver metastases; (2) Radiographic characteristics of NET of the liver lesions; (3) Negative metastatic workup by positron emission tomography (PET) scan; (4) Lack of extrahepatic tumour recurrence during the past 3 mo; (5) In the presence of positive findings for lymph node metastases by PET scan, the finding should become negative for 6 mo before re-listing; and (6) In the presence of extrahepatic solid organ metastases, the case will be permanently delisted.

There is no uniformly accepted selection criteria for NET-LT. Some of the above mentioned factors are still debated and waiting for validation, *i.e.,* patients age, primary resection before LT, hepatic tumour burden, and wait time for disease stabilization[45].

The high recurrence rate after NET-LT (31%-57%) remains an important clinical problem[40]. Available data on neoadjuvant or adjuvant therapy in NET-LT are scarce. Most of clinical experience comes from the series of patients who underwent liver resection[46-48].

For patients with unresectable primary GEP-NET and liver metastases, multivisceral transplantation (MVT) is also an option. Data on this treatment are limited by small case series and quality of the reported outcome. In the systematic review by Moris *et al*[40], the authors found that only 5.7% of patients from single center studies had MVT with various outcomes.

For patients with NET liver metastases beyond resection or LT, there is a number of liver-directed therapies. Ablative methods include microwave ablation, radiofrequency ablation, cryotherapy, and irreversible electroporation. Ischemia and necrosis of NET liver metastases can be achieved by occlusion of the arterial blood supply. Various methods are being used: Bland embolization, chemoembolization, drug eluting beads, and transarterial radioembolization (^{90}Ytrium). Detailed application of these methods is beyond the scope of this review.

EXTRAHEPATIC METASTASES

The most common metastatic NEN sites are the liver, other intraperitoneal sites, bone, and the lung. Liver metastases occur in 40%-95% of cases[4], but peritoneal metastases can be a part of the metastatic tumour load in approximately 20% of cases[13]. The most common primary site for peritoneal metastases is the small bowel. Presence of peritoneal metastases has an adverse impact on patient survival, irrespective of the hepatic metastases[49,50]. For patients with well-differentiated G1/G2 NETs, complete cytoreductive surgery can prolong overall and disease free survival. In a study from France, patients with peritoneal metastasis were treated by peritonectomy with or without partial hepatectomy[48]. The 5-year and 10-year OS rates were 69% and 52%, respectively, and the 5-year and 10-year disease free survival rates were 17% and 6%, respectively. The benefit from addition of hyperthermic intraperitoneal chemotherapy to complete cytoreductive surgery is questionable, according to the authors of that study. For high-grade NEN peritoneal metastases, only medical treatment is advised[17].

HIGH-GRADE GEP-NEN

Recent WHO classification of the NEN (Table 1) distinguished two groups of high-grade NENs[2]. Those are well-differentiated NETs G3 with a Ki-67 index > 20% and poorly-differentiated NECs. The

Table 2 Clinical trials for surgical intervention in neuroendocrine neoplasm with open recruitment

Study title	Resection of metastatic PNETs after induction system treatment	Single-cell sequencing and establishment of models in NEN	Endoscopic ultrasound-guided radiofrequency ablation for the treatment	Prophylactic cholecystectomy in midgut NET patients who require primary tumor surgery
Primary site	Pancreas	GEP NEN	Pancreas	Jejunum, ileum, proximal colon
Study type	Observational	Observational	Interventional	Interventional
Multicentric	No	No	Yes	Yes
Primary purpose	NA	NA	Treatment	Treatment
Allocation	NA	NA	NA	Randomized
Estimated enrollment	180 participants	200 participants	70 participants	100 participants
Estimated study completion date	July 25, 2025	December 2022	June 1, 2021	April 2025

NEN: Neuroendocrine neoplasm; PNET: Pancreatic neuroendocrine tumour; NET: Neuroendocrine tumour; GEP: Gastroenteropancreatic; NA: Non-announced.

term NENs G3 covers both types of those malignancies. The NEN G3 patients are a heterogeneous group concerning prognosis and treatment benefit. GEP NECs are usually highly aggressive, with a propensity for early metastases and dismal prognosis[51]. In the SEER database, the median survival is 34 mo with localized disease, 14-16 mo with regional disease, and 5 mo with distant disease[52]. Data on the NET G3 subgroup are extremely scarce, and they are mainly located in the pancreas and have a better prognosis than NEC[51].

The treatment recommendations for NEN G3 patients are mostly expert consensus supported by heterogeneous retrospective studies. The opinion is that surgery alone is rarely curative and that patients with limited disease should receive multimodality based treatment. The 5-year survival for localized disease depends on the primary site; the best is for colorectal, stomach, and pancreas primaries (40%-50%)[52]. Metastatic surgery for GEP NEC is not recommended and the treatment is with systemic chemotherapy (etoposide and a platinum agent)[53].

A National Cancer Database Study summarized the treatment and outcome of 1861 patients with high-grade NENs[54]. Over 64% of patients was in stage IV of the disease at the moment of diagnosis. The most common primary site was the large bowel (26.6%). Only about 28% of the study population were amenable for surgery. The median survival was 9.3 mo. That study did not distinguish NETs G3 and NECs due to disparity of study period and the novel WHO classification.

FUTURE PERSPECTIVES

Most of the ongoing or recently finished clinical trials examined medical therapies in advanced NENs, demonstrating prolongation of the progression free survival[55]. NEN clinical trials pose logistical challenges due to the relative rarity of NENs and the necessity of multi-centric collaboration to ensure adequate recruitment. This is especially relevant to the concept of surgical trials in metastatic NENs, where only a quarter of patients may be amenable for surgery.

There are four ongoing, still recruiting, NEN clinical trials with surgical intervention (diagnostic or curative) (Table 2)[56]. Two are observational. One of those studies gives medical or surgical treatment dependent of patients' decision. Two studies are interventional and multicentric. None of those trials opens new surgical fields. For that to happen, new diagnostic and predictive tools must be developed. Clift *et al*[55] proposed three key areas: (1) The development of increasingly informative functional imaging; (2) The integration with imaging of real-time multianalyte genomic analysis of individual tumour; and (3) The application of system biology strategies to a multidimensional assessment of the relationship of the metabolome, the microbiome, and the proliferome to neuroendocrine neoplasia and the delineation of disease progression[55].

CONCLUSION

Treatment of solitary NEN is often limited to tumour and local lymph node resection. When metastases appear, a multidisciplinary approach is often mandatory. A great variety of treatment modalities combined with a low incidence rate of NENs and their heterogeneity makes this group of tumours a clinical challenge. Patients should be treated in experienced centers with access to the above mentioned modalities. Even in advanced metastatic NETs, selected groups of patients can reach a 5-year OS rate over 50%.

FOOTNOTES

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MINIREVIEWS

Gastrostomy tubes: Fundamentals, periprocedural considerations, and best practices

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Abstract

Gastrostomy tube placement is a procedure that achieves enteral access for nutrition, decompression, and medication administration. Preprocedural evaluation and selection of patients is necessary to provide optimal benefit and reduce the risk of adverse events (AEs). Appropriate indications, contraindications, ethical considerations, and comorbidities of patients referred for gastrostomy placement should be weighed and balanced. Additionally, endoscopist should consider either a transoral or transabdominal approach is appropriate, and radiologic or surgical gastrostomy tube placement is needed. However, medical history, physical examination, and imaging prior to the procedure should be considered to tailor the appropriate approach and reduce the risk of AEs.

Key Words: Gastrostomy; Gastropexy; Enterostomy; Decompression; Enteral nutrition; Endoscopy

Core Tip: We reviewed 179 articles and compiled suggested considerations, especially for endoscopists, in the preprocedural evaluation of gastrostomy candidates. Patients referred to for gastrostomy tube placement should be evaluated for indications, contraindications, ethical considerations, and comorbidities. Additionally, the proceduralist should consider whether radiologic or surgical tube placement may be more appropriate, and whether a transoral or transabdominal approach is appropriate. Prior to the procedure, physical examination, imaging, and other interventions should be performed to reduce adverse events.

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INTRODUCTION

Percutaneous gastrostomy is a method of inserting a tube transabdominally into the stomach to provide nutrition, decompress, and/or administer medication. The first of these is the most common indication for gastrostomy tube placement and is critical to preserve nutritional status and improve prognosis for a wide spectrum of conditions and illnesses[1]. Minimally invasive methods of gastrostomy placement have been developed and include, but are not limited to, percutaneous endoscopic gastrostomy (PEG). Since this is an invasive procedure associated with a number of potential adverse events (AEs), appropriate patients and technique selection is essential.

Over the past decade, all-cause mortality from PEG placement has decreased approximately 40% despite AE rates, time to placement, indications, and comorbidities of patients having generally remained the same[2]. This could be attributable to better patient selection and optimization of placement technique. However, there is still a considerable patient cohort that is exposed to PEG and/or other gastrostomy tube placement without adequate preprocedural planning[3].

In this review, we discuss gastrostomy tube indications, contraindications, optimal gastrostomy technique, informed consent, physical exam tenets, and imaging considerations as well as management of anticoagulation and antibiotic prophylaxis. We also provide practical pearls to decrease the risk of various AEs and equip the proceduralist with a comprehensive preprocedural approach, as summarized in Table 1.

GASTROSTOMY TUBE INDICATIONS

Regardless of clinical context, gastrostomy tube placement is mostly indicated to provide nutrition and bypass obstruction. In certain conditions such as gastric volvulus, gastrostomy tube can be utilized for gastropexy procedure, though these are beyond the scope of the discussion.

It is appropriate to place the gastrostomy tube in patients with underlying conditions that require more than four weeks of artificial enteral nutrition. Such conditions include Guillain-Barre syndrome, acute stroke, intracranial trauma, anorexia nervosa, hyperemesis gravidarum, severe burns, facial trauma, esophageal disease, malnutrition especially in patients prior to transplantation, and head and neck tumors undergoing treatment[4]. Moreover, it may also be appropriate to place gastrostomy tubes permanently in certain conditions with poor prognosis to improve quality of life. Such conditions include neurological diseases like multiple sclerosis and amyotrophic lateral sclerosis, advanced head and neck tumors, oropharyngeal malformations, advanced esophageal or gastric malignancy, rheumatologic disorders associated with esophageal dysfunction such as scleroderma, cystic fibrosis, and amyloidosis[5] (Table 2).

CONTRAINDICATIONS

Relative contraindications include recent gastrointestinal (GI) bleeding, hemodynamic instability, ascites, respiratory failure, peritoneal carcinomatosis, and anatomical alterations[2]. Absolute contraindications include mechanical obstruction of the GI tract unless procedure is indicated for decompression, active peritonitis, uncorrectable coagulopathy, and bowel ischemia[5] (Table 3).

Table 1 Periprocedural pearls for gastrostomy tube placement

Recognize indications, relative contraindications, and absolute contraindications for gastrostomy tube placement
Ensure appropriate informed consent and discussion of the benefits of gastrostomy tubes
Ensure correct selection of gastrostomy technique:
Transoral techniques should be first line except in select indications where transabdominal techniques maybe more appropriate
Placement by radiology is appropriate when the endoscopist is not trained in the transoral or transabdominal technique necessary or lacks availability of materials
Laparoscopic tube placement should be utilized when endoscopic or radiographic gastrostomy fails or is contraindicated
Perform certain periprocedural interventions to reduce adverse events:
Physical exam for oropharyngeal and abdominal wall abnormalities, ascites, and obesity
Hold anticoagulation and antiplatelet therapy appropriately and correct coagulopathy to avoid bleeding
Administer antibiotic prophylaxis targeting skin flora thirty minutes prior to procedure to prevent infection
Drain ascites beforehand and avoid gastrostomy tube placement if fluid reaccumulation is expected to occur within 7-10 d
Obtain cross-sectional imaging (*e.g.*, computed tomography) if colonic interposition and other suspected anatomical abnormalities are suspected
Use reverse Trendelenburg patient positioning, proper transillumination and palpation of anterior gastric wall, and use of safe track maneuver during initial needle puncture to prevent inadvertent liver or colonic puncture
Minimize external bumper traction and ensure tube is rotatable to prevent buried bumper syndrome and ulceration
Consider abdominal binders to restrict access, gastropexy devices, and low-profile gastrostomy button with detachable tubing to prevent patient tube dislodgement

Table 2 Select Indications for gastrostomy placement

Palliative venting for malignant obstruction and peritoneal carcinomatosis[20,46,120-124]	Can reduce symptoms of nausea and vomiting without a cumbersome NG tube
Head and neck malignancy[20,125-130]	Reactive rather than prophylactic gastrostomy can reduce treatment related critical weight loss
Esophageal malignancy[131-136]	Achieves adequate nutritional status better than self-expandable metal stent insertion
Ventilator-dependent respiratory failure including COVID-19[137-144]	Early enteral nutrition can decrease complication rates and length of stay due to a catabolic state in prolonged ventilation
Stroke with dysphagia[145-147]	Can be placed after 28 d if prolonged enteral nutrition is needed
Non-stroke neurologic disease[148-155]	Supported in amyotrophic lateral sclerosis. No guideline specific recommendations in Parkinson's disease, multiple sclerosis complicated by dysphagia, cerebral palsy, or trauma patients with severe cerebral injury but has been effective
Pregnancy complicated by severe hyperemesis gravidarum[156-159]	Successfully performed in up to a 29 wk gestation with favorable maternal and fetal outcomes
Gastric bypass	Can be performed in concurrence with surgery to avoid reoperation in patients who are at higher risk for an anastomotic leak or gastro-enteric obstruction[20,160,161]

METHODS OF MINIMALLY INVASIVE GASTROSTOMY TUBE PLACEMENT

Percutaneous gastrostomy has supplanted open gastrostomy and can be performed with tube introduction transorally or transabdominally, using endoscopic (Figure 1), imaging (Figure 2), or laparoscopic guidance (Figure 3)[2].

Endoscopic placement: Brief overview of technique

With endoscopic guidance for PEG, the "pull" (Ponsky-Gauderer) technique[6,7], "push-over-wire" (Sacks-Vine) technique[8,9], and "introducer" (Russell)[10,11] technique can be used depending on training or operator preference. The introducer method is the only true transabdominal method that can be used to avoid transoral passage of the PEG tube. For patients with near-obstructing head and neck malignancy, the "SLiC" technique can be performed with a small-bore endoscopy if fluoroscopy cannot be used[12].

Transoral approach is usually performed in both push-over-wire and pull techniques. Upper endoscopy is performed to insufflate and transilluminate the stomach. A site for placement is chosen *via* endoscopic visualization combined with manual palpation of the stomach. After local anesthesia is

Table 3 Select relative contraindications to gastrostomy placement

	Comments
Certain alterations in abdominal anatomy and motility[2,5]	Open abdomen, ostomy sites, drain tubes, and surgical scars can alter or preclude location for gastrostomy tube placement
Altered oropharyngeal anatomy[2]	Vocal cord paralysis, active radiation, head/neck tumors, facial and skull fractures, and high cervical fractures can obstruct the gastrostomy tube and create an airway emergency
Massive refractory ascites[2,162,163]	Increased risk for bacterial peritonitis, impairment of stoma tract maturation, and tube dislodgement if ascites rapidly reaccumulates over 7-10 d despite paracentesis or PleurX catheter placement; gastropexy devices can increase success
Upper GI bleeding from ulcer or varices[2]	Bleeding peptic ulcers and esophageal varices can have high rates of recurrent bleeding; bleeding from stress gastropathy, gastritis, or angiodysplasia are less likely to recur, and do not need a delay in enteral access
Obesity[2]	Shifting of panniculus increases the risk of tube dislodgement from the stomach into the peritoneal space
Early feeding in stroke with dysphagia[20,29,164-166]	Enteral tubes prior to 28 d rather than temporary NG tubes had greater development of pressure ulcers, sepsis, pneumonia, and GI bleeding over 2 yr
Nutrition in terminal metastatic malignancy[2,167,168]	Administration of nutrition beyond specific patient request plays a minimal role in comfort and does not improve complication rate, survival, or functionality in terminal malignancy
VP shunts[20,46,169,170]	May increase risk of ascending meningitis
Irreversible dementias[171-179]	Does not improve mortality or rehospitalization rate

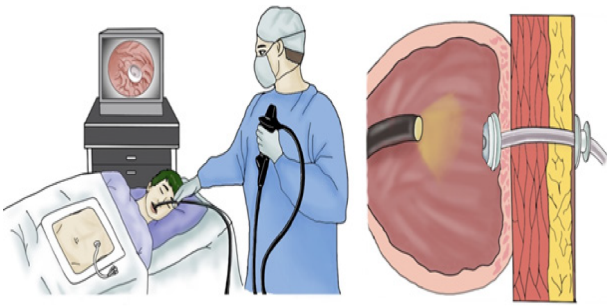

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Figure 1 Endoscopic gastrostomy tube placement.

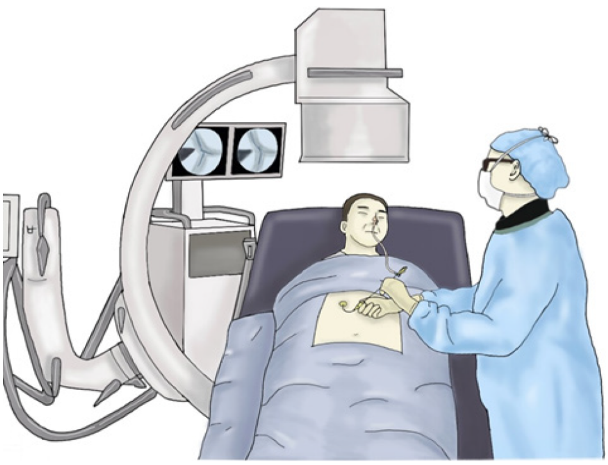

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Figure 2 Radiologic gastrostomy tube placement.

given through the chosen site and a small cutaneous incision is performed to the fascia. A catheter over needle is passed percutaneously into the stomach. A snare is passed through the endoscope.

Subsequently with the pull method, the needle is removed and a silk suture loop ("string") is passed through the remaining catheter into the stomach. The snare that passed through the endoscope grasps the string. The string is pulled out *via* endoscope through the mouth. The wire loop of the string is then

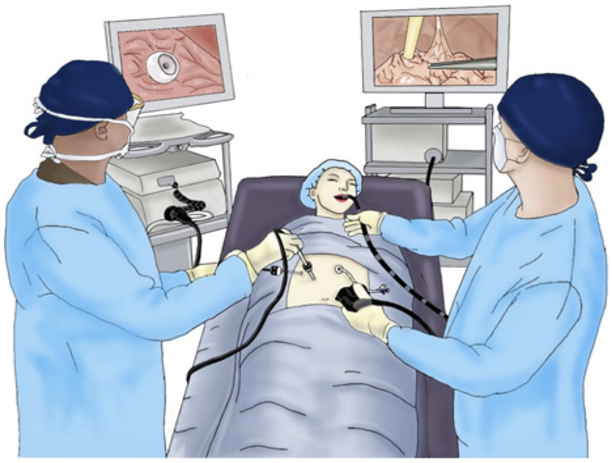

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Figure 3 Laparoscopic-assisted endoscopic gastrostomy tube placement.

tied to the wire loop of the PEG tube. The tube is then "pulled" *via* string back through the mouth to the stomach, and then out the abdominal wall. The endoscope is then reinserted to confirm placement.

With the push-over-wire technique, a guidewire instead is placed into the stomach after needle removal. Similarly, the endoscope pulls the wire through the mouth *via* snare. The PEG tube is placed over guidewire exiting the mouth and pushed out through the stomach and abdominal wall. To accomplish this, a long plastic tapered dilator is fused to the tip of the PEG tube to facilitate passage[13].

Unlike the push-over-wire and pull methods, the introducer method avoids PEG tube contact with the oropharyngeal cavity[13,14]. This technique is more employed in fluoroscopic placement by radiology, though can be performed by the endoscopist as well. The initial steps are similar wherein a trocar is placed into the stomach with endoscopic visualization, and guidewire is passed into the stomach. The wire is held by endoscopic snare to secure it. Two to four T-fasteners are then deployed into the stomach *via* cannula around the trocar for gastropexy. The tract through which the guidewire passes is then dilated serially, and a peel-away sheath is passed over the wire[13]. There are other variations in which other gastropexy methods are used such as a double-lumen gastropexy device[11]. The PEG tube is passed through the sheath over wire and sheath removed, with balloon tip inflation to secure the tube in the stomach[13].

The SLiC technique is similar to the introducer technique but avoids the need for T-fasteners which are not widely available[12]. After a blunt 7-8 mm AutoSuture Mini Step Trocar is placed into the stomach with endoscopic visualization, the blunt needle within is withdrawn leaving the radially expandable sleeve in place. A tapered blunt dilater with cannula is inserted to expand the trocar sleeve radially. The dilator is then removed from the cannula, leaving a self-anchoring 7-8 mm working port through the cannula. A metal stylet is passed through a 20 french Malecot catheter (the PEG tube) and together they are inserted into the port. The port surrounding the PEG tube is then removed while the tube is held in place with endoscopic verification.

Radiologic placement: Brief overview

With fluoroscopy, computed tomography (CT), or ultrasound guidance, percutaneous radiological gastrostomy (PRG) can be performed transabdominally with push type A technique (Seldinger) and push type B technique (Peel-away sheath). If desired, PRG can achieve gastropexy similar to the introducer technique with T-fasteners or other devices[15-17]. Similar to the PEG "push-over-wire" technique, hybrid per-oral image guided gastrostomy technique (PIG) has also been used for transoral placement[18,19]. Alternatively, percutaneous transesophageal gastrotubing (PTEG) with image guidance can be used to place esophagostomy when gastrostomy is contraindicated such as massive refractory ascites, hostile abdomen, or massive peritoneal carcinomatosis[20-25].

Laparoscopic placement: Brief overview

Gastrostomy tube placement can be performed with laparoscopic guidance. Percutaneous laparoscopic assisted gastrostomy (PLAG) requires two midline trocars to perform gastropexy with sutures and place the tube[20,26-29]. A novel hybrid laparoscopic-assisted PEG (LAPEG) is a combination of endoscopy with laparoscopic visualization[30-34], as shown in Figure 3.

Comparison of endoscopic gastrostomy methods

Although the use of each technique depends on institution and clinical scenario, transoral PEG placement is often first-line, though variation exists across institutions. The pull technique may have lower rates of AEs in non-oropharyngeal cancer patients, especially for palliative decompression[35]. Additionally, a larger and more robust tube can be placed with transoral technique. The smaller diameter of available introducer trocars limits transabdominal technique. This may lead to higher rate of tube blockage and occlusions[36,37]. Transoral technique also allows placement of mushroom type catheters without need for gastropexy. Lastly, transoral technique can present a lower minor bleeding rate (0.6% *vs* 6.6%) likely due to the additional needle punctures needed for gastropexy and use of a larger trocar[38].

Though technically more complicated for the endoscopist, the introducer technique could provide a stronger gastropexy with T-fasteners and avoid tube dislodgement[39], especially in patients with neurologic impairment[40,41]. Furthermore, this method is associated with a lower rate of mild peristomal wound infection[42]. The introducer method is more effective than the transoral method in patients with oropharynx or esophageal stricture from radiation, inflammation, or malignancy. Recent studies showed that the introducer technique is widely used in patients with advanced head and neck malignancy due to lower rates of AEs and PEG site metastases related to possible contact with malignant cells with the pull technique[43-47]. However, some institutions continue to use the transoral technique given the low incidence of abdominal wall metastases and the need for large randomized controlled trials comparing the procedural *vs* metastatic risk[48].

Overall, the pull technique has a higher rate of infection but a lower rate of bleeding compared to the introducer technique[38]. Therefore, the type of technique for gastrostomy tube placement should be chosen based on patient characteristics and operator's skill. The introducer technique should be considered in patients with head and neck malignancy. However, further studies are warranted.

The Russell introducer technique is inferior to the SLiC technique described in the prior section, and may also be technically harder for the endoscopist. First, the size of the PEG tube is limited by the extent of dilation that can be achieved and using larger dilators without T-fasteners increases the likelihood of the stomach being pushed away from the abdominal wall. Second, T-fasteners may not be readily available at all institutions. The Mini Step Trocar used in the SLiC technique dilates axially in one step without the need of T-fasteners[12]. Third, the balloon catheter used in the introducer technique has a greater chance of rupture and dislodgement than mushroom catheters including the Malecot catheter used in the SLiC technique[49]. Thus, in selected patients in whom the conventional push-over-wire or pull techniques cannot be performed, the SLiC technique should be considered over the introducer technique where larger PEG tube are preferred and T-fasteners are not available. Other modified introducer methods involving direct placement of bumper-button-type catheters have been described [50,51] and can also be considered over the Russell technique if preferred.

Comparison of endoscopic, radiologic, and laparoscopic gastrostomy tube placement methods

There is a large confusion of nomenclature in the surgical, radiological, and gastroenterological literatures. For endoscopic placement, the pull and push-over-wire methods are performed transorally. There are no differences in the success and AE rate between both methods. Thus, either method can be used depending on operator's experience, though the pull method is more widely employed[13,52,53]. Several studies comparing the "pull" *vs* "push" method are referring to a comparison between the transoral and transabdominal introducer methods or other "push" trocar methods. Multidisciplinary guidelines describe transoral gastrostomy as the pull PEG technique and transabdominal gastrostomy as type A or B push PRG techniques[2].

If the less common PIG technique is readily available, the choice of transoral PEG *vs* PIG technique depends on institutional preference and operator capability due to similar AE rates[18,19]. PRG *vs* transoral PEG placement parallels the choice of transoral *vs* transabdominal PEG technique in the previous section. Only a large meta-analysis study reported a higher success rate but lower morbidity rate in PRG technique[54], but other previous studies showed lower rates of AEs, mortality, and readmission in PEG technique especially in those with head and neck malignancy[20,55,56]. In contrast, several studies demonstrated a similar AE rate between PRG and PEG technique[42,57-61]. However, the AE profile of each study may be different. Despite lower rates of bleeding and pain, PEG pull technique could cause more superficial wound infection and buried bumpers than PRG technique[60]. PRG may be considered if transabdominal PEG cannot be performed due to lack of endoscopic training or resources.

Endoscopic feeding tube placement has the advantage of placement at bedside as opposed to the radiology suite for PIG/PRG or operating room for PLAG[13]. This may be particularly useful in critically-ill patients. Transabdominal PEG should be favored over transoral PEG in patients with obstruction or stricture due to oropharyngeal mass and those with head and neck malignancy who are at risk of tumor seeding from the PEG site. However, if the endoscopist lacks experience or resources are unavailable, the gastrostomy tube placement by interventional radiology is more appropriate.

PLAG is a safe and preferred method of placement if PEG or PRG cannot be performed due to unsuccessful endoscopic trans-illumination and finger palpation, inadequate imaging window, or inability to insufflate the stomach[28,62]. It does not preclude PEG placement, as it can be used when PEG is contraindicated to ensure that there is no obstruction or blood vessels at the site of tube placement. Such conditions include morbid obesity, need for lysis of adhesions, organ interposition, gastric varices, large hiatal hernia, ileus, intraabdominal mass, gravid uterus, ascites, use of peritoneal dialysis, or altered anatomy due to gastric bypass[30,63]. Though PEG technique has been utilized in altered Roux-en-Y anatomy with double balloon enteroscopy, it requires fluoroscopy and is not widely used[20]. In pediatric patients, PLAG is more preferred in to avoid serious AEs such as intestinal fistula formation[64-66]. Laparoscopic placement should also be considered when jejunostomy is needed for more durable long-term enteral access compared to jejunal extension tubing[67].

LAPEG is a hybrid approach for gastrostomy tube placement as it allows direct visualization of all cavities. If available, it can be considered over PLAG due to the advantage of luminal visualization. It also allows transoral tube placement, conferring the advantages described in prior sections over transabdominal method. However, this technique requires physicians with advanced expertise in laparoscopy with PLAG, increased peritoneal insufflation, and placement of multiple ports[30-34].

APPROPRIATE INFORMED CONSENT AND MANAGING EXPECTATIONS

Gastrostomy tube placement should involve the informed and educated consent of the patient in order to respect patient autonomy over perceived beneficence. Informed consent for gastrostomy tube placement is often inadequate[42,68,69]. Legal precedence over the past thirty years has determined that artificial nutrition should not be thought of as different from any other medical therapy, and that there is no obligation to provide it if it is unwanted[2,70]. If the patient cannot provide consent, the consent of the health care proxy from an advanced directive should be obtained. The living will should be followed if the patient is considered terminally ill[2,70].

Appropriate expectations must be set about what benefit the gastrostomy tube can provide for the patient. Clinical indications can start the decision-making process but are rarely adequate alone[20]. Social support should also be evaluated, as it plays a significant role at reducing gastrostomy tube dependence[71]. In conditions such as anorexia from advanced malignancy, it has been suggested that gastrostomy tube not even be offered due to an inability to utilize nutrients from feeding[72]. In conditions such as a permanent vegetative state, gastrostomy tube can be offered but should be recommended against due to inability of the patient to experience any quality of life. In contrast, if the patient has uncomplicated dysphagia with preserved quality of life otherwise, gastrostomy tube should be offered and recommended due to unequivocal nutritional benefit[73]. Furthermore, in malignant gastrointestinal obstruction, gastrostomy tube venting provides clear symptomatic benefit.

Decision-making is most difficult in equivocal indications such as recurrent strokes, and can lead to decision regret among surrogate decisionmakers[74]. Gastrostomy tubes that are frequently placed into elderly or neurological impaired patients have a significant financial burden on the healthcare system associated with dislodgement[75]. Gastrostomy insertion in such patients provides a greater health-related quality of life improvement for caregivers than patients[20,76], purportedly due to greater ease of medication administration and greater sense of accomplishment by the caregiver[70]. The intervention can provide physiologic benefit in prolonged life but may not actually improve quality of life. Given that data on long term functional outcomes are often lacking, decision-makers focus on short-term procedural safety and potential for improved nutrition[77]. A limited feeding trial can be discussed, but strict criteria on what constitutes a successful response to feeding should be defined in discussion with the patient or health care proxy[20].

PRE-PROCEDURAL PHYSICAL EXAM AND IMAGING CONSIDERATIONS

Physical examination may help identify certain contraindications to gastrostomy tube placement and prevent occurrence of AEs. The oropharynx and head should be inspected for features that preclude endoscopic approach such as facial fractures or complete obstruction. An anesthesia or sedation team should additionally look for features that may impact sedation such as stridor, large neck circumference, or presence of obstructive sleep apnea to reduce procedure-related cardiopulmonary AEs[78].

The abdomen should be examined for ascites and obesity, which can increase the risk of tube dislodgement, failed transillumination, or failed gastropexy. To avoid puncture of liver, the caudal and lower edge of the liver should be identified with percussion before gastrostomy placement[78]. Any devices such as VP shunts should be noted as well so that the endoscopist can be aware of any infection risk. The patient’s mental status should be examined to determine ability to consent.

Abdominal imaging with CT or radiography can be obtained prior to the procedure if abnormal anatomy is suspected or known due to prior surgery. Certain patients requiring gastrostomy tubes may have structural deformities of the spine, previous abdominal surgery, or chronic constipation, which predispose transposition of the transverse colon in front of the anterior gastric wall. Preprocedural abdominal radiographs can be obtained and subsequent enema administration can be performed to decompress the colon if interposed on imaging[79,80]. Furthermore, use of abdominal x-ray after insufflation of 500 cc of air may help identify an optimal gastric puncture point[81]. Concordance between pre-procedural CT scan and abdominal radiography was reported to be approximately 73% [82]. CT scan increased the success rate of gastrostomy tube placement from 77% to 98% due to high sensitivity of adequate window identification[82].

ANTIBIOTIC PROPHYLAXIS

Patients undergoing PEG tube placement are more prone to infection due to poor nutrition, advanced age, immunocompromise, age, and comorbidities (diabetes, obesity, malnutrition). Infection may occur more frequently with transoral technique due to exposure to oral flora and is one of the most common AEs of external bolster traction[48,71-80]. Major peristomal infection is rare, seen in less than 1.6% of cases. The incidence of minor infection ranges from 5.4%-30%[20,83,84].

Pre-procedural antibiotic prophylaxis is recommended to reduce infectious AEs. Pooled analysis of thirteen randomized control trials evaluating use of prophylactic antibiotics during PEG tube placement showed a significant reduction in incidence of peristomal infection[85]. The introducer technique can be used to avoid oral flora contamination with the pull method to confer lower infection risk[64,86] especially in head and neck cancer patients with overgrowth of oral flora related to tumor[44]. However, there are some reports of increased intraperitoneal abscess and leakage with the introducer method[87]. Prophylactic antibiotics may still be needed regardless of technique[88].

The choice of antibiotic does not necessarily seem to matter if appropriate cutaneous flora is covered. According to the ASGE guideline, antibiotic prophylaxis with IV cefazolin 1 g or equivalent antibiotic thirty minutes before gastrostomy tube placement is recommended to cover cutaneous organisms if patient has not already received appropriate antibiotics[89]. One clinical trial found that administering a single dose of oral Bactrim through PEG tube after insertion is not inferior to a single dose of intravenous 1.5 g cefuroxime before insertion[90]. Another study showed that three doses of IV cefuroxime prior to the procedure with post-procedural betadine spray modestly decreased the rate of stomal infection during the first week[20]. In contrast, a clinical trial found no significant differences between 2 g of cefotaxime and 0.5-4 g of piperacillin-tazobactam prior to the procedure as normal skin flora was mostly considered as a cause of topical wound infection[84].

MANAGEMENT OF ANTIPLATELET AND ANTICOAGULANT AGENTS AND COAGULOPATHY

Gastrostomy placement is a high-risk procedure according to consensus GI society guidelines and moderate risk procedure according to SIR guidelines in patients receiving anticoagulant or antiplatelet therapy[20,83,91-94]. The risk of bleeding should be weighed against thromboembolic event risk after stopping medication. Additionally, resumption of medication is dependent on achieving proper hemostasis[2].

Patients on antiplatelet agents do not necessarily need to have low-dose aspirin withheld. Thienopyridines such as clopidogrel, prasugrel, ticagrelor, and ticlopidine should be withheld 5-7 d before gastrostomy placement. They can be resumed one day after the procedure with the exception of the non-loading dose of clopidogrel, which can be resumed as early as six hours after. Aspirin should additionally be started in the interim if the patient is not already taking it when temporarily discontinuing these antiplatelet agents. There have been certain studies that have had findings in opposition to these consensus statements. Even with use of uninterrupted antithrombotic therapy with clopidogrel and aspirin, risk of significant bleeding was found to be minimal or nonsignificant as compared to holding therapy[95-97]. A risk/benefit discussion should be held with patients who have a higher risk of thromboembolism such as those with coronary artery disease and drug eluting stent placement within the past twelve months or bare stent placement within the past month. A loading dose of thienopyridine can be considered on recontinuation in these patients as well[2,20,83,91-94].

For patients on anticoagulation, patients with higher risk of thromboembolism are those with thrombophilia conditions, deep venous thrombosis within past three months, atrial fibrillation with mitral valve stenosis or prosthetic valve, and metal mitral valve. Warfarin should be discontinued five days before gastrostomy placement. In high risk patients, low molecular weight heparin (LMWH) can be substituted to bridge the patient, with a dose withheld on the morning of the procedure. In low risk patients, INR should be checked to ensure it is less than 1.8 pre-procedure. Warfarin can then be resumed the evening of the procedure. DOACs such as apixaban should be discontinued in high risk patients for the appropriate drug-specific interval[20] and be resumed one to three days after. For heparin products prior to procedure, unfractionated heparin should be withheld six hours before, prophylactic LMWH should be held one dose before, and therapeutic LMWH should be held two doses before[2,20,83,91-94]. Use of uninterrupted heparin products were shown to be independent predictors of bleeding[96,97].

Prior to procedure, platelets, INR, aPTT should the checked. INR should be corrected to a range of 1.5-1.8 and platelets should be corrected to at least 50 x 10^9/L. There is no consensus on correcting aPTT, though there is a trend towards correcting for values 1.5 x above normal limits. In chronic liver disease patients, fibrinogen levels should be checked as well. INR should be corrected to below 2.5, platelets should be corrected to above 30x10^9/L, and fibrinogen should be corrected to above 100 mg/dL[92,93].

AES AND APPROACH TO PREVENTION AND MANAGEMENT

Gastrostomy tubes are associated with various potential AEs. There are various measures which can be taken to mitigate these, as discussed hereinafter.

Aspiration

Aspiration related to the gastrostomy tube procedure occurs in about 0.3%-1% of cases, and was associated with supine position, deeper sedation, advanced age, and neurologic impairment[20,46,98]. The endoscopist should avoid excessive sedation, have prior evaluation by a sedation team, aspirate all gastric contents before gastrostomy tube placement, suction all insufflated air after gastrostomy tube is placed, and minimize procedural time[78].

Bleeding

Acute bleeding is a rare AE, which occurs roughly 1%. Of these, less than 0.5% requires blood transfusion and laparotomy due to bleeding[87,99-101]. The endoscopist should consider blood transfusion and temporarily holding anticoagulation per guidelines mentioned in prior section. Additionally, if the patient is particularly prone to bleeding, the pull technique should be considered over the introducer technique[38]. Cutaneous puncture should be performed lateral to the rectus muscle. Puncture of anterior gastric wall should be performed at the mid to distal body of the stomach and equidistant from the lesser and greater curvatures to avoid arterial injury[102,103]. Underlying lesions that can cause bleeding (*i.e.* ulcer, erosion, or angioma) should also be assessed.

Perforation and pneumoperitoneum

Inadvertent perforation of the intestines is a rare but potentially fatal AE. The endoscopist can minimize this, among other means, by performing a safe track maneuver to ensure no intervening loops of the bowel[2]. With high intragastric insufflation pressure during endoscopy, air may escape during gastrostomy tube insertion or needle puncture leading to pneumoperitoneum. Transient subclinical pneumoperitoneum is a common benign finding that is usually asymptomatic, but a minority of patients can have signs and symptoms of peritonitis. Carbon dioxide rather than ambient air may be used for insufflation to significantly reduce the severity of pneumoperitoneum[78,104]. Internal bolster placement below the upper body of the stomach can be used to prevent pneumoperitoneum[102].

Peristomal infection

Infection of the peristomal site can be prevented with appropriate pre-procedural antibiotic prophylaxis as described prior. Patients who have comorbid diabetes, obesity, poor nutritional status, or long-term corticosteroid administration have not only a higher incidence of mortality[105] but also infection risk [106]. Additionally, patients with diabetes, chronic kidney disease, pulmonary tuberculosis, or alcoholism could be at risk for the rare development of necrotizing fasciitis around the ostomy site[107-109]. Particular attention should be paid to patients with such comorbid conditions to prevent infection. Standard infection control measures such as aseptic surgical field preparation and preprocedural hand disinfection[78]. As expanded upon in the next sections, introducer technique has been associated with reports of intraperitoneal abscess[87]. The transoral approach has risks as well since it can drag oropharyngeal flora along with the tube, leading to increased peristomal infection rate[42]. If transoral technique is used in high risk chronically hospitalized patients, nasopharyngeal decolonization of MRSA and mouthwash with oral chlorhexidine solution can be considered to reduce peristomal infection[20,78].

Fungal tube degradation

Degradation of PEG tube by fungal colonization has been shown to cause PEG tube failure up to 37% of the time by 250 d and 70% of the time up to 450 d[110]. Fungal growth leads to brittleness, cracking, and obstruction of tube. Though there is no definitive management, the endoscopist should consider polyurethane tubing over silicone tubing to increase resistance to degradation[111,112].

Buried bumper syndrome

Buried bumper syndrome is a partial or complete growth of gastric mucosa over the internal bumper in the stomach. This could lead to migration of the bumper through the gastric wall and gastrostomy tract, which can cause abscess formation, leakage around the gastrostomy site, immobile gastrostomy tube, abdominal pain, and possible resistance to formula infusion. Risk factors include poor wound healing, malnutrition, significant weight gain due to successful nutrition, placement of internal bumper in the upper gastric body, and excess tension between the internal and external bumpers[2,102].

To reduce the risk of buried bumper, the endoscopist should place the outer bumper tight enough to ensure proper gastropexy but loose enough to allow room for post-procedural tissue swelling. The external bumper should be subjected to a very low traction without tension. The next day, the outer bumper should be loosened and rotated to allow back and forth movement at least 1 cm with minimum resistance. The tube should also be covered to prevent inadvertent tugging. The tube needs to be rotated daily and moved inward from 2 to 10 cm once the gastrostomy tract is healed around 7-10 d. Subsequent restricted movement, pain or leakage around the site should be evaluated for buried bumper as early endoscopic intervention can preserve the feeding tube[78,113,114]. The most common signs of buried bumper syndrome is an inability to move the PEG tube inward[78].

Ulceration

Ulceration or erosion from PEG tube can be found up to 1.2% of all cases. This is usually caused by friction of the gastric wall opposite to or underneath the internal bumper[20,87,100,115]. Similar to preventing buried bumper syndrome, the endoscopist should avoid excess tension between the internal and external bumpers, rotate the tube daily, and move the tube inward after the gastrostomy tract is healed[78]. The mucosa under the internal bumper should be visualized after placement, and excess lateral traction on the tube should be avoided[2].

Colonic injury and fistulae

Excessive gastric and small bowel insufflation can lead to bowel transposition and gastric rotation[80]. If the colon is accidentally punctured or cannulated, fistulous tracts can later form between stomach, colon, and skin. Many patients are asymptomatic but can develop severe diarrhea after feeding, fecal discharge around the tube, and even peritonitis and sepsis[78]. If the gastrostomy tube is replaced into a gastrocolocutaneous fistula, the tube could miss the gastrostomy and enter the colon creating a new colocutaneous fistula. The proceduralist can mitigate such AEs with safe track technique to avoid initial puncture of colon. Reverse Trendelenburg positioning, proper transillumination, and finger imprinting may help. If misplaced gastrostomy tube is suspected, radiographic imaging (CT) should be performed with subsequent removal of the misplaced tube[2,116].

Liver injury

Similar to colonic interposition, the lateral segment of the liver can interpose between the abdominal wall and stomach, leading to possible injury during gastrostomy placement. Injuries may be associated with bleeding but could be asymptomatic. As mentioned previously, caudal edge of the liver should be identified with physical exam before puncture[78].

Gastric outlet obstruction

Gastric outlet obstruction is usually seen in pediatric patients due to migration of the internal bumper and obstruction of the pyloric channel. It can occur in adults if catheter with internal balloon is used, and the balloon migrates into the pylorus or proximal small bowel. This can be prevented by reducing the length of tube inserted into the gastric lumen, though caution must be taken to avoid excess tension at the gastrostomy tube site[80].

Tube dislodgement and removal

Maturation of the gastrostomy tract usually occurs within the first seven to ten days after placement but can take weeks longer if there is concurrent malnutrition, ascites, or steroid treatment. If gastrostomy tube is removed during this period, it should be replaced endoscopically or radiographically as an immature tract can result in free perforation. Altered mental status including delirium and dementia increase the risk for accidental tube removal. Additionally, internal bolster placement in the upper body of the stomach increases risk of dislodgement[102]. Measures should be taken to reduce such events, such as using abdominal binders or elastic bandage to restrict access, gastropexy devices at time of tube placement, proper gastrostomy site choice, and use of low-profile gastrostomy button with detachable extension tubing. The latter is already used in the pediatric population to reduce risk of dislodgement [78,117].

Tube occlusion

Tube occlusion when feeding can be caused by obstruction of the internal lumen or mechanical tube failure. Smaller bore feeding tubes (less than 10-12 French) are more prone to occlusion with repeated gastric residual aspiration[118]. The endoscopist should consider placing larger bore tubes if possible [119].

Gastrostomy tract tumor seeding

Transoral approach of PEG tube placement may increase risk of tumor seeding in patients with head and neck malignancy due to contact with malignant cells during tube insertion[43-47]. Thus, transabdominal methods such as the introducer, SLiC, PRG, and LAPEG techniques should be highly considered in these patients.

CONCLUSION

PEG has gained increasing acceptance as a safe and effective technique to provide enteral nutrition for a wide variety of indications. However, the preprocedural evaluation and selection of patients remains paramount to provide optimal benefit while reducing risk of AEs. The endoscopist should examine indications, contraindications, ethical considerations, and comorbidities of patients referred for gastrostomy placement. Additionally, the endoscopist should consider whether radiologic or surgical tube placement may be more appropriate, and whether a transoral or transabdominal technique is best. If gastrostomy placement appears indicated, physical exam, imaging, and other interventions should be performed to reduce procedure-related AEs.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Laparoscopic-assisted *vs* open transhiatal gastrectomy for Siewert type II adenocarcinoma of the esophagogastric junction: A retrospective cohort study

Qi-Ying Song, Xiong-Guang Li, Li-Yu Zhang, Di Wu, Shuo Li, Ben-Long Zhang, Zi-Yao Xu, Ri-Li-Ge Wu, Xin Guo, Xin-Xin Wang

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Abstract

BACKGROUND
The studies of laparoscopic-assisted transhiatal gastrectomy (LTG) in patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG) are scarce.

AIM
To compare the surgical efficiency of LTG with the open transhiatal gastrectomy (OTG) for patients with Siewert type II AEG.

METHODS
We retrospectively evaluated a total of 578 patients with Siewert type II AEG who have undergone LTG or OTG at the First Medical Center of the Chinese People's Liberation Army General Hospital from January 2014 to December 2019. The short-term and long-term outcomes were compared between the LTG (n = 382) and OTG (n = 196) groups.

RESULTS

Compared with the OTG group, the LTG group had a longer operative time but less blood loss, shorter length of abdominal incision and an increased number of harvested lymph nodes (P < 0.05). Patients in the LTG group were able to eat liquid food, ambulate, expel flatus and discharge sooner than the OTG group (P < 0.05). No significant differences were found in postoperative complications and R0 resection. The 3-year overall survival and disease-free survival performed better in the LTG group compared with that in the OTG group (88.2% *vs* 79.2%, P = 0.011; 79.7% *vs* 73.0%, P = 0.002, respectively). In the stratified analysis, both overall survival and disease-free survival were better in the LTG group than those in the OTG group for stage II/III patients (P < 0.05) but not for stage I patients.

CONCLUSION

For patients with Siewert type II AEG, LTG is associated with better short-term outcomes and similar oncology safety. In addition, patients with advanced stage AEG may benefit more from LTG in the long-term outcomes.

Key Words: Adenocarcinoma of the esophagogastric junction; Siewert type II; Laparoscopic-assisted transhiatal gastrectomy; Open transhiatal gastrectomy

Core Tip: Our objective was to compare the surgical efficiency of laparoscopic-assisted transhiatal gastrectomy (LTG) with the open transhiatal gastrectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction. We found that LTG was associated with better short-term outcomes and similar oncology safety. In addition, patients with advanced stage adenocarcinoma of the esophagogastric junction may benefit more from LTG in 3-year overall survival and disease-free survival.

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INTRODUCTION

In recent decades, the global incidence of gastric cancer has declined annually while the incidence of adenocarcinoma of the esophagogastric junction (AEG) has presented an upward trend, especially in Asian countries[1-5]. Although there are many controversies concerning the optimal treatment for AEG patients, surgery is still the cornerstone of therapeutic strategies[6]. According to the results of the nationwide clinical trial (JCOG 9502) in Japan, the transhiatal approach is recommended for Siewert type II/III AEG patients with esophageal invasion within 3 cm[7,8]. Since the first report of laparoscopic-assisted transhiatal gastrectomy (LTG) by Kitano *et al*[9] in 1994, LTG has developed rapidly worldwide. With the improvement of laparoscopic technology and the optimization of equipment, a large number of countries have successively carried out LTG for gastric cancer because it provides not only better short-term outcomes but also comparable oncologic safety and survival in comparison with open transhiatal gastrectomy (OTG), especially in early-stage and distal gastric cancer[10-13]. Conversely, due to the lack of scientific evidence, the feasibility of LTG in proximal gastric cancer is still controversial. Moreover, peripheral lymphatic drainage pathways of Siewert type II AEG are more complicated as the particularity of the anatomical location, and LTG surgery with D2 lymphadenectomy remains more challenging than other gastric cancer sites[14,15].

At present, the studies on the short-term and long-term clinical effects of Siewert type II AEG regarding LTG and OTG are limited[16-20]. Thus, this study retrospectively analyzed the clinical data of Siewert type II AEG patients in our hospital, compared the short-term and long-term outcomes of LTG and traditional OTG and aimed to explore the feasibility of LTG treatment of Siewert type II AEG.

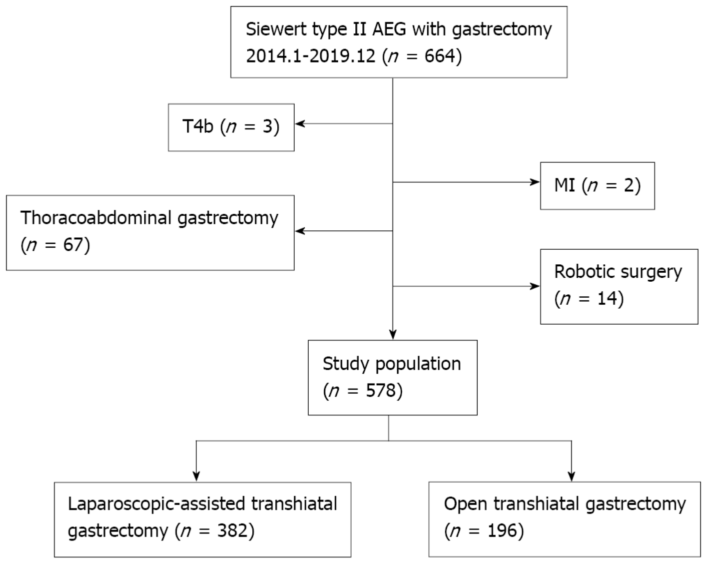

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Figure 1 Flow chart of patient selection. AEG: Adenocarcinoma of the esophagogastric junction.

MATERIALS AND METHODS

Patients

This work retrospectively reviewed patients with Siewert II AEG who have undergone gastrectomy at the First Medical Center of Chinese PLA General Hospital in China from January 2014 to December 2019. The inclusion criteria contained: (1) Histologically proven Siewert type II AEG; (2) Surgery *via* either OTG or LTG with total or proximal gastrectomy with D2 lymphadenectomy; (3) Staging T1-4a, N0-3, M0 (according to the 8th edition of the TNM staging system of the American Joint Committee on Cancer)[21]; and (4) Esophageal invasion < 3 cm. The exclusion criteria were presented as following: (1) Patients with a secondary malignancy within 5 years; (2) American Society of Anesthesiologists physical status score > 3; (3) Only underwent palliative resection or combined organ resection; and (4) Received preoperative chemotherapy of radiotherapy. Finally, a total of 578 patients were pooled into the study (LTG = 382, OTG = 196).

This study has been registered on Clinical-Trial.gov (ChiCTR2100053647) and approved by the Ethics Committee of Chinese PLA General Hospital.

Surgical procedures

LTG: The patient was placed in a supine position and given general anesthesia by employing a 5-hole method. After exploring the relevant positions of various tissues in the abdominal cavity and the location and size of the tumor, a radical total and proximal gastrectomy was performed in this study. Gastrectomy and D2-lymphadenectomy were completed. Then, a small incision was made in the middle of the abdomen to reconstruct the digestive tract. Gastric tube construction and esophagogastrostomy were often performed after proximal gastrectomy. After total gastrectomy, most patients underwent esophagojejunostomy and jejunojejunostomy (Roux-en-Y reconstruction).

OTG: The positioning and anesthesia of the patients remained the same as those of the LTG group. An incision was made in the middle of the abdomen to enter the abdominal cavity. Other operative details such as gastrectomy, lymphadenectomy and reconstruction were the same as those in the LTG group.

Clinical parameters and follow-up

We retrospectively collected the following clinical and pathological factors available in our clinical database: Age, sex, body mass index, smoking/drinking history, American Society of Anesthesiologists score, tumor size, histopathological grade, TNM stage, operation time, intraoperative blood loss, length of abdominal incision, length of proximal margin, number of harvested lymph nodes (LNs), number of positive LNs, resection status (R-status) of margin, postoperative recovery (the time to liquid diet, ambulation, first flatus or defecation and discharge) and postoperative complications (anastomotic leakage, anastomotic stenosis, abdominal abscess, pneumonia, arrhythmia and wound infection). All postoperative complications were classified with the application of the Clavien-Dindo grading system [22].

In addition, postoperative patients were periodically followed up with blood tests, physical examinations and chest/abdominal computed tomography scans through outpatient visits. The follow-up

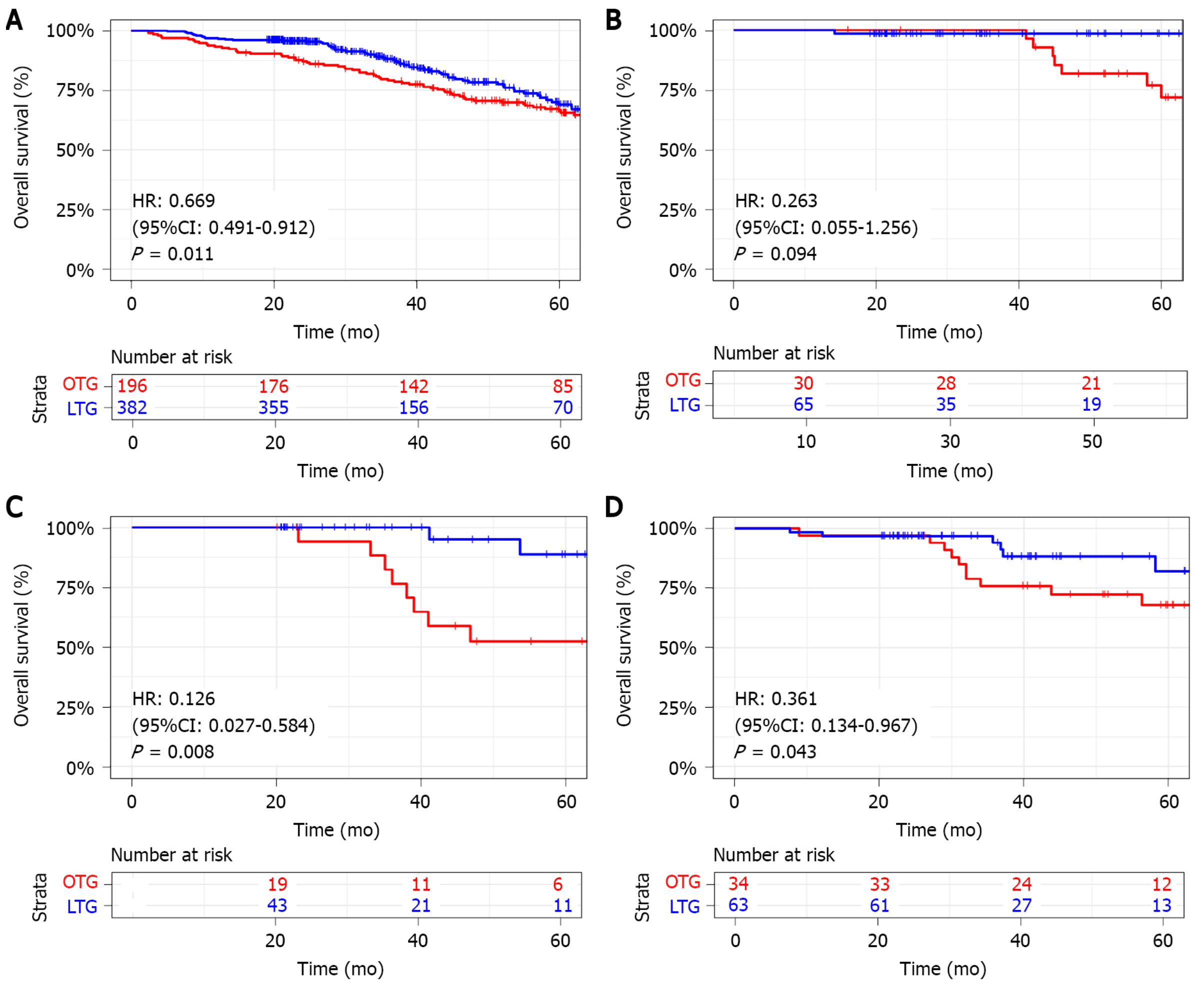

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Figure 2 Comparison of overall survival rates between the laparoscopic-assisted transhiatal gastrectomy and open transhiatal gastrectomy groups. A. Comparison of overall survival rates between the laparoscopic-assisted transhiatal gastrectomy (LTG) and open transhiatal gastrectomy (OTG) groups for all patients; B: Comparison of overall survival rates between the LTG and OTG groups for stage I patients; C: Comparison of overall survival rates between the LTG and OTG groups for stage II patients; D: Comparison of overall survival rates between the LTG and OTG groups for stage III patients. CI: Confidence interval; HR: Hazard ratio.

interval was every 3–6 mo for the first 2 years and every 6–12 mo for the subsequent 3 years. All surviving patients were followed up annually thereafter until death. Overall survival (OS) was calculated from the time of surgery to death due to any cause or latest follow-up. Disease-free survival (DFS) was calculated as the time from surgery to first recurrence or death because of any reason.

Statistical analysis

Continuous data were presented as mean ± standard deviation with *t* test if normally distributed or as the median (interquartile range) with Mann-Whitney *U* test if not normally distributed. Dichotomous variables were compared with the χ^2 test or Fisher test. Survival analysis was performed by the Kaplan-Meier curves based on the log-rank test. Statistical analysis was done by IBM SPSS (version 26.0.0.0). The figures were plotted with RStudio (version 1.4.1717). Bilateral $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological characteristics

As shown in Figure 1, a total of 578 patients were eligible (512 male and 66 female) for our study, of which 382 (66.1%) patients underwent LTG and 196 (33.9%) patients underwent OTG. The demographic information of the participants was presented in Table 1. No significant difference could be observed in the distribution of baseline features between the two groups.

Table 1 Clinicopathological characteristics for patients in two cohorts

Characteristics	LTG, *n* = 382	OTG, *n* = 196	*P* value
Age in yr	64 (58, 69)	63 (59, 69)	0.816[a]
Sex, *n* (%)			
Female	44 (11.5)	22 (11.2)	1.000
Male	338 (88.5)	174 (88.8)	
BMI (kg/m^2)	24.45 (22.10, 26.70)	24.40 (22.50, 27.25)	0.389[a]
Smoking history, *n* (%)			0.635
No	280 (73.3)	148 (75.5)	
Yes	102 (26.7)	48 (24.5)	
Drinking history, *n* (%)			0.773
No	212 (55.5)	112 (57.1)	
Yes	170 (44.5)	84 (42.9)	
ASA, *n* (%)			
1	201 (52.6)	100 (51.0)	0.396
2	164 (42.9)	82 (41.8)	
3	17 (4.5)	14 (7.1)	
Tumor size (cm)	3.49 ± 1.60	3.69 ± 1.62	0.161
Grade, *n* (%)			0.267
1-2	132 (34.6)	58 (29.6)	
3-4	250 (65.4)	138 (70.4)	
T stage, *n* (%)			0.860
T1-T2	129 (33.8)	64 (32.7)	
T3-4a	253 (66.2)	132 (67.3)	
N stage, *n* (%)			0.602
N0	168 (44.0)	81 (41.3)	
N1-N3	214 (56.0)	115 (58.7)	
TNM stage, *n* (%)			0.544
I	107 (28.0)	49 (25.0)	
II	120 (31.4)	70 (35.7)	
III	155 (40.6)	77 (39.3)	

[a]Mann-Whitney *U* test. ASA: American Society of Anesthesiologists; BMI: Body mass index; LTG: Laparoscopic-assisted transhiatal gastrectomy; OTG: Open transhiatal gastrectomy.

Perioperative outcomes

Perioperative outcomes are shown in Table 2. The LTG group experienced a significantly longer operation time (230.14 ± 58.92 min *vs* 198.4 ± 56.76 min, $P < 0.001$) but significantly decreased blood loss (200.42 ± 304.34 mL *vs* 275.77 ± 384.72 mL, $P = 0.010$) and significantly shorter abdominal incision (9.66 ± 1.73 cm *vs* 18.12 ± 3.92 cm, $P < 0.001$) in comparison with the OTG group. Patients with LTG were sooner able to take a liquid diet (3.65 ± 2.56 d *vs* 4.62 ± 2.59 d, $P < 0.001$) and expel flatus or defecation (3.87 ± 2.17 d *vs* 5.62 ± 2.35 d, $P < 0.001$) after the operation, indicating the restoration of the intestinal function. Additionally, patients in the LTG group were able to ambulate after 2.93 ± 2.04 d, which is fewer days than the OTG group required (4.13 ± 2.55 d) ($P < 0.001$). In addition, the duration of postoperative hospitalization of the LTG group was significantly shorter than that in OTG groups [9 (8, 11) d *vs* 10 (9, 12) d, $P < 0.001$].

Postoperative complications occurred in 5.0% of patients after LTG and in 4.6% of patients after OTG ($P = 0.840$). There existed no significant difference between the two groups in terms of anastomotic leakage, anastomotic stenosis, abdominal abscess, pneumonia, arrhythmia or wound infection ($P > 0.05$).

Table 2 Perioperative outcomes (mean ± SD)/median (interquartile range)

	LTG, n = 382	OTG, n = 196	P value
Operation time in min	230.14 ± 58.92	198.4 ± 56.76	< 0.001
Blood loss in m	200.42 ± 304.34	275.77 ± 384.72	0.010
Length of abdominal incision in cm	9.66 ± 1.73	18.12 ± 3.92	< 0.001
Length of proximal margin in cm	1.15 ± 0.72	1.16 ± 0.77	0.986
R-status, n (%)			0.879
R0	380 (99.5)	194 (99.0)	
R1/2	2 (0.5)	2 (1.0)	
Number of harvested LNs	28.81 ± 12.16	26.20 ± 12.23	0.015
Number of positive LNs	3.72 ± 6.33	3.61 ± 5.30	0.842
Time to liquid diet in d	3.65 ± 2.56	4.62 ± 2.49	< 0.001
Time to first flatus or defecation in d	3.87 ± 2.17	5.62 ± 2.35	< 0.001
Time to ambulation in d	2.93 ± 2.04	4.13 ± 2.55	< 0.001
Postoperative hospitalization in d	9 (8, 11)	10 (9, 12)	< 0.001[a]
Postoperative complication, n (%)	19 (5.0)	9 (4.6)	0.840
Clavien–Dindo ≥ IIIa	18 (4.7)	8 (4.1)	0.729
Anastomotic leakage	13 (3.4)	5 (2.6)	0.577
Abdominal abscess	2 (0.5)	1 (0.5)	1.000
Anastomotic stenosis	2 (0.5)	1 (0.5)	1.000
Pneumonia	0	1 (0.5)	0.339[b]
Arrhythmia	1 (0.3)	0	1.000[b]
Wound infection	1 (0.3)	1 (0.5)	1.000[b]
Mortality	0	0	

[a]Mann-Whitney *U* test.
[b]Fisher's test.
LNs: Lymph nodes; LTG: Laparoscopic-assisted transhiatal gastrectomy; OTG: Open transhiatal gastrectomy.

Furthermore, the complications of Clavien-Dindo grade III or higher were comparable in both groups (P = 0.729). No mortality existed within 30 d postoperatively in either group. Further details are presented in Table 2.

According to the histopathological analysis, the rate of complete tumor resection (R0) could be achieved in 99.5% in the LTG group and 99.0% in the OTG group (P = 0.879). The number of the harvested LNs was significantly higher in the LTG groups (28.81 ± 12.16 *vs* 26.20 ± 12.23, P = 0.015). In addition, the number of positive LNs was similar in the two groups (P > 0.05). Apart from that, the length of the proximal margin was also comparable between the two groups (P = 0.597).

Survival

The median follow-up time was 38.94 mo (Interquartile range: 23.28-59.93) for all patients. In comparison with the OTG group, the LTG group showed a better 3-year OS (88.2% *vs* 79.2%, P = 0.011) (Figure 2A). Then, we performed a stratified analysis of survival according to the TNM stage. For patients with stage I, there existed no significant difference in 3-year OS between the two groups, but patients in the LTG group with stage II and stage III had a better 3-year OS compared with that of the OTG group [Stage II: hazard ratio (HR): 0.126, 95% confidence interval (CI): 0.027-0.584, P = 0.008; Stage III: HR: 0.361, 95%CI: 0.134-0.967, P = 0.043] (Figure 2B-D).

Recurrence

The rate of recurrence presented no significant difference in the LTG and OTG groups (12.8% *vs* 10.7%, P = 0.547). The patterns of recurrence were listed in Table 3. Distributions of recurrence for LTG were similar to that for OTG, and there existed no differences in organ metastasis (liver, lung, bone, brain, pancreas), anastomotic recurrence, peritoneal dissemination, lymph node metastasis or others (P > 0.05).

Table 3 Patterns of recurrence

	LTG, *n* = 382	OTG, *n* = 196	*P* value
Recurrence, *n* (%)			
No	333 (87.2)	175 (89.3)	0.547
Yes	49 (12.8)	21 (10.7)	
Liver metastasis, *n* (%)			
No	372 (97.4)	193 (98.5)	0.590
Yes	10 (2.6)	3 (1.5)	
Lung metastasis, *n* (%)			
No	376 (98.4)	192 (98.0)	0.941
Yes	6 (1.6)	4 (2.0)	
Bone metastasis, *n* (%)			
No	377 (98.7)	193 (98.5)	1.000
Yes	5 (1.3)	3 (1.5)	
Brain metastasis, *n* (%)			
No	380 (99.5)	193 (98.5)	0.445
Yes	2 (0.5)	3 (1.5)	
Pancreas metastasis, *n* (%)			
No	381 (99.7)	194 (99.0)	0.555
Yes	1 (0.3)	2 (1.0)	
Anastomotic recurrence, *n* (%)			
No	369 (96.6)	189 (96.4)	1.000
Yes	13 (3.4)	7 (3.6)	
Peritoneal dissemination, *n* (%)			
No	377 (98.7)	196 (100.0)	0.257
Yes	5 (1.3)	0 (0.0)	
Lymph node metastasis, *n* (%)			
No	377 (98.7)	196 (100.0)	0.257
Yes	5 (1.3)	0 (0.0)	
Others, *n* (%)			
No	378 (99.0)	196 (100.0)	0.364
Yes	4 (1.0)	0 (0.0)	

LTG: Laparoscopic-assisted transhiatal gastrectomy; OTG: Open transhiatal gastrectomy.

The 3-year DFS was significantly better in the LTG group than that in the OTG group (79.7% *vs* 73.0%, P = 0.002) (Figure 3A). After stratification by TNM stage, the 3-year DFS was similar between the two groups in stage I patients. However, for stage II and stage III patients, the 3-year DFS was better in the LTG group compared with that of OTG group with significant difference (Stage II: HR: 0.191, 95%CI: 0.052-0.709, P = 0.013; Stage III: HR: 0.386, 95%CI: 0.161-0.924, P = 0.033) (Figure 3B-D).

DISCUSSION

Recently, the prevalence of Siewert type II AEG has risen rapidly, and most patients are diagnosed as an advanced stage with a poor prognosis at the first visit[23]. Complete removal of the tumor and adequate regional LN resection remains the only curative treatment for AEG[6]. Since the first report of laparoscopic-assisted gastrectomy, laparoscopic techniques have developed quickly in gastrointestinal tumors

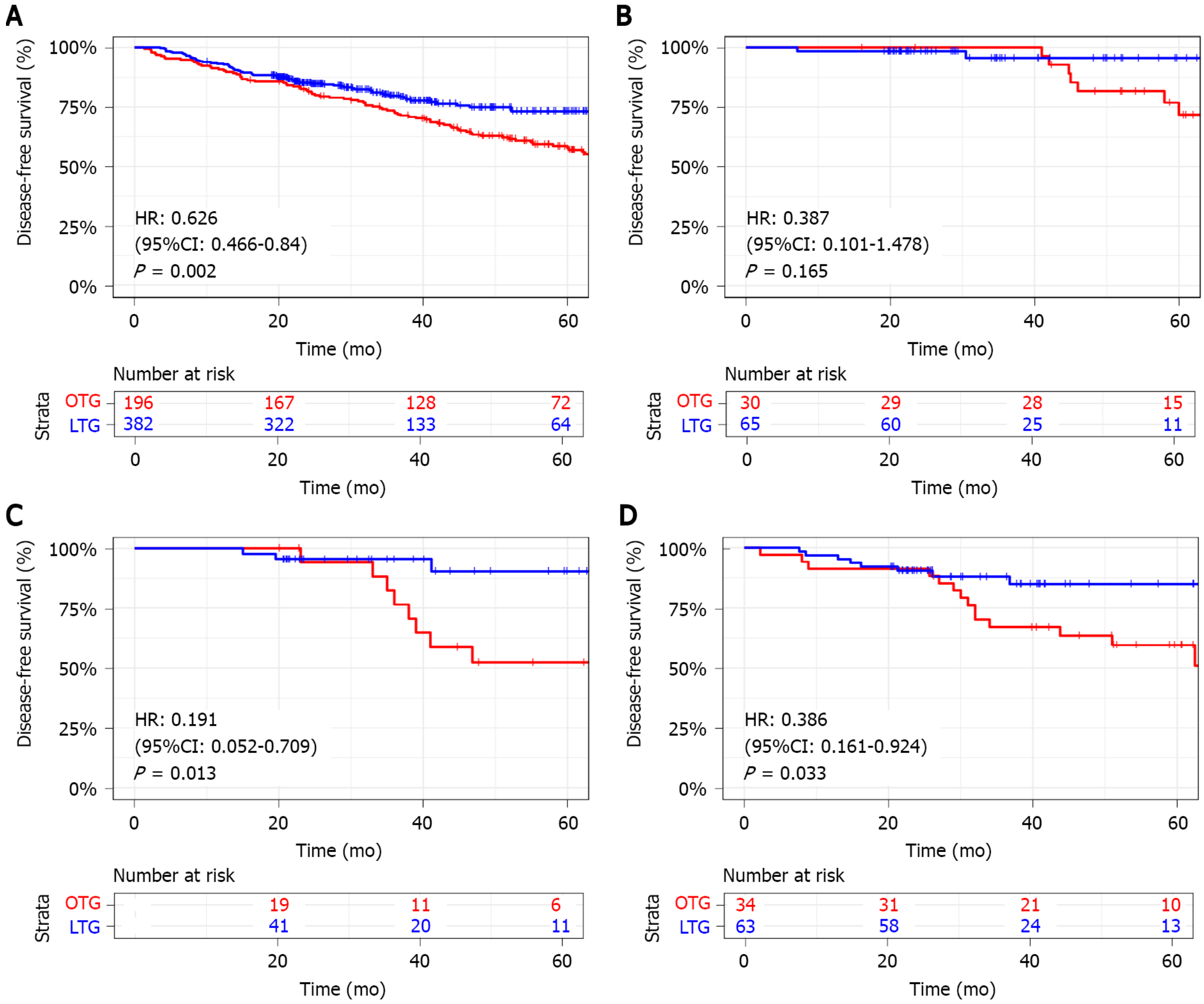

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Figure 3 Comparison of disease-free survival rates between the laparoscopic-assisted transhiatal gastrectomy and open transhiatal gastrectomy groups. A: Comparison of disease-free survival rates between the laparoscopic-assisted transhiatal gastrectomy (LTG) and open transhiatal gastrectomy (OTG) groups for all patients; B: Comparison of disease-free survival rates between the LTG and OTG groups for stage I patients; C: Comparison of disease-free survival rates between the LTG and OTG groups for stage II patients; D: Comparison of disease-free survival rates between the LTG and OTG groups for stage III patients. CI: Confidence interval; HR: Hazard ratio.

[9,24]. However, due to the lack of scientific evidence, the safety and feasibility of LTG in the treatment of Siewert type II AEG still remain controversial[16,17]. In the present study, LTG for Siewert type II AEG showed longer operation times but less blood loss, shorter abdominal incision and faster recovery compared with OTG. The obtained results were similar to the previous studies[17,18,20]. A large number of studies have demonstrated that LTG was comparable for morbidity and mortality to OTG for gastric cancer while few of them were focused on AEG[25-28]. In this study, no significant difference was observed in postoperative complications between the LTG group and OTG group for Siewert type II AEG. Apart from that, the complications of Clavien-Dindo grade III or higher were comparable in both groups. These results suggested that LTG can be safely performed and provide better short-term outcomes for patients diagnosed with Siewert type II AEG.

Ensuring the safety of oncology is critical to the choice of surgical strategy. Shi *et al*[17] compared 132 patients with LTG and 264 patients with OTG. After propensity score matching, the number of harvested LNs showed no significant difference for AEG. By contrast, Sugita *et al*[18] suggested an increased number of dissected LNs in the LTG group compared with OTG for Siewert type II AEG[18]. In the current work, there existed a higher number of harvested LNs in the LTG group than that in the OTG group. The previous studies reported that the number of harvested LNs is an important prognostic factor for patients with AEG[29,30]. In addition, other oncological parameters in terms of length of proximal margin, R0 resection and the number of positive LNs were comparable between the two groups. As a result, the oncological safety of LTG is equivalent to OTG.

Regarding the long-term outcomes, we found that the distribution of recurrence patterns was similar in the two groups. Shi *et al*[17] reported that there existed no significant difference for OS between the LTG and OTG groups[17]. Nevertheless, their study population included not only Siewert type II but also type III AEG. In addition, Huang *et al*[19] and Sugita *et al*[16] suggested that Siewert type II patients in the LTG group had significantly better OS than that in the OTG group[16,19]. The existing limitations included short observation period and small population, respectively. We observed a better 3-year OS and DFS of LTG for Siewert type II AEG patients compared with those treated with OTG. Moreover, we conducted a stratified analysis based on the TNM stage. Patients with stage I exhibited no survival benefit from LTG, while patients with stage II and III also revealed better survival outcomes in the LTG group.

Undoubtedly, our study has some limitations. First, this study was a single-center, retrospective cohort study. In addition, the follow-up compliance of patients is limited, and the specific death and the patterns of recurrence of some patients remain unknown. Thus, prospective randomized controlled studies are still needed.

CONCLUSION

In conclusion, LTG is a safe and feasible treatment for Siewert type II AEG. Meanwhile, patients with advanced stage AEG may benefit more from LTG in the long-term outcomes.

ARTICLE HIGHLIGHTS

Research background

Due to the lack of scientific evidence, the feasibility of laparoscopic-assist transhiatal gastrectomy (LTG) in patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG) is still controversial.

Research motivation

To compare the feasibility of LTG with the traditional open transhiatal gastrectomy (OTG) in patients with Siewert type II AEG.

Research objectives

We retrospectively evaluated and compared the short-term and long-term outcomes for patients with Siewert type II AEG treated with LTG and OTG and aimed to explore the feasibility of LTG treatment of Siewert type II AEG.

Research methods

We retrospectively evaluated 578 patients with Siewert type II AEG who have undergone LTG or OTG at the First Medical Center of the Chinese People's Liberation Army General Hospital from January 2014 to December 2019. The short-term and long-term outcomes were compared between the LTG (n = 382) and OTG (n = 196) groups.

Research results

Compared with the OTG group, the LTG group had less surgical trauma and a faster recovery after surgery. No significant difference was present between the two groups regarding oncological safety. The 3-year overall survival and disease-free survival were better in the LTG group than those in the OTG group (88.2% *vs* 79.2%, P = 0.011; 79.7% *vs* 73.0%, P = 0.002, respectively). In the stratified analysis, both overall survival and disease-free survival were better in the LTG group than those in the OTG group for stage II/III patients (P < 0.05) but not for stage I patients.

Research conclusions

For patients with Siewert type II AEG, LTG is associated with better short-term outcomes and similar oncology safety. In addition, patients with advanced stage AEG may benefit more from LTG in the long-term outcomes.

Research perspectives

Well-designed multicenter prospective randomized controlled studies are still needed.

FOOTNOTES

Author contributions: Song QY, Li XG and Zhang LY contributed equally to this article; Song QY and Wang XX designed the experiment; Li XG and Zhang LY performed the experiment; Li S and Zhang BL collected data; Wu D and Xu ZY analyzed the data; Song QY and Wu RLG created the tables and figures based on the data; Song QY, Li

XG and Zhang LY wrote the initial draft; Guo X and Wang XX modified the draft.

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ORIGINAL ARTICLE

Retrospective Study

How to examine anastomotic integrity intraoperatively in totally laparoscopic radical gastrectomy? Methylene blue testing prevents technical defect-related anastomotic leaks

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Abstract

BACKGROUND

Intraoperative methylene blue testing (IMBT), air leak testing, or endoscopy is used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer. Totally laparoscopic radical gastrectomy has been widely used to treat gastric cancer in the last few decades. However, reports on testing anastomotic integrity in totally laparoscopic radical gastrectomy are limited.

AIM

To explore the effects of IMBT on the incidence of postoperative anastomotic leaks (PALs) and identify the risk factors for PALs in totally laparoscopic radical gastrectomy.

METHODS

From January 2017 to December 2019, patients who underwent totally laparoscopic radical gastrectomy at the Shaanxi Provincial People's Hospital were retrospectively analyzed. According to whether or not they experienced an IMBT, the patients were divided into an IMBT group and a control group. If the IMBT was positive, an intraoperative suture was required to reinforce the anastomosis. The difference in the incidence of PALs was compared, and the risk factors were investigated.

RESULTS

This study consisted of 513 patients, 211 in the IMBT group and 302 in the control group. Positive IMBT was shown in seven patients (3.3%) in the IMBT group, and no PAL occurred in these patients after suture reinforcement. Multivariate analysis showed that risk factors for predicting positive IMBT were body mass index (BMI) > 25 kg/m^2 (hazard ratio [HR] = 8.357, *P* = 0.009), operation time > 4 h (HR = 55.881, *P* = 0.002), and insufficient surgical experience (HR = 15.286, *P* = 0.010). Moreover, 15 patients (2.9%) developed PALs in 513 patients, and the rates of PALs were significantly lower in the IMBT group than in the control group [2 of 211 patients (0.9%) *vs* 13 of 302 patients (4.3%), *P* = 0.0026]. Further analysis demonstrated that preoperative complications (HR = 13.128, *P* = 0.017), totally laparoscopic total gastrectomy (HR = 9.075, *P* = 0.043), and neoadjuvant chemotherapy (HR = 7.150, *P* = 0.008) were independent risk factors for PALs.

CONCLUSION

IMBT is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy, thus preventing technical defect-related anastomotic leaks. Preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are independent risk factors for PALs.

Key Words: Anastomotic leak; Gastric neoplasms; Totally laparoscopic radical gastrectomy; Methylene blue; Risk factors

Core Tip: We reviewed the outcomes of 513 consecutive patients with gastric cancer who underwent totally laparoscopic radical gastrectomy with and without intraoperative methylene blue testing at Shaanxi Provincial People's Hospital from January 2017 to December 2019. We found that intraoperative methylene blue testing is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy and could reduce the incidence of postoperative anastomotic leaks. Preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are independent risk factors for postoperative anastomotic leaks.

Citation: Deng C, Liu Y, Zhang ZY, Qi HD, Guo Z, Zhao X, Li XJ. How to examine anastomotic integrity intraoperatively in totally laparoscopic radical gastrectomy? Methylene blue testing prevents technical defect-related anastomotic leaks. *World J Gastrointest Surg* 2022; 14(4): 315-328

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide, ranking fifth in incidence and third in mortality[1]. Totally laparoscopic radical gastrectomy has been widely used to treat gastric cancer[2-4]. Postoperative anastomotic leak (PAL) is a severe complication, and occurs in 1.7%-5.7% of patients with gastric cancer[5-7]. These complications could prolong hospital stay, increase medical expenses, cause poor quality of life, and subsequently worsen the long-term survival of patients[8-10].

It is well known that the defects of intraoperative anastomotic techniques are closely related to PALs [11-13]. Therefore, some PALs might be avoided if insufficiently integral anastomoses were immediately reinforced. Intraoperative methylene blue testing (IMBT), intraoperative air leak test, or intraoperative endoscopy has been used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer[6,14-15]. However, to the best of our knowledge, no study has assessed the integrity of anastomosis during totally laparoscopic radical gastrectomy. Compared with open surgery, totally laparoscopic radical gastrectomy has the disadvantages of two-dimensional images, poor hand-eye coordination, limited operating space, fulcrum effect, and lack of haptic feedback[16-17]. Furthermore, according to the ERAS guidelines, abdominal drains should not routinely be placed after gastrectomy, which requires high-quality anastomosis[18-19]. Thus, a reliable anastomosis leak test is vital during totally laparoscopic radical gastrectomy.

In this study, we used IMBT to check the anastomotic integrity of esophagojejunostomy or gastrojejunostomy during totally laparoscopic radical gastrectomy. This is the first study to assess the anastomotic integrity during totally laparoscopic radical gastrectomy. We aimed to explore the effects of IMBT on the incidence and risk factors for PALs.

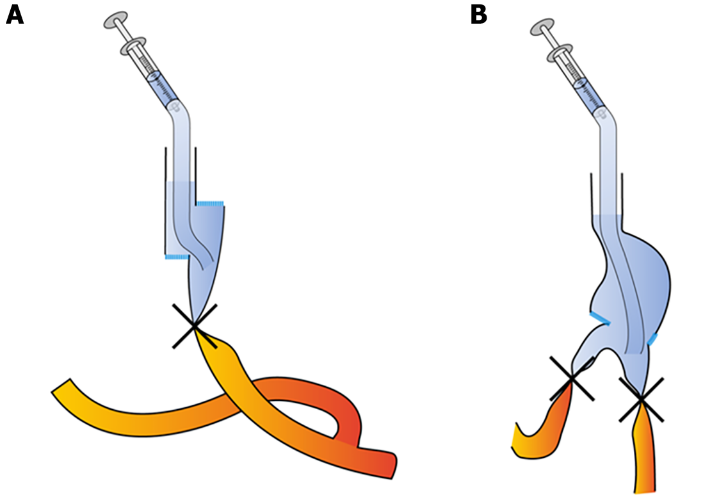

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Figure 1 Schematic representation of intraoperative methylene blue testing. A: Overlap anastomosis; B: Billroth-II anastomosis.

MATERIALS AND METHODS

Patients

We performed a retrospective review of patients who underwent totally laparoscopic radical gastrectomy from January 2017 to December 2019. In our department, some surgeons think that IMBT is useful, while others are skeptical regarding its effects. Thus, two groups were formed: An IMBT group and a control group. Staging of the tumor was performed following the eighth edition of the AJCC Guidelines for gastric cancer[20]. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

The inclusion criteria were: (1) Patients who underwent totally laparoscopic radical gastrectomy for gastric cancer and adenocarcinoma of the gastroesophageal junction from January 2017 to December 2019; (2) Gastric cancer or adenocarcinoma of the gastroesophageal junction diagnosed *via* endoscopy and pathological identification; and (3) Patients whose surgical and demographic data were complete and reliable. The exclusion criteria were: (1) Patients who underwent totally laparoscopic distal gastrectomy that used Billroth-I anastomosis; (2) Those who were converted to open surgery; (3) Those who were found to have distant metastases intraoperatively; (4) Those who did not undergo radical resection; and (5) Those who gave up treatment or were transferred to another hospital.

Surgical methods and postoperative management

All surgeries were performed laparoscopically. Totally laparoscopic total gastrectomy was reconstructed *via* an overlap anastomosis[21], and totally laparoscopic distal gastrectomy was reconstructed *via* a Billroth-II anastomosis[22]. Lymph node dissection was performed according to the Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4)[23]. This study used a 45-mm linear stapler (Johnson Company, United States) for the overlap anastomosis and a 60-mm linear stapler (Johnson Company, United States) for the Billroth-II anastomosis. In our department, we preferred the Billroth II anastomosis and Roux-en-Y esophagojejunostomy rather than the Billroth I anastomosis. A Billroth I anastomosis needs to preserve a large residual stomach, leading to insufficient tumor margins and significant anastomotic tension when the tumor location is relatively high and the diameter is large. In China, most gastric cancer cases are found in advanced stages, and the diameter of the tumor is often large compared to Japan and Korea[24-26]. In addition, Billroth I anastomosis has a greater risk of remnant gastritis and reflux esophagitis[27-28].

Postoperative management was conducted according to the Japanese Gastric Cancer Treatment Guidelines (ver.4)[23]: The nasogastric tube was removed on postoperative day 1, and the abdominal drainage tube removed on postoperative day 5 without symptoms or inflammatory reactions. Abdominal CT, gastrointestinal tract angiography, or endoscopy was performed when an anastomotic leak was suspected.

Methylene blue testing technique

For the patients that underwent totally laparoscopic total gastrectomy, we performed IMBT as follows (Figure 1A): After the digestive tract reconstruction (Figure 2A and A’), the nasogastric tube (18F) was delivered 5 cm from the distal end of the anastomotic stoma, gauze was wrapped around the anastomosis, and then the jejunum was clamped using an intestinal clamp 5 cm distal to the anastomosis. Next, normal saline was injected through the nasogastric tube to rinse and observe

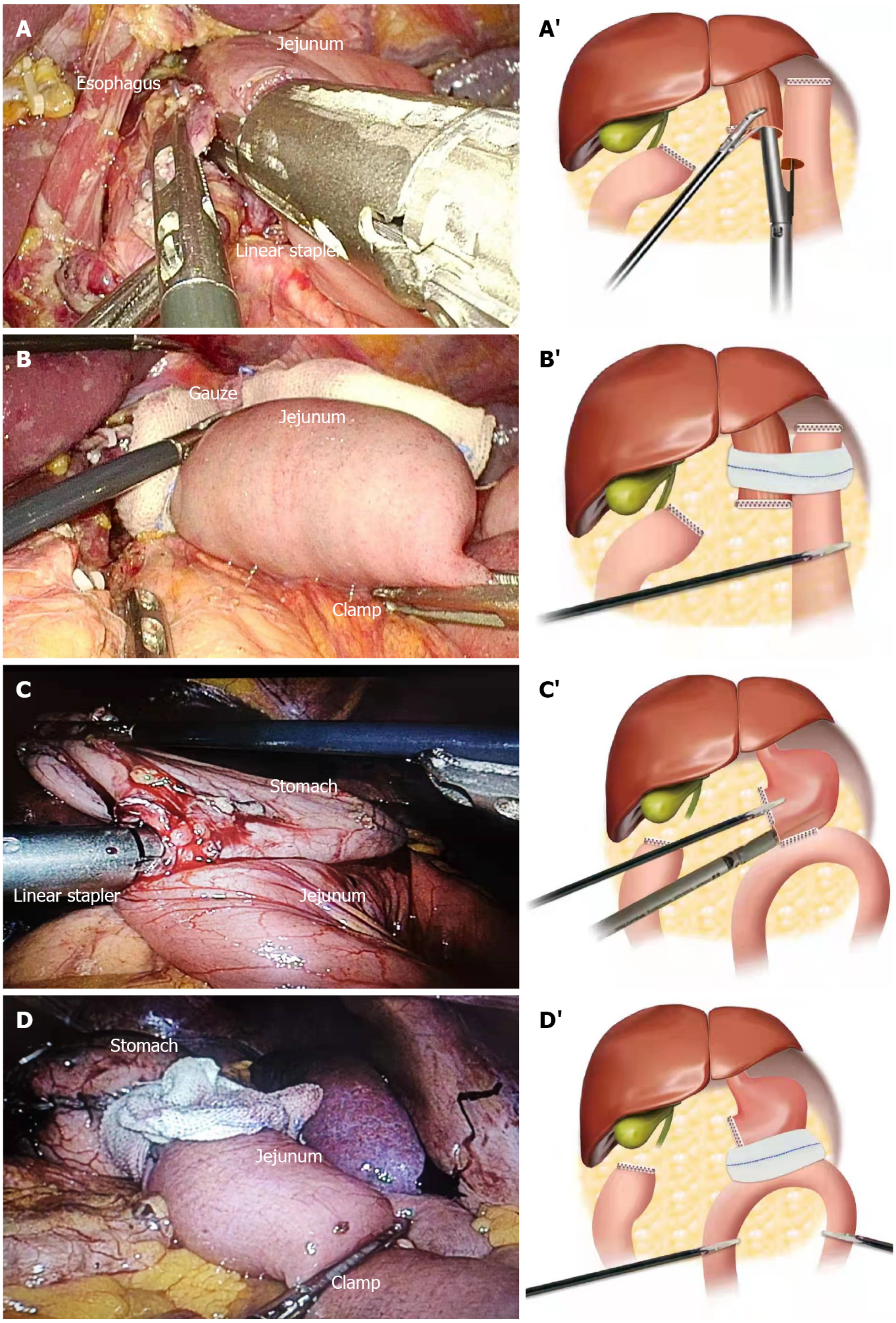

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Figure 2 Surgery pictures and schematic pictures of intraoperative methylene blue testing. A: Surgery picture of esophagojejunostomy (overlap method); A': Schematic picture of esophagojejunostomy (overlap method); B: Surgery picture of intraoperative methylene blue testing in totally laparoscopic total gastrectomy; B': Schematic picture of intraoperative methylene blue testing in totally laparoscopic total gastrectomy; C: Surgery picture of Billroth-II anastomosis; C': Schematic picture of Billroth-II anastomosis; D: Surgery picture of intraoperative methylene blue testing in totally laparoscopic distal gastrectomy; D': Schematic picture of intraoperative methylene blue testing in totally laparoscopic distal gastrectomy.

whether continuous bright red liquid flowed out of the nasogastric tube when pumping back. If the liquid was detected, we looked for and stopped the bleeding and then flushed repeatedly until the clear liquid was pumped back out. Next, we dissolved 2 mL (20 mg) of methylene blue into 50 mL of normal saline and injected it through the nasogastric tube in order to make the methylene blue liquid disperse evenly around the anastomosis (Figure 2B and B'). Finally, we observed whether the gauze around the

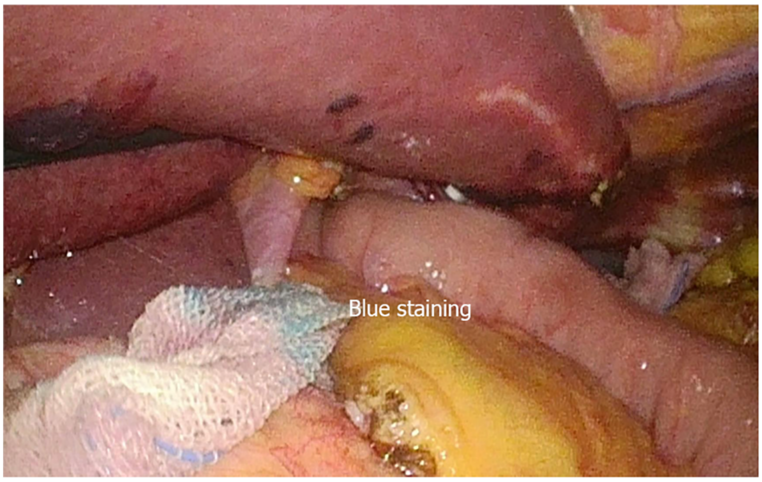

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Figure 3 Positive results of intraoperative methylene blue testing.

anastomosis was stained blue; if there was blue staining (Figure 3), we identified the leak according to the blue-stained site, sutured it, and then changed the gauze and repeated the process.

For the patients who underwent totally laparoscopic distal gastrectomy, IMBT was performed as follows (Figure 1B): The nasogastric tube (18F) was indwelled 5 cm from the distal end of the anastomotic stoma after the digestive tract reconstruction (Figure 2C and C′). Next, we wrapped the anastomosis with gauze, and closed it with clamps 5 cm distal to the anastomosis. Then, the anastomosis was flushed with normal saline through the nasogastric tube; the needle was pumped back to observe whether there was bright red liquid flowing out of the nasogastric tube. If red liquid was present, we looked for and stopped the bleeding. The flushing was repeated until the clear liquid was extracted from the nasogastric tube. Next, 5 mL (50 mg) of methylene blue was dissolved into 500 mL of normal saline and injected through the nasogastric tube in order to evenly distribute the methylene blue liquid around the anastomosis (Figure 2D and D′). Finally, if blue liquid was present, we repeated the above procedures.

Definitions

We defined preoperative complications as one or more of the following: Anemia, malnutrition, diabetes, or pulmonary dysfunction. The World Health Organization's definition of anemia was used to define anemia: Hb concentration of < 12 g/dL in women and < 13 g/dL in men[29]. Malnutrition was defined by the European Society of Clinical Nutrition and Metabolism (ESPEN) criteria[30], which suggested two methods used to diagnose malnutrition: Method one: Body mass index (BMI) < 18.5 kg/m^2; method two: Unintentional weight loss combined with a low age-related BMI (< 20 kg/m^2 in subjects < 70 years or < 22 kg/m^2 in those ≥ 70 years) or low fat-free mass index (FFMI) (< 17 kg/m^2 in men and < 15 kg/m^2 in women). Positive IMBT was defined as the visualization of methylene blue on the gauze surrounding the anastomosis. PAL was defined as meeting one of the following criteria: (1) Gastrointestinal contents or bile-like fluid drained from the abdominal drainage tube; (2) Gastrointestinal radiography showed leakage of the contrast medium from the drainage tube; (3) Methylene blue was extracted from the abdominal drainage tube after the oral administration of methylene blue; (4) Abdominal CT examination showed that the gastrointestinal wall was incomplete, revealing gas and fluid leaks around the anastomosis; and (5) Anastomotic leaks were found under endoscopy after surgery.

Statistical analysis

Analyses were performed with statistic software SPSS for Windows Version 25.0 (SPSS Inc., Chicago, Illinois, United States). Measurement data are expressed as the mean ± SD (normal distribution) or median (non-normal distribution). Count data are expressed as cases (rate). Univariate analysis was performed by the Chi-square test or a Fisher's exact test when appropriate. Variables with P < 0.05 in the univariate analysis were included in multivariate analysis, which was conducted using the logistic regression model. P < 0.05 was considered statistically significant.

RESULTS

From January 2017 to December 2019, a total of 513 patients that underwent totally laparoscopic radical gastrectomy were analyzed retrospectively (211 patients in the IMBT group and 302 patients in the

Table 1 Demographic, surgical, and tumor characteristics of patients according to whether an intraoperative methylene blue testing was performed or not

Variable		IMBT group (211 cases)	Control group (302 cases)	χ^2	*P* value
Gender	Male	130	182	0.095	0.759
	Female	81	120		
Age (yr)	< 75	143	196	0.457	0.499
	≥ 75	68	106		
BMI (kg/m^2)	< 25	155	211	0.784	0.376
	≥ 25	56	91		
Preoperative complications	Present absent	88123	111191	1.282	0.257
Neoadjuvant chemotherapy	Present absent	43168	61241	0.003	0.960
Degree of tumor differentiation	High	72	92	0.785	0.672
	Medium	95	142		
	Low	44	68		
Postoperative tumor pathological stage[1]	I	32	62	3.298	0.192
	II	62	94		
	III	117	146		
Surgeon's experience	< 50 cases	21	24	0.624	0.429
	≥ 50 cases	190	278		
Mode of surgery	TLTG	101	146	0.025	0.875
	TLDG	111	156		
Operation time	< 4h	143	189	1.465	0.226
	≥ 4h	68	113		
Amount of bleeding ≥ 400 mL	Present	79	100	1.024	0.312
	Absent	132	202		

[1]According to the 8th AJCC TNM staging system for gastric cancer. IMBT: Intraoperative methylene blue testing; TLTG: Totally laparoscopic total gastrectomy; BMI: Body mass index; TLDG: Totally laparoscopic distal gastrectomy.

control group). Complete data of the intraoperative and postoperative findings are shown in Figure 4. The baseline data of the patients in the two groups are consistent, as shown in Table 1.

Risk factors for positive IMBT

Seven patients (3.3%) had positive IMBT in the IMBT group, as detailed in Table 2. These cases were managed by additional suturing, none had a PAL, and the mean postoperative hospital stay was 10.3 ± 1.1 d. Univariate analysis showed that surgeons with insufficient surgical experience (< 50 cases of totally laparoscopic radical gastrectomy) were associated with a higher rate of positive IMBT (14.3% *vs* 2.1%, *P* = 0.021). Other risk factors included operation time > 4 h, neoadjuvant chemotherapy, and a body mass index (BMI) > 25 kg/m^2 (*P* = 0.008, 0.033, and 0.021, respectively), as shown in Tables 3 and 4. Multivariate analysis identified BMI > 25 kg/m^2, operation time > 4 h, and insufficient surgical experience as independent risk factors for positive IMBT (*P* = 0.009, 0.002, and 0.010, respectively), as detailed in Table 5.

Comparison of incidence of PALs

PAL occurred in 15 (2.9%) patients, including 2 in the IMBT group and 13 in the control group. The rate of PALs was significantly lower in the IMBT group than in the control group [2 of 211 patients (0.9%) *vs* 13 of 302 patients (4.3%), *P* = 0.0026].

Risk factors for PALs

The clinical characteristics of the patients with anastomotic leaks are shown in Table 6. The diagnosis time of PALs was 5.8 ± 2.0 d after surgery, postoperative hospital stay was 19.3 ± 3.5 d, and the

Table 2 Characteristics of positive intraoperative methylene blue testing

Patient No.	Location of leak on anastomotic wall	Operation model	Dehiscence	Management	PAL	Postoperative hospital stays (d)
1	Posterior wall	TLTG	Present	Suturing	No	10
2	Posterior wall	TLTG	Absent	Suturing	No	9
3	Posterior wall	TLTG	Absent	Suturing	No	11
4	Joint opening	TLTG	Absent	Suturing	No	10
5	Joint opening	TLTG	Absent	Suturing	No	11
6	Left wall	TLDG	Absent	Suturing	No	12
7	Left wall	TLDG	Present	Suturing	No	9

IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; TLTG: Totally laparoscopic total gastrectomy; TLDG: Totally laparoscopic distal gastrectomy.

Table 3 Clinicopathological characteristics of the patients according to the results of intraoperative methylene blue testing and postoperative anastomotic leaks

Variable	IMBT group	IMBT		*P* value	Control group	PAL		*P* value
		Negative	Positive (%)			Negative	Positive (%)	
Cases	211	204	7 (3.3)	-	302	289	13(4.3)	-
Gender								
Male	130	126	4 (3.1)	1.0	182	173	9 (4.9)	0.575
Female	81	78	3 (3.7)		120	116	4 (3.3)	
Age (yr)								
< 75	143	139	4 (2.8)	0.541	196	191	5 (2.6)	0.70
≥ 75	68	65	3 (4.4)		106	98	8 (7.5)	
BMI (kg/m^2)								
< 25	155	153	2 (1.3)	0.021	211	206	5 (2.4)	0.025
≥ 25	56	51	5 (8.9)		91	83	8 (8.8)	
Preoperative complications								
Absent	123	120	3 (2.4)	0.454	191	187	4 (2.0)	0.018
Present	88	84	4 (4.5)		111	102	9 (8.1)	
Neoadjuvant chemotherapy								
Absent	168	165	3 (1.8)	0.033	241	234	7 (2.9)	0.028
Present	43	39	4 (9.3)		61	55	6 (9.8)	
Degree of tumor differentiation								
High	72	70	2 (2.8)	0.784	92	88	4 (4.3)	1.000
Medium	95	92	3 (3.2)		142	136	6 (4.2)	
Low	44	42	2 (4.5)		68	65	3 (4.6)	
Postoperative tumor pathological stage[1]								
I	32	30	2 (6.3)	0.493	62	59	3 (4.8)	0.754
II	62	60	2 (3.2)		94	89	5 (5.3)	
III	117	114	3 (2.6)		146	141	5 (3.4)	

[1]According to the 8th AJCC TNM staging system for gastric cancer. IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; BMI: Body mass index.

Table 4 Surgical variables according to the results of intraoperative methylene blue testing and postoperative anastomotic leaks

Variable	IMBT group	IMBT		*P* value	Control group	PAL		*P* value
		Negative	Positive (%)			Negative	Positive (%)	
Cases	211	204	7 (3.3)	-	302	289	13 (4.3)	-
Operation time (h)								
< 4	143	142	1 (0.7)	0.008	184	177	7 (4.0)	0.577
≥ 4	68	62	6 (8.8)		118	112	6 (5.1)	
Amount of bleeding (mL)								
< 400	132	130	2 (1.5)	0.136	202	194	8 (4.0)	0.765
≥ 400	79	74	5 (6.3)		100	95	5 (5.0)	
Mode of operation								
TLTG	100	95	5 (5.0)	0.200	146	136	10 (6.8)	0.046
TLDG	111	109	2 (1.8)		156	153	3 (1.9)	
Surgeon's experience (cases)								
< 50	21	18	3(14.3)	0.021	24	21	3 (12.5)	0.074
≥ 50	190	186	4 (2.1)		278	268	10 (3.6)	

IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; TLTG: Totally laparoscopic total gastrectomy; TLDG: Totally laparoscopic distal gastrectomy.

abdominal drainage tube placement time was 17.3 ± 3.2 d. All 15 patients improved and were discharged from the hospital, and no one died. In the univariate analysis, patients with BMI > 25 kg/m^2 (8.8% *vs* 2.4%, *P* = 0.025), preoperative complications (8.1% *vs* 2.0%, *P* = 0.018), totally laparoscopic total gastrectomy (6.8% *vs* 1.9%, *P* = 0.046), and neoadjuvant chemotherapy (9.8% *vs* 2.9%, *P* = 0.028) were associated with PALs, as shown in Tables 3 and 4. Multivariate analysis showed that preoperative complications (hazard ratio [HR] = 13.128, *P* = 0.017), totally laparoscopic total gastrectomy (HR = 9.075, *P* = 0.043), and neoadjuvant chemotherapy (HR = 7.150, *P* = 0.008) were independent risk factors for PALs (Table 5).

DISCUSSION

Anastomotic leaks are among the most common and severe complications after totally laparoscopic radical gastrectomy and are the main risk factor for patients' postoperative death[8-10]. The integrity of the anastomosis, which is closely related to the anastomotic technique, is a prerequisite for tissue healing and is essential for preventing anastomotic leaks[6,12]. In totally laparoscopic radical gastrectomy, we used IMBT to check the integrity of the anastomosis. The results showed that IMBT reduces the incidence of PALs, which is consistent with the IMBT results in open total gastrectomy[14].

Several methods are available to assess the integrity of the anastomosis. An intraoperative air leak test was proposed by Kanaji to check anastomotic integrity during open radical gastrectomy[6] and showed that this test reduces the occurrence of postoperative anastomotic leaks; however, the intraoperative air leak test did not show the exact site of the leaks and only depicted the approximate area. Celik *et al*[14] showed a low incidence of anastomotic leaks in the methylene blue testing group (3.7% *vs* 14.4%, *P* = 0.007) in which methylene blue is injected *via* a nasogastric tube to check the integrity of the anastomosis during an open total gastrectomy. Some researchers[31] who performed an intraoperative endoscopic examination during laparoscopic gastric bypass surgery showed a low incidence of anastomotic leaks (0 *vs* 8%, *P* = 0.0412) and a low reoperation rate (0 *vs* 8%, *P* = 0.0412). However, it is a challenge to find gastroscopic instruments as well as an experienced endoscopist. Our study confirmed that IMBT is an important method for assessing anastomotic integrity in totally laparoscopic radical gastrectomy, which detects anastomoses and pinpoints the areas of the leaks. Furthermore, we examined the anastomosis during totally laparoscopic distal gastrectomy, whereas previous studies focused on esophagojejunal

Table 5 Risk factors for positive intraoperative methylene blue testing and postoperative anastomotic leaks analyzed by multivariate analysis

Variable	B	Standard deviation	Wald	Exp(B)	Odds ratio (95%CI)		*P* value
					Lower limit	Upper limit	
IMBT							
BMI ≥ 25 kg/m^2	2.123	0.810	6.862	8.357	1.707	40.922	0.009
Neoadjuvant chemotherapy	1.326	0.805	2.715	3.767	0.778	18.245	0.099
Operation time ≥ 4 h	4.023	1.319	9.303	55.881	4.212	741.381	0.002
Inexperienced surgeons	2.727	1.052	6.719	15.286	1.944	120.167	0.010
PAL							
BMI > 25 kg/m^2	1.289	0.858	2.259	3.630	0.676	19.498	0.133
Preoperative complications	2.575	1.081	5.671	13.128	1.577	109.268	0.017
Neoadjuvant chemotherapy	1.967	0.740	7.063	7.150	1.676	30.506	0.008
TLTG	2.206	1.091	4.083	9.075	1.069	77.070	0.043

IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; BMI: Body mass index; TLTG: Totally laparoscopic total gastrectomy.

anastomotic leaks after total gastrectomy.

This study found seven IMBT-positive patients whose anastomosis was reinforced with sutures, and none of them developed PALs. Our study indicated that patients with an operative time > 4 h, those with a BMI > 25 kg/m^2, and insufficient surgical experience were associated with a higher risk of positive IMBT. Previous studies have shown that technically relevant factors such as prolonged operative time, excessive BMI, and inexperience of the surgeon are strongly associated with the occurrence of PALs[6,32-33]. Therefore, we recommend performing IMBT in patients with these high-risk factors.

However, two patients (0.9%) with negative IMBT developed PALs in this study, meaning that the cause of the anastomotic leaks is complex. This study found that patients with preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are at a higher risk for PALs. Previous studies have indicated that anemia, malnutrition, and pulmonary insufficiency are also strongly associated with the occurrence of PALs[13,32,34], and are consistent with the results of our study. Kawamura *et al*[35] showed that the rate of anastomotic leaks is significantly higher in the laparoscopic total gastrectomy group (5.0 %) than in the laparoscopic distal gastrectomy group (1.2%), which is consistent with our study. However, there is still controversy about whether neoadjuvant chemotherapy leads to PALs. Gorur *et al*[36] reported that chemotherapy affects cell proliferation and the formation of collagenous fiber, which is a key component of anastomotic healing. Some studies reported that neoadjuvant chemotherapy does not increase the risk of PALs[37,38]. Our study suggested that neoadjuvant chemotherapy is a risk factor for PALs. We hypothesized that patients undergoing neoadjuvant chemotherapy have increased tissue toughness and adhesion within the abdominal cavity, resulting in increased surgical damage, thus leading to PALs. Therefore, we should pay close attention to patients with the above-mentioned risk factors.

This study has its limitations. First, it is a single-center retrospective study, which needs to be further confirmed by a multicenter, randomized controlled study with a larger sample size. Second, our study did not compare the IMBT, intraoperative air leak test, and intraoperative endoscopy. Finally, the methylene blue testing could not prevent PALs caused by non-technical factors.

CONCLUSION

In summary, IMBT can find technical defects within an anastomosis, and suturing can reduce the incidence of anastomotic leaks after totally laparoscopic radical gastrectomy. Independent risk factors associated with PALs include preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy.

Table 6 Characteristics of postoperative anastomotic leaks

Patient No.	Group	Day of diagnosis after surgery (d)	TLTG or TLDG	Tumor staging[1]	Procedure used for patients	Time of placement of abdominal drainage tube (d)	Postoperative Hospital stays (d)
1	IMBT group	6	TLTG	IIB	Drainage	15	16
2	IMBT group	8	TLTG	IIIA	Second surgery + Drainage	20	21
3	Control group	4	TLTG	IA	Drainage	18	19
4	Control group	5	TLTG	IIA	Drainage	13	15
5	Control group	9	TLTG	IIB	Drainage	19	21
6	Control group	8	TLTG	IIB	Drainage	12	14
7	Control group	5	TLTG	IIIC	Drainage	18	20
8	Control group	3	TLTG	IIIC	Drainage	16	18
9	Control group	8	TLTG	IIB	Second surgery + Drainage	21	24
10	Control group	7	TLTG	IIIB	Second surgery + Drainage	22	25
11	Control group	7	TLTG	IIIC	Second surgery + Drainage	17	21
12	Control group	5	TLDG	IIIA	Drainage	12	14
13	Control group	3	TLDG	IIA	Second surgery + Drainage	17	18
14	Control group	3	TLDG	IIIA	Second surgery + Drainage	19	20
15	Control group	6	TLDG	IIIC	Second surgery + Drainage	20	23

[1]According to the 8th AJCC TNM staging system for gastric cancer. PAL: Postoperative anastomotic leak; TLTG: Totally laparoscopic total gastrectomy; TLDG: Totally laparoscopic distal gastrectomy.

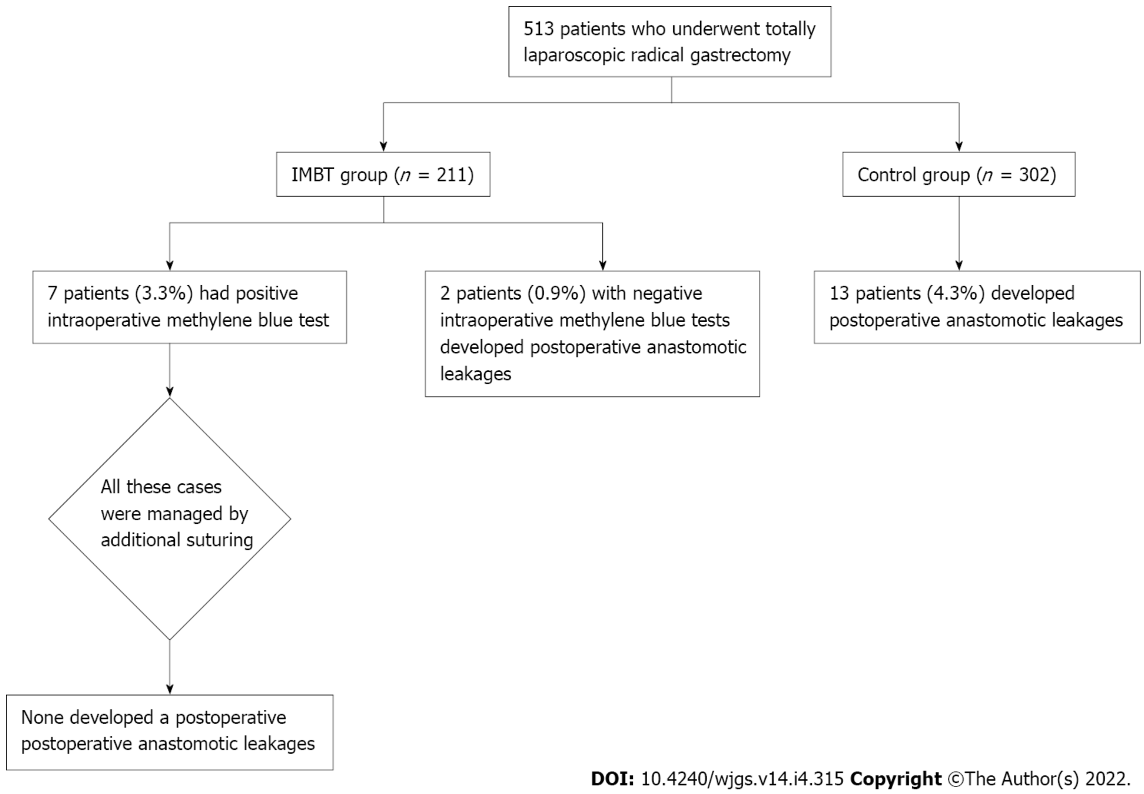

Figure 4 Schematic representation of study protocol and results. IMBT: Intraoperative methylene blue testing.

ARTICLE HIGHLIGHTS

Research background

We hypothesized that intraoperative methylene blue testing (IMBT) could reduce the incidence of postoperative anastomotic leaks (PALs) in totally laparoscopic radical gastrectomy.

Research motivation

IMBT, air leak testing, or endoscopy is used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer. To the best of our konwledge, this is the first study to assess the anastomotic integrity during totally laparoscopic radical gastrectomy.

Research objectives

To explore the effects of IMBT on the incidence of PALs and identify the risk factors for PALs in totally laparoscopic radical gastrectomy.

Research methods

The difference in the incidence of PALs was compared between the IMBT group and the control group. Logistic regression analysis was used to clarify the risk factor for positive IMBT and PALs.

Research results

Positive IMBT was shown in 7 patients (3.3%) in the IMBT group, and no PAL occurred in these patients after suture reinforcement. Moreover, 15 patients (2.9%) developed PALs, and the rate of PALs was significantly lower in the IMBT group than in the control group [2 of 211 patients (0.9%) *vs* 13 of 302 patients (4.3%), $P = 0.0026$]. Further analysis demonstrated that preoperative complications (hazard ratio [HR] = 13.128, $P = 0.017$), totally laparoscopic total gastrectomy (HR = 9.075, $P = 0.043$), and neoadjuvant chemotherapy (HR = 7.150, $P = 0.008$) were independent risk factors for PALs.

Research conclusions

IMBT can find technical defects within an anastomosis, and suturing can reduce the incidence of PALs in totally laparoscopic radical gastrectomy. Independent risk factors associated with PAL include preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy.

Research perspectives

Randomized controlled trials are expected to be conducted to measure the effects of IMBT.

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FOOTNOTES

Author contributions: Deng C designed and performed the research and wrote the paper; Liu Y, Zhang ZY, and Qi HD designed the research and supervised the report; Guo Z and Zhao X provided clinical advice; Li XJ designed and performed the research and supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Shaanxi Provincial People's Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes of endoscopic resection of superficial nonampullary duodenal epithelial tumors: A 10-year retrospective, single-center study

Joon Hyun Cho, Ki Young Lim, Eun Jung Lee, Si Hyung Lee

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Abstract

BACKGROUND

Although premalignant duodenal lesions such as adenomas are uncommon, the incidences of these lesions have increased in recent times, and thus, the demand for minimally invasive treatments such as endoscopic resection (ER) has also increased. However, ER in the duodenum is more challenging than ER in other locations of the gastrointestinal tract.

AIM

To evaluate the safety and efficacy of ER for superficial nonampullary duodenal epithelial tumors (SNADETs)

METHODS

We performed a retrospective observational study on 56 consecutive patients (58 lesions) diagnosed with SNADETs that underwent ER from January 2011 to December 2020 at Yeungnam University Hospital. Patient demographics, lesion characteristics, and procedural and technical data were collected, and clinical outcomes, including procedure-related complications, completeness of resection, and recurrence were analyzed.

RESULTS

Median patient age was 57 years [range, 26–77, 30 (53.6%) men]. Endoscopic mucosal resection (EMR) was performed on 57 lesions (98.3%) and snare polypectomy on one (1.7%). Lesions consisted of 52 adenomas with low-grade dysplasia (89.7%), 3 adenomas with high-grade dysplasia (5.2%), and 3 intramucosal adenocarcinomas (5.2%). There were 16 cases of intraprocedural bleeding (27.6%) and 1 case of delayed bleeding (1.7%), and all these 17 cases were successfully managed endoscopically. No perforation or procedure-related death occurred. Larger lesion size was associated with an increased risk of EMR-related bleeding (P = 0.033). During a median follow-up period of 23 mo (range 6–100 mo), no local recurrence occurred, despite the fact one-third of the patients (19 lesions, 32.8%) underwent piecemeal resection and 3 patients (3 lesions, 5.2%) that underwent *en bloc* resection had a pathologically determined positive lateral margin. No patient died from a primary duodenal neoplasm.

CONCLUSION

The majority of SNADETs can be safely and curatively resected by EMR, and thus, based on consideration of the high incidence of fatal complications attributable to ESD, we conclude EMR, including piecemeal resection, should be considered the treatment of first choice for SNADETs.

Key Words: Duodenum; Adenoma; Endoscopic mucosal resection; Endoscopic resection; Superficial nonampullary duodenal epithelial tumor

Core Tip: This long-term retrospective observational study shows that superficial nonampullary duodenal epithelial tumors (SNADETs) can be safely and curatively managed by endoscopic mucosal resection (EMR), even after piecemeal resection. Therefore, based on consideration of the high incidence of fatal complications attributable to endoscopic submucosal dissection in duodenum, we recommend that EMR, including piecemeal resection, be considered the treatment of first choice for SNADETs. However, we caution that because of its technical difficulty, EMR on duodenum should only be performed by highly skilled endoscopists. In addition, we emphasize that more attention is required during EMR of a large duodenal tumor because lesion size is positively associated with the risk of EMR-related bleeding.

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INTRODUCTION

Superficial nonampullary duodenal epithelial tumors (SNADETs) such as primary duodenal adenomas and adenocarcinomas are rare compared with other gastrointestinal (GI) tract cancers. However, as the use of screening endoscopy continues to increase and endoscopic skills and technology improve, small early SNADETs are being diagnosed more frequently[1]. The adenoma-carcinoma sequence is also accepted for lesions in the small bowel[2,3], and reported malignant transformation rates of duodenal adenoma range from 30% to 85%[4,5]. Therefore, once diagnosed, surgical excision and endoscopic resection (ER) are the initial considerations, and ER is generally preferred over operative interventions because of its less invasive nature.

However, the duodenum is the most challenging location in the GI tract for ER. Several anatomic features of the duodenum contribute to these difficulties, such as a narrow lumen, a ''C-loop'' that reduces endoscope stability, the presence of Brunner's glands in the deep mucosal and submucosal layers that stiffen the wall and lead to poor mucosal lifting, a thin deep muscle layer that increases the risk of complications like perforation, and difficulties associated with accessing sites if emergency or salvage surgery becomes necessary[6-8].

Endoscopic submucosal dissection (ESD) is regularly performed at expert centers in South Korea for superficial lesions of the esophagus, stomach, or colorectum. ESD has a high *en bloc* resection rate, which enables accurate histopathological assessments. However, we refrain from aggressive duodenal ESD because the procedure is technically difficult and associated with a higher incidence of consequential perforation than at other sites in the GI tract[9-11]. Although endoscopic mucosal resection (EMR) is a safer, easier, and quicker procedure than ESD, EMR results in fewer *en bloc* resections[12-18]. Even though debate continues as to which ER method is preferable, EMR is currently recognized as the standard procedure for the endoscopic treatment of SNADETs.

Duodenal lesions that require ER are limited in number, and thus, although several reports have been published, little information is available on the long-term clinical outcomes of ER for SNADETs. In this study, we evaluated the safety and efficacy of ER for the treatment of SNADETs and associated factors using a 10-year follow-up.

MATERIALS AND METHODS

Patients

We retrospectively analyzed our institutional database for patients that underwent duodenal ER between January 2011 and December 2020. During this period, 56 consecutive patients with 58 lesions underwent ER for SNADETs. In all cases, these were primary tumors without a previous history. Patients with polyposis syndrome, an ampullary duodenal tumor, or a neuroendocrine tumor were excluded. Written informed consent was obtained from all patients before they underwent ER, and the study protocol was reviewed and approved beforehand by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2021-10-045).

Patient demographics, lesion characteristics, and procedural descriptions were collected from the institutional database and electronic medical records. Data on the use of antiplatelet or anticoagulant medication or nonsteroidal anti-inflammatory drugs (NSAIDs) were also obtained for analysis. Follow-up was defined as time between ER and recurrence, death, or loss to follow-up. If none of these events was documented, the end of the follow-up period was defined as the time of last patient contact before June 30, 2021.

Endoscopic procedure and follow-up

Suitability for ER was determined based on endoscopic appearance as determined by high-definition white light endoscopy and narrow-band imaging in patients with histologically confirmed adenoma or adenocarcinoma confined to mucosa. Suspected invasive neoplasia was deemed unsuitable for endoscopic resection. Patients on antiplatelet and/or anticoagulant medications were instructed to consult with their prescribing physicians for permission to withhold medications before ER. EMR was carried out by highly skilled endoscopists. With patients under propofol and midazolam sedation and cardiorespiratory function monitoring, conventional EMR was performed using a snare-assisted technique with submucosal injection of methylene blue-tinted normal saline containing a small amount of epinephrine (0.01 mg/mL) using a single-use 21-gauge needle (Olympus, Japan). Two types of oval electrosurgical snares were used of diameter 15 or 25 mm (Olympus). In one case, standard snare polypectomy was performed without submucosal injection.

The EMR technique was individualized on a case-by-case basis. *En bloc* resection was attempted if a lesion had a largest diameter of < 2.0 cm and < 25% of the luminal circumference. Piecemeal resection was conducted for larger lesions and when there was endoscopic evidence of residual tumor after an *en bloc* resection attempt. Adjunctive coagulation using a hot-biopsy forceps (Boston Scientific, Natick, MA, USA) or an argon plasma coagulation (APC) unit (ERBE, Elektromedizin, Tuebingen, Germany) was sometimes used to reduce the risk posed by any residual tumor, based on endoscopist judgment when the residual portion was too small to remove using a snare. Prophylactic clip placement was performed to reduce the risk of delayed bleeding and perforation when technically possible, depending on lesion location and size, and endoscope stability[9,13,16,19]. EMR was performed only after hospital admission.

After endoscopic treatment, routine chest and abdominal radiography were performed to evaluate possible adverse events, such as perforation and aspiration pneumonia. Routine second-look endoscopy was performed 1 d after EMR. After discharge, follow-up endoscopy was performed at 6 and 12 mo post-EMR during the first year and annually thereafter. If recurrence was suspected, forceps tissue sampling was performed, and further endoscopic treatment such as EMR, and/or ablation were performed at the discretion of the endoscopist.

Clinical outcomes and adverse events

Outcomes were classified as short- or long-term. Short-term outcomes included ER success, which included *en bloc* resection and complete resection rates, and procedure-related complications, which included bleeding and perforation. *En bloc* resection was defined as lesion resection as a single piece, and piecemeal resection as resection resulting in multiple pieces. Complete resection was defined as resection with no endoscopic or histologic evidence of residual tumor tissue at resection sites, irrespective of whether *en bloc* resection was undertaken. EMR-related bleeding was categorized as intraprocedural or delayed bleeding requiring directed intervention. Intraprocedural bleeding was defined as persistent bleeding during the procedure that did not cease spontaneously and required endoscopic intervention involving the injection of diluted epinephrine solution (1:10000), snare-tip soft coagulation, coagulation forceps, or hemoclip placement. Delayed bleeding was defined as any bleeding that prompted medical intervention after the procedure. Perforation was diagnosed endoscopically during procedures or based on the presence of free air in post-procedural chest or abdomen radiographs.

Long-term outcomes included local recurrence and disease-specific survival rates of patients followed for > 6 mo. Incomplete follow-up data were retrieved in various ways, such as by telephone contact or correspondence with patients, families, or referring physicians. Local recurrence was defined as the presence of a tumor on or adjacent to a previous endoscopic resection scar.

Statistical analysis

Data were analyzed using SPSS version 20.0 for Windows (SPSS Inc, Chicago, IL, United States). All variables are presented as mean ± SD, medians and ranges, or absolute numbers and proportions. For univariate analyses, categorical variables were analyzed using the chi-square test or Fisher's exact test. A multivariable logistic regression model was used to identify independent predictors of outcomes and adverse events. Significant variables (P-values < 0.05) by univariate analysis and variables with clinical correlations were included in the multivariate model. Multivariate comparisons are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-sided and statistical significance was accepted for P values < 0.05.

RESULTS

Patient characteristics

Over the ten-year study period, 56 patients underwent 57 EMR and 1 snare polypectomy procedures. Two patients had two duodenal adenomas, and all lesions were treated simultaneously. The baseline clinicopathologic characteristics of the study population are summarized in Table 1. The patients included 30 men (53.6%) and 26 women of median age 57 years (range 26-77 years). Six patients (10.7%) were on at least 1 antiplatelet medication, and no patient was taking an anticoagulant or NSAID. Nine lesions (15.5%) were located in the duodenal bulb, 47 (81.0%) in the 2nd portion, and 2 (3.4%) in the 3rd portion. Colonoscopy was performed in 69.6% of the patients with SNADETs, and colorectal adenomas were found in 46.2% of these patients. Macroscopic types were classified as Is in 24 patients (41.4%), IIa or IIb in 24 (41.4%), and Ip in 10 (17.2%). Based on the pathologies of biopsy specimens before EMR, there were 55 (94.8%) low-grade dysplasia (LGD) lesions, 2 (3.4%) high-grade dysplasia (HGD) lesions, and 1 (1.7%) adenocarcinoma.

EMR and complications

En bloc resection was achieved successfully for 39 lesions (67.2%), and 19 lesions (32.8%) were resected piecemeal, which resulted in two resected specimens in each case (Table 2). Lesion sizes was categorized into 4 groups for further analysis, that is, a < 10 mm group [n = 20 (34.5%)], a ≥ 10 to < 15 mm group [n = 26 (44.8%)], a ≥ 15 to < 20 mm group [n = 7 (12.1%)], and a ≥ 20 mm group [n = 5 lesions (8.6%)]. Twenty-nine lesions (50.0%, 10 lesions that underwent *en bloc* resection and all of 19 lesions treated by piecemeal resection) underwent adjunctive coagulation by hot biopsy or APC to eliminate residual tumor risk. Immediate closure after EMR was performed for 48 lesions (82.8%) by prophylactic clip placement.

Sixteen lesions (27.6%) developed EMR-related bleeding; 15 were intraprocedural and 1 was delayed. All intraprocedural bleedings were successfully controlled endoscopically. Ten of these patients underwent endoscopic hemostasis with hemoclips and electrocoagulation. Only electrocoagulation was needed for five patients with bleeding. Delayed bleeding occurred in 1 EMR case despite prophylactic clipping and was successfully managed endoscopically with hemoclips and electrocoagulation. No patient required further surgical or radiological treatment. Neither perforation nor procedure-related mortality occurred.

Histopathological results

The pathologic results of ER specimens are summarized in Table 3. Median tumor size as determined by histopathology was 12 mm (range 4-20 mm). There were 52 adenomas with LGD, 3 adenomas with HGD, and 3 intramucosal adenocarcinomas. Lateral margins were estimated pathologically to be negative for 36 (62.1%), positive for 3 (5.2%), and inconclusive for 19 (32.8%) lesions, and vertical margins were negative for 50 (86.2%), positive for 0 (0 %), and inconclusive for 8 (13.8%) lesions.

Factors associated with EMR-related bleeding

Increasing lesion size was significantly associated with a higher risk of EMR-related bleeding (P = 0.033) (Table 4), but antiplatelet use, piecemeal resection, tumor location, macroscopic type, and pathology were not found to be associated with bleeding risk. Multivariate logistic regression analysis to identify independent predictors of EMR-related bleeding could not preformed due to only 17 events.

Long-term outcomes

Six of the 56 patients followed for less than 6 mo were excluded from the analysis of long-term outcomes. All 22 patients (22 lesions) with a histopathologic result of an inconclusive or positive resection margin were followed for more than 6 mo (median follow-up duration 28 mo; range 12–101 mo). Clinicopathologic data and the outcomes of 3 cases of incomplete resection are summarized in Table 5, and long-term outcomes are summarized in Table 6. All 3 lesions of incomplete resection with a positive lateral margin were those that had undergone adjunctive coagulation. Of the 50 patients (52 lesions) followed for more than 6 mo, 2 died and 48 survived, but these deaths were not ascribed to a

Table 1 Baseline characteristics of the study subjects

Patients	**56**
Median age, yr (range)	57 (26-77)
Male, *n* (%)	30 (53.6)
Number of lesions, *n* (%)	
1	54 (96.4)
2	2 (3.6)
Medications, *n* (%)	
Aspirin	3 (5.3)
Clopidogrel	1 (1.8)
Dual antiplatelets	2 (3.6)
Anticoagulants	0
NSAIDs	0
Patients that underwent colonoscopy	39 (69.6)
Colonoscopy positive for adenoma	18 (46.2)
Lesions	**58**
Location, *n* (%)	
Bulb	9 (15.5)
Second portion	47 (81.0)
Third portion	2 (3.4)
Macroscopic type, *n* (%)	
Ip	10 (17.2)
Is	24 (41.4)
IIa or IIb	24 (41.4)
Biopsy diagnosis, *n* (%)	
Adenoma/LGD	55 (94.8)
Adenoma/HGD	2 (3.4)
Adenocarcinoma	1 (1.7)

NSAID: Nonsteroidal anti-inflammatory drug; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

primary duodenal tumor. One patient succumbed to aspiration pneumonia and the other patient to colon cancer with multiple liver metastases. In addition, none of the 50 patients experienced local recurrence during follow-up (median follow-up duration 23 mo; range 6–100 mo).

DISCUSSION

In this 10-year retrospective study, we investigated the safety and efficacy of EMR for SNADETs. The results obtained suggest that the prognoses of patients treated by EMR are excellent. In the present study, no death was attributable to a primary duodenal tumor. Furthermore, no local recurrence occurred, although one-third of the patients underwent piecemeal EMR, and no perforation or procedure-related mortality occurred. These findings affirm that EMR of SNADETs has excellent safety and efficacy profiles.

The oncologic long-term outcomes of patients with tumors that are not resected in an *en bloc* fashion are of considerable importance. In the present study, *en bloc* resection was achieved in 67.2%, piecemeal resection in 32.8%, and complete (R0) resection in 62.1%. Due to the risks associated with ESD, endoscopists at our institute chose EMR or polypectomy for all 58 lesions, even for lesions > 20 mm. Considering the effects of *en bloc* resection on oncologic outcomes, this low proportion is obviously unsatisfactory. However, it was largely the result of attempting to minimize mucosal defects due to

Table 2 Endoscopic treatment and complications for the 58 lesions

Treatment methods, *n* (%)	
EMR	57 (98.3)
Snare polypectomy	1 (1.7)
Lesion size, mm, *n* (%)	
Size < 10	20 (34.5)
10 ≤ size < 15	26 (44.8)
15 ≤ size < 20	7 (12.1)
20 ≤ size	5 (8.6)
Results of resection, *n* (%)	
En bloc	39 (67.2)
Piecemeal	19 (32.8)
Adjunctive coagulation, *n* (%)	29 (50.0)
Prophylactic clip placement, *n* (%)	48 (82.8)
Complication, *n* (%)	
Intraprocedural bleeding	16 (27.6)
Delayed bleeding	1 (1.7)
Perforation	0 (0)

EMR: Endoscopic mucosal resection.

Table 3 Histopathologic results for the 58 lesions

Tumor size, mm, median (range)	12 (4–20)
Final pathology, *n* (%)	57 (98.3)
Adenoma/LGD	52 (89.7)
Adenoma/HGD	3 (5.2)
Intramucosal adenocarcinoma	3 (5.2)
Lateral margin, *n* (%)	
Negative	36 (62.1)
Positive	3 (5.2)
Inconclusive	19 (32.8)
Vertical margin, *n* (%)	
Negative	50 (86.2)
Positive	0 (0)
Inconclusive	8 (13.8)
Complete (R0) resection	36 (62.1)

LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

concerns about perforation and bleeding and to enable prophylactic clipping. Fortunately, no local recurrences or death attributable to primary duodenal tumors occurred even after a median follow-up of 23 mo.

Median tumor size (12 mm) in this study was smaller than the 22 to 25 mm sizes reported in Western studies, which also reported higher incidences of local recurrence (14.4%-30.8%) after EMR (*en bloc* rates varied from 23.5% to 31.0%)[20,21]. On the other hand, other studies on smaller lesions have reported local recurrence incidence rates between 5.8% and 8.3% and *en bloc* rates of 69.2%-82% (R0 30%-59%) for

Table 4 Factors associated with endoscopic mucosal resection -related bleeding

	Bleeding (+) (*n* = 17)	Bleeding (-) (*n* = 41)	*P* value
Antiplatelet use			0.661
Yes	1 (14.3)	6 (85.7)	
No	16 (31.4)	35 (68.6)	
Lesion size, mm, *n* (%)			**0.033**
Size < 10	1 (5.0)	19 (95.0)	
10 ≤ size < 15	8 (30.8)	18 (69.2)	
15 ≤ size < 20	4 (57.1)	3 (42.9)	
20 ≤ size	4 (80.0)	1 (20.0)	
Results of resection, *n* (%)			0.218
En bloc	9 (23.1)	30 (76.9)	
Piecemeal	8 (42.1)	11 (57.9)	
Location, *n* (%)			0.855
Bulb	2 (22.2)	7 (77.8)	
Second portion	15 (31.9)	32 (68.1)	
Third portion	0 (0)	2 (100)	
Macroscopic type, *n* (%)			0.950
Ip	2 (20.0)	8 (80.0)	
Is	7 (29.2)	17 (70.8)	
IIa or IIb	8 (33.3)	16 (66.7)	
Final pathology			0.345
Adenoma/LGD	14 (26.9)	38 (73.1)	
Adenoma/HGD and adenocarcinoma	3 (50.0)	3 (50.0)	

LGD: Low-grade dysplasia; HGD: High-grade dysplasia

Table 5 Clinicopathologic data and outcomes for 3 cases of incomplete resection

Patient	Age (yr)	Location	Tumor Size	Pathology	Resection type	Treatment method	Vertical/lateral margin	Result of follow-up biopsy	Follow-up (mo)
1	72	Bulb	20	Intramucosal adenocarcinoma	*En bloc*	EMR	-/+	-	29
2	71	Bulb	20	LGD	*En bloc*	EMR	-/+	-	27
3	75	2^{nd} portion	10	LGD	*En bloc*	EMR	-/+	-	17

LGD: Low-grade dysplasia; EMR: Endoscopic mucosal resection.

lesions of approximately 10 mm[18,22,23]. Tomizawa *et al*[24] reported adenoma size, incomplete snare resection, and piecemeal resection were associated with duodenal adenoma recurrence by univariate analysis (multivariate analysis was not performed). Incomplete snare resection and piecemeal resection are likely consequences of larger lesions. However, others have reported incomplete resection, including piecemeal resection, was not associated with the long-term recurrence of SNADETs[25,26]. In the present study, one-third of patients underwent piecemeal EMR, but no recurrence was observed during follow-up. In a study on 75 duodenal adenomas treated by EMR, the residual tumor rate was 14.5% and the recurrence rate over a median follow-up of 59 mo was 10.9%[27]. However, all but one of these recurrences were successfully treated endoscopically and achieved favorable long-term outcomes.

Table 6 Long-term outcomes (*n* = 50 patients and 52 lesions)

Recurrence, *n* (%)	0 (0%)
Death by duodenal neoplasm	0 (0%)
All-cause mortality	2 (3.6%)
Follow-up period median (range)	23 (6-100) mo
No. of follow-up endoscopies	
2	9
3 or 4	28
5 ≤	13

Although it is not clear how much effect piecemeal resection has on local recurrence, it appears piecemeal resection may not have a significant negative effect on the long-term outcomes of duodenal adenomas. Therefore, we believe that EMR, including EMR with piecemeal resection, offers an acceptable alternative to ESD for the treatment of duodenal adenoma.

Despite considerable technical advances in ER for superficial neoplasms of the GI tract, duodenal endoscopic treatment is considered a high-risk procedure that is more challenging than ER in other GI tract locations for several reasons[6-8]; (1) Endoscope and accessory maneuverability are restricted by the small-caliber, angulated, and fixed-in-place duodenal lumen; (2) Rich vascularity poses a bleeding risk; and (3) The risk of perforation is increased by a thin duodenal wall, retroperitoneal location, and surrounding structures. Although EMR techniques have not been standardized for SNADETs, the approach used should be similar to that adopted for polyps in other parts of the GI tract with added consideration of the thin duodenal wall. However, it is sometimes difficult to obtain successful results by conventional EMR due to insufficient lifting after submucosal injection. A new technique, underwater endoscopic mucosal resection (UEMR) was developed recently in the United States for the treatment of SNADETs, and its usefulness has been reported[28]. Subsequently, several studies were performed in Japan[29-31] to remove SNADETs of less than 20 mm by *en bloc* resection and to reduce treatment-related complications. During UEMR, superficial lesions float up into the snare as protruding lesions, and thus, are easily snared and removed, even when lesions are flat or sessile and difficult to remove by conventional EMR[32]. Theoretically, UEMR is safe because the underwater procedure decreases thermal damage to the duodenal wall and submucosa is cut shallower than during EMR. Additionally, post-UEMR defects are small and soft, and defects are easily closed using endoclips[32]. A retrospective observational study[33] on two different types of subjects, that is, prospectively collected consecutive 104 UEMR cases and 204 EMR cases as historical controls, demonstrated that the technical success rate of UEMR was significantly higher than that of EMR. However, *en bloc* resection and R0 resection rates of UEMR were significantly lower than those of EMR, and no significant difference in adverse events was observed. Further prospective study is warranted to evaluate the efficacy of UEMR.

Duodenal lesions of > 20 mm cannot usually be removed *en bloc* by EMR. Several recent studies of the efficacy of ESD for the treatment of SNADETs have reported *en bloc* and complete resection rates of 80%–100%[6,10,11,22]. However, even experts have reported duodenal ESD complication rates of 6.6% to 31.6% for intraprocedural perforation, 0% to 14.3% for delayed perforation, and 0% to 18.4 % for delayed bleeding[10,11,22,34]. Furthermore, reported emergency surgery rates range from 3.3 to 14.3 % in this technically difficult and dangerous situation. Of course, it is preferable to resect such lesions *en bloc* using ESD but performing duodenal ESD is exceptionally difficult, as evidenced by higher complication incidences. In contrast, EMR is recognized as a safer, easier, quicker procedure, with considerably lower risks of intraprocedural perforation (0%-2.7 %), delayed perforation (0%-2.0%), and emergency surgery (2.7%-4.0 %)[12-16,18]. In addition, several other factors should be borne in mind. (1) Mucosal resection–related perforations are not as easily recognized in duodenum as in other parts of the GI tract[35], any delay in the diagnosis of iatrogenic perforation increases the risk of subsequent surgery [26]; (2) Perforation of the duodenum, particularly of the 2nd portion, requires immediate surgery because bile and pancreatic juice have the deleterious effects on surrounding organs; and (3) The risk of delayed perforation in duodenum is also high[9,36], and this can result in serious consequences in the absence of prompt diagnosis and surgery. Thus, the risks of perforation associated with ESD require careful consideration. Furthermore, no head-to-head comparison of the long-term adenoma recurrence–free rates of ESD and EMR has been performed to date. In our opinion, the risks associated with ESD are greater than the benefits of *en bloc* resection in some cases. Given the considerable technical skills and time required for ESD, it is not routinely recommended for the endoscopic treatment of duodenal tumors, particularly for lesions < 20 mm.

Reported bleeding rates during or after ER of SNADETs vary, in part, because of the different definitions of bleeding used, but nevertheless, are consistently greater than those reported for ER of colorectal adenomas. Ahmad *et al*[37] reported a bleeding frequency of 33% for duodenal EMR, and Lé pilliez *et al*[16] reported a frequency of 25%. In the present study, clinically significant bleeding, which was defined as any bleeding that requires intervention, occurred in 29.3% of lesions, which is similar to the results mentioned above. Klein *et al*[21] reported a higher EMR-related bleeding rate of 43%, which was probably due to a greater proportion of large lesions (29 lesions > 40 mm) in their cohort. Most of the bleeding cases (15/16) in the present study were intraprocedural bleedings. The thin muscular layer of the duodenum is easily perforated by transmural thermal injury during hemostasis procedures, and intraprocedural bleeding is generally considered an undesirable complication. However, Lépilliez *et al* [16] did not consider it a true complication, because it can often be controlled by endoscopic clip application, ablative therapy, or adrenaline injection without serious complication. In addition, as there is no standardized definition for intraprocedural bleeding, it is difficult to determine whether reported bleeding cases in various studies were clinically significant, and therefore, discussions on the management of intraprocedural bleeding during duodenal EMR tend to subjective. Our analysis showed lesion size was significantly associated with a higher risk of EMR-related bleeding, although multivariate analysis could not preformed because there were only 17 events. Even though patients that experienced bleeding required additional hospitalization, all bleeding cases were successfully managed endoscopically, and neither surgical intervention nor interventional radiology was required.

Furthermore, no case of intraprocedural or delayed perforation was encountered, and delayed bleeding occurred only in 1 case (1.7%), which had undergone prophylactic clip placement. Forty-eight lesions (82.8%) underwent prophylactic clip placement based on perceived higher risk because we believe clip placement reduces complications by protecting mucosal defects from pancreatic juice and bile[6,13,16,18,19]. Yamamoto *et al*[22] also reported the absence of bleeding after prophylactic clipping during duodenal ER. Although a larger study is required to precisely determine the effect of prophylactic clipping, results published to date support its use based on considerations of technical difficulties associated with location, size, or scope instability[9,16,18].

Previous studies have shown that 4.8–13.5% of cases in which lesions were initially diagnosed as duodenal adenoma by biopsy were finally diagnosed as adenocarcinoma after resection[13,16]. Okada *et al*[38] reported that HGD in biopsy samples and a lesion diameter of > 2 cm predict progression to adenocarcinoma and suggested that erythematous lesions and lesions with surface nodularity present the risk of progression and recommended their removal. In the present study, EMR resulted in 1.8% of lesions (1/55) being upgraded from LGD to HGD and 3.6% of lesions (2/55) being upgraded from LGD to intramucosal adenocarcinoma. This discrepancy between biopsy samples and resected specimens suggests that relatively large adenoma lesions and adenoma lesions exhibiting surface changes are better to treated by EMR rather than APC.

The major strength of our study is that it covers a 10-year span and benefits from meticulous, long-term follow-up in terms of determining clinical outcomes regarding the safety and efficacy of EMR for SNADETs and natural history after EMR. Our findings reinforce notions that the vast majority of SNADETs can be safely and curatively resected by EMR, even when resection is piecemeal, and that larger lesions size are associated with EMR-related bleeding, which has implications for risk management and surveillance strategies.

The limitations of our study are that it was a single center, retrospective study with a relatively small sample size, and some patients were lost during follow-up to other institutions. Nevertheless, the study documents both short-term outcomes, including complications, and long-term outcomes after EMR for SNADETs.

CONCLUSION

Summarizing, most SNADETs can be safely and effectively managed by EMR undertaken by an expert endoscopist, and EMR may be considered a first-line treatment for SNADETs due to the high incidence of fatal complications attributable to ESD in duodenum. We believe the risks of performing *en bloc* resection by ESD exceed its benefits in some cases, therefore, even piecemeal resection by EMR is a better proposition based on the excellent prognoses observed in this study.

ARTICLE HIGHLIGHTS

Research background

Superficial nonampullary duodenal epithelial tumors (SNADETs) are uncommon, but small early SNADETs are now being diagnosed more frequently, and thus, the demand for endoscopic resection (ER) has increased. However, the duodenum is the most challenging location in the gastrointestinal tract for ER.

Research motivation

Duodenal lesions that require ER are limited in number, and thus, although several reports have been published on the topic, little information is available on the long-term clinical outcomes of ER for SNADETs.

Research objectives

The objective of this investigation was to evaluate the safety and efficacy of ER for the treatment of SNADETs and associated factors using a 10-year follow-up.

Research methods

This retrospective analysis was conducted on 56 consecutive patients with 58 lesions who underwent endoscopic mucosal resection (EMR; 57 lesions), and snare polypectomy (one lesion) for SNADETs from January 2011 to December 2020. Patient demographics, lesion characteristics, and procedural and technical data were collected, and clinical outcomes, including procedure-related complications, completeness of resection, and recurrence were analyzed.

Research results

Lesions consisted of 52 adenomas with low-grade dysplasia, 3 adenomas with high-grade dysplasia, and 3 intramucosal adenocarcinomas. There were 16 cases of intraprocedural bleeding (27.6%) and 1 case of delayed bleeding (1.7%), and these 17 cases were successfully managed endoscopically. No perforation or procedure-related death occurred. Larger lesion size was associated with an increased risk of EMR-related bleeding. During a median follow-up period of 23 mo (range 6–100 mo) no local recurrence occurred, despite the fact one-third of the patients (19 lesions, 32.8%) underwent piecemeal resection and 3 patients (3 lesions, 5.2%) that underwent *en bloc* resection had a pathologically determined positive lateral margin.

Research conclusions

The majority of SNADETs can be safely and curatively resected by EMR, even when resection is piecemeal. However, larger lesions are associated with EMR-related bleeding, which has implications for risk management and surveillance strategies.

Research perspectives

This study covers a 10-year period and benefits from meticulous, long-term follow-up in terms of determining clinical outcomes that reflect the safety and efficacy of EMR for SNADETs and natural history after EMR. Further larger-scale studies are needed to determine the long-term outcomes of ER for SNADETs.

FOOTNOTES

Author contributions: Cho JH and Lee SH designed the study; Cho JH, Lim KY, and Lee EJ performed the research; Cho JH, Lim KY, and Lee EJ analyzed the data; Cho JH wrote the paper; Lee SH and Cho JH revised the manuscript.

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CASE REPORT

Subacute liver and respiratory failure after segmental hepatectomy for complicated hepatolithiasis with secondary biliary cirrhosis: A case report

Wen-Juan Fan, Xiao-Jing Zou

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Abstract

BACKGROUND

Despite being a benign disease, hepatolithiasis has a poor prognosis because of its intractable nature and frequent recurrence. Nonsurgical treatment is associated with high incidences of residual and recurrent stones. Consequently, surgery *via* hepatic lobectomy or segmental hepatectomy has become the main treatment modality. Clinical management and resolution of complicated hepatolithiasis with bilateral or diffuse intrahepatic stones remain very difficult and challenging. Repeated cholangitis and calculous obstruction may result in secondary biliary cirrhosis, a limiting factor in the treatment of hepatolithiasis.

CASE SUMMARY

A 53-year-old woman with a 5-year history of intermittent abdominal pain and fever was admitted to the hepatopancreatobiliary surgery department following worsening symptoms over a 3-d period. Blood tests revealed elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and total bilirubin, as well as anemia. Magnetic resonance cholangiopancreatography showed dilatation of the intrahepatic, left and right hepatic, common hepatic, and common bile ducts, and multiple short T2 signals in the intrahepatic and common bile ducts. Abdominal computed tomography showed splenomegaly and splenic varices. The diagnosis was bilateral hepatolithiasis and choledocholithiasis with cholangitis. Surgical treatment included hepatectomy of segments II and III, cholangioplasty, left hepaticolithotomy, second biliary duct exploration, choledocholithotomy, T-tube drainage, and accretion lysis. Surgical and pathological findings confirmed secondary biliary cirrhosis. Liver-protective therapy and anti-infectives were administered. The patient developed liver and respiratory failure, severe abdominal infection, and septicemia. Eventually, her family elected to discontinue treatment.

CONCLUSION

Liver transplantation, rather than hepatectomy, might be a treatment option for complicated bilateral hepatolithiasis with secondary liver cirrhosis.

Key Words: Hepatolithiasis; Hepatectomy; Liver failure; Biliary cirrhosis; Septicemia; Case report

Core Tip: Treatment of complicated hepatolithiasis with bilateral intrahepatic stones is challenging. In this case of complicated hepatolithiasis with diffuse intrahepatic stones, liver imaging before surgery showed a normal morphology, but nodular and atrophic changes observed during segmental hepatectomy indicated cirrhosis. Preoperatively, the patient's liver function was Child-Pugh class B, and the presence of splenomegaly indicated decompensated liver cirrhosis. Postoperatively, the patient experienced persisting elevated total bilirubin and worsened coagulation function. The patient ultimately experienced liver failure, respiratory failure, and septicemia resulting from severe biliary infection. Further treatment was discontinued at the family's request.

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INTRODUCTION

Hepatolithiasis is defined by the presence of gallstones in all bile ducts peripheral to the confluence of the right and left hepatic ducts, regardless of the coexistence of gallstones in other parts of the biliary tract[1]. It is prevalent primarily in Southeast Asia and in the southeastern coastal regions of China[2]. Obstruction caused by stones can lead to serious complications, including bile duct inflammation, liver cirrhosis, liver atrophy, or malignant transformation, and these contribute to hepatolithiasis being the most common cause of death among the nonmalignant diseases of the biliary tract[3]. As such, aggressive treatment is needed for all cases.

Although nonsurgical techniques are effective in resolving cholestasis and providing temporary relief (*via* removal) of stones, they cannot completely clear a sclerotic hepatobiliary system and may predispose the patient to subsequent recurrence. Hepatectomy has become a primary treatment for hepatolithiasis, applied most often to unilobar, particularly left-sided, hepatolithiasis[4]. Despite recent improvements in surgical and nonsurgical management of hepatolithiasis, difficulties remain in the treatment of complicated hepatolithiasis with bilateral stones. Surgery is still the mainstay of the treatment for complex hepatolithiasis cases. However, secondary biliary cirrhosis develops in 6.0%-7.4% of patients, and more than half experience moderate to severe Child-Pugh class B or C liver dysfunction [5]. The secondary biliary cirrhosis itself may further complicate treatment of the underlying hepatolithiasis. Herein, we present a patient with complicated bilateral hepatolithiasis and secondary biliary cirrhosis who failed treatment after undergoing segmental hepatectomy.

CASE PRESENTATION

Chief complaints

On July 30, 2021, a 53-year-old woman presented at the hepatopancreatobiliary surgery department of our hospital, complaining of intermittent abdominal pain with fever that she had experienced for 5 years but which had worsened over the previous 3 d.

History of present illness

The patient reported having developed intermittent abdominal pain with fever 5 years previously, describing the symptoms as having appeared every 2 or 3 mo over that time. She denied nausea, vomiting, or diarrhea during that time. In the immediate 3 d before her admission to our department,

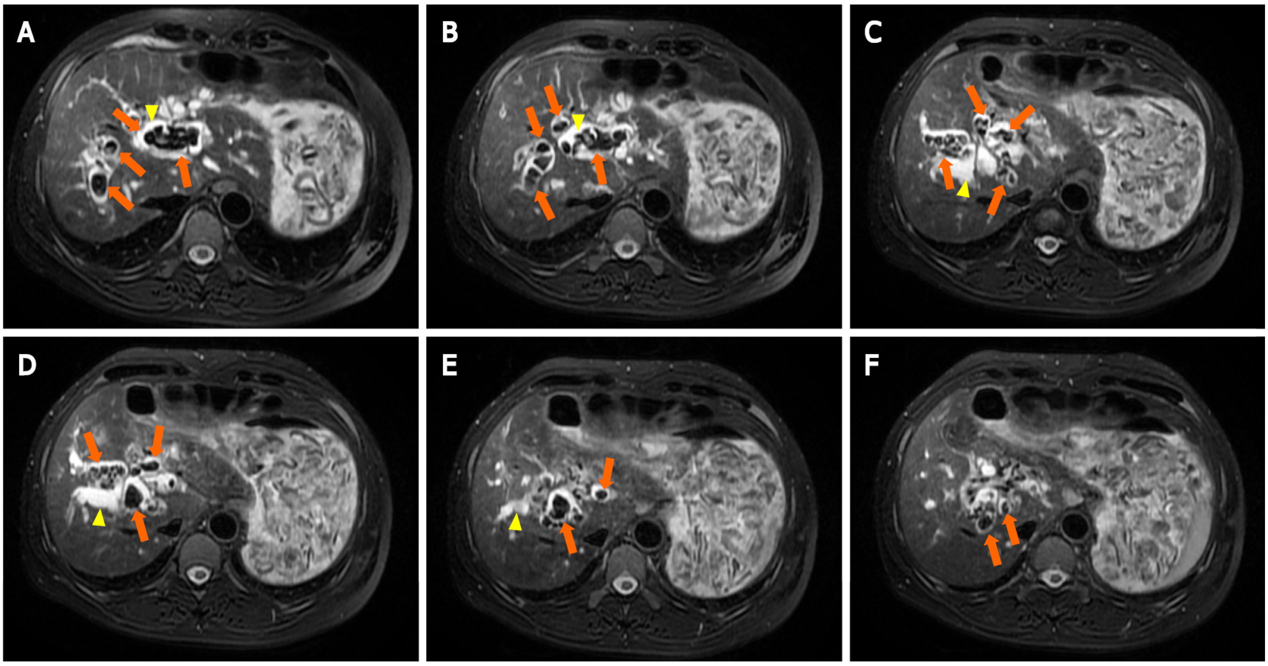

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Figure 1 Preoperative magnetic resonance cholangiopancreatography. A-C: Representative multiple short T2 signals in the intrahepatic and common bile ducts (orange arrows), and obvious intrahepatic duct, left and right hepatic duct dilatation (yellow arrows); D-F: Representative multiple short T2 signals in the intrahepatic and common bile ducts (orange arrows), and obvious intrahepatic duct and left and right hepatic duct dilatation (yellow arrows).

her symptoms had worsened, presenting with hyperpyrexia and chills that were accompanied by jaundice.

History of past illness

The patient had undergone a cholecystectomy 8 years prior. She had no history of other chronic diseases.

Personal and family history

The patient had no history of smoking or drinking. She denied a history of allergies and her family history was unremarkable.

Physical examination

At admission, the patient's temperature was 39.0 °C, heart rate was 104 beats *per* min, respiratory rate was 21 breaths *per* min, and blood pressure was 117/85 mmHg. She had a yellow coloration to her overall skin and sclera. Abdominal examination revealed tenderness in the right quadrant, without rebound tenderness. Lung and heart examinations were normal.

Laboratory examinations

Blood workup in anticipation of surgical intervention revealed a normal white blood cell (WBC) count (4.01×10^9 cells/L), moderate anemia (hemoglobin of 80.0 g/L; normal range: 115.0-150.0 g/L), hypoproteinemia (25.3 g/L; normal range: 35.0-52.0 g/L), and elevated levels of alanine aminotransferase (ALT) (39 U/L; normal range: ≤ 33 U/L), aspartate aminotransferase (AST) (141 U/L; normal range: ≤ 32 U/L), total bilirubin (TBIL) (185.4 μmol/L; normal range: ≤ 21 μmol/L), direct bilirubin (DBIL) (146.3 μmol/L; normal range: ≤ 8 μmol/L), alkaline phosphatase (ALP) (162 U/L; normal range: 35-102 U/L), and γ-glutamyl transpeptidase (γ-GT) (135 U/L; normal range: 6-42 U/L). The coagulation markers were within normal range [prothrombin time (PT), 13.6 s; normal range: 11.5-14.5 s] and tests for hepatitis B and C were negative. The patient's Child-Pugh score was 7, indicating class B. Six days after surgery (August 12, 2021), her TBIL reached a peak of 357 μmol/L; her DBIL was 255.5 μmol/L, ALP was 167 U/L, and γ-GT was 47 U/L. Eight days after surgery (August 14, 2021), arterial blood gas analysis showed a pH of 7.410, PaO_2 of 66.3 mmHg, and $PaCO_2$ of 43.9 mmHg, indicating acute respiratory distress syndrome. Ten days after surgery (August 16, 2021), the WBC count reached a peak of 29.81×10^9/L, with 90.7% of neutrophils, and elevated high-sensitivity C-reactive protein (103.7 mg/L; normal range: < 1 mg/L) was detected. Sixteen days after surgery (August 22, 2021), PT reached a peak of 19.5 s; her prothrombin activity (PTA) (normal range: 75.0%-125.0%) was 51%, international normalized ratio (INR) (normal range: 0.80-1.20) was 1.69, and activated partial thromboplastin time was 23.7 s (normal

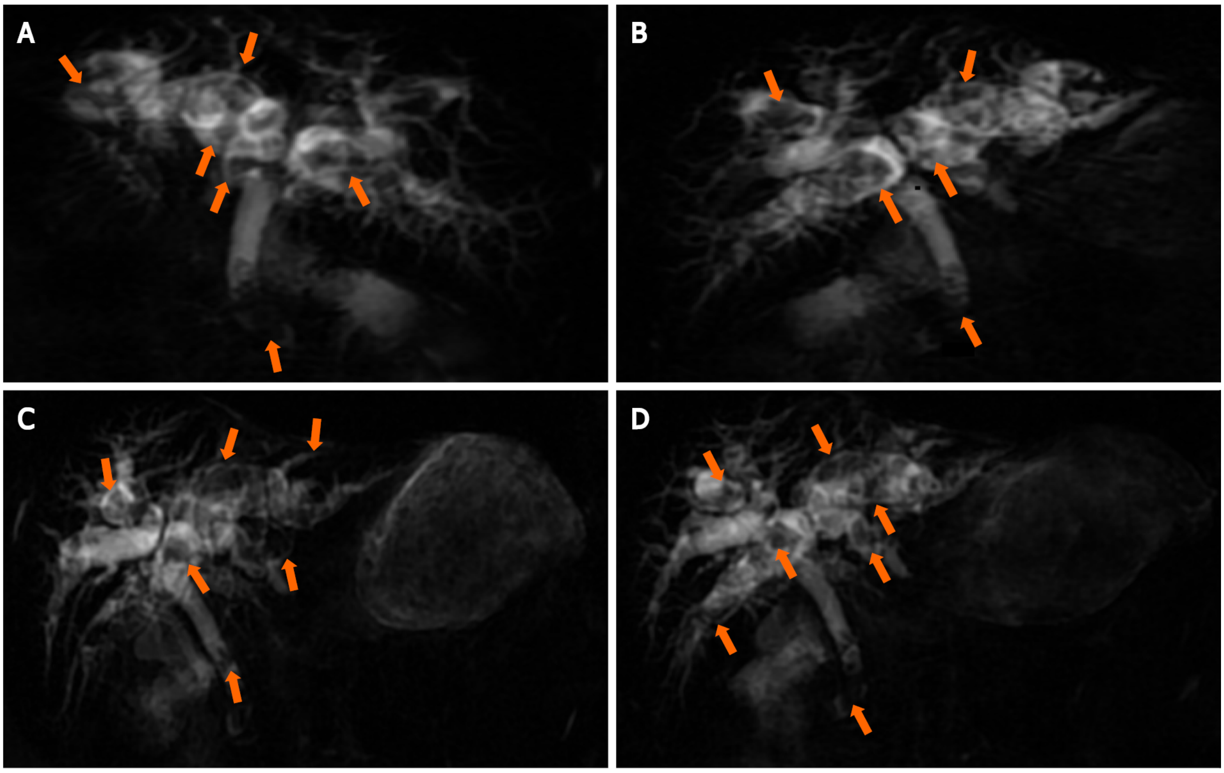

Figure 2 Preoperative multiplanar reconstruction magnetic resonance cholangiopancreatography. A and B: Representative multiple short T2 signals in the intrahepatic duct common bile duct (orange arrows); C and D: Representative multiple short T2 signals in the intrahepatic duct common bile duct (orange arrows).

range: 29.0-42.0 s). Autoimmune hepatitis-associated antibody tests were negative for anti-mitochondrial antibody and weakly positive for anti-soluble liver antigen antibody. T-tube drainage fluid was Rivalta (+), with a karyocyte count of 1600 × 10^6 cells/L and neutrophil percentage of 62%. Twenty-five days after surgery (August 31, 2021), her blood ammonia level peaked, at 70 µmol/L.

Eleven days after surgery (August 17, 2021), the T-tube drainage fluid and subcutaneous drainage fluid cultures tested positive for *Enterococcus faecalis* and *Candida parapsilosis*; sputum cultures were also positive for *Candida parapsilosis*. Eighteen days after surgery (August 24, 2021), cultures of sputum and catheter fluid (sensitive to piperacillin/tazobactam and amikacin) and blood (sensitive to piperacillin/tazobactam and cefepime) were positive for *Pseudomonas aeruginosa*.

Imaging examinations

Magnetic resonance cholangiopancreatography in anticipation of surgical intervention showed normal liver volume and left-to-right lobe proportion but splenomegaly and splenic varices. The gallbladder (removed 8 years prior) was absent from the imaging view, and the pancreas appeared normal. Magnetic resonance imaging revealed dilatation of the intrahepatic, left and right hepatic, common hepatic, and common bile ducts, and multiple short T2 signals in the intrahepatic and common bile ducts. Figure 1 shows the intrahepatic duct dilatation and multiple short T2 signals in the intrahepatic duct, which indicated multiple stones. Multiplanar reconstruction also showed multiple short T2 signals in the intrahepatic and common bile ducts (Figure 2). Abdominal and pelvic contrast-enhanced computed tomography (CT) showed multiple nodular high-density shadows in the intrahepatic and extrahepatic bile ducts, with the largest ones up to 8 mm in length. Contrast-enhanced CT also showed intrahepatic and extrahepatic bile ducts dilatation, portal vein narrowing, splenomegaly (Figure 3A), splenic varices (Figure 3B), collateral circulation expansion (Figure 3C), and spontaneous spleno-renal shunting (Figure 3D).

At day 6 postoperatively (August 12, 2021), abdominal CT showed multiple nodular high-density shadows in the right hepatic and common bile ducts with intrahepatic and extrahepatic bile duct dilatation (Figure 4). Eight days after surgery (August 14, 2021), a bedside chest X-ray showed bilateral pulmonary diffuse patchy high-density shadows and bilateral pleural effusion, which indicated bilateral pulmonary infection (Figure 5A). Fourteen days after surgery (August 20, 2021), chest CT showed bilateral pulmonary nodular and patchy shadows and left pulmonary atelectasis, indicating pulmonary infection (Figure 5B–D). Pathology findings following evaluation of a 13 cm × 6.5 cm × 5 cm liver specimen included dilatation of multiple intrahepatic ducts, with a maximum diameter of 2 cm and

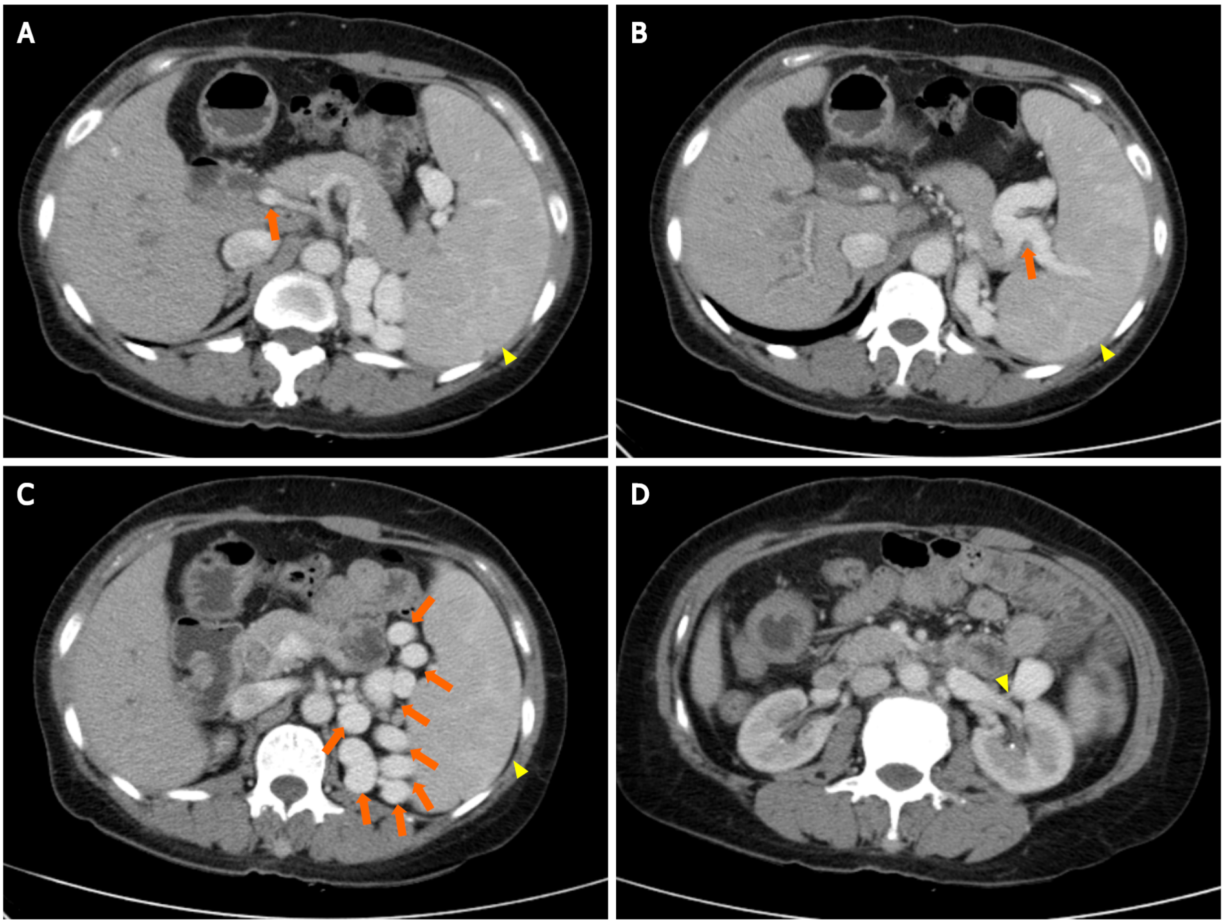

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Figure 3 Preoperative abdominal and pelvic contrast-enhanced computed tomography images. A: Narrowed portal vein (orange arrow) and splenomegaly (yellow arrow); B: Splenic varices (orange arrow) and splenomegaly (yellow arrow); C: Collateral circulation expansion (orange arrows) and splenomegaly (yellow arrow); D: Spontaneous spleno-renal shunt (yellow arrow).

containing multiple, brown stones. Histopathology included intrahepatic duct dilatation with stones and inflammatory cell infiltration of the bile duct walls (Figure 6). Proliferation of fibrous tissue in portal tracts divided the liver parenchyma into irregular regenerative nodules (pseudolobules) that had lost the normal architecture and central veins (Figure 7A–C). Hepatic cords were poorly arranged in foci, with two layers of cells and enlarged cells that included binucleate forms (Figure 7D–F).

MULTIDISCIPLINARY EXPERT CONSULTATION

Doctor Yu, Associate Chief Physician, MD, Respiratory Department

The systemic infection is severe, the current anti-infective treatments are effective, and respiratory support therapy should be continued.

Doctor Ding, Associate Chief Physician, MD, Infectious Disease Department

The patient's TBIL has not declined with treatment and the pulmonary infection is severe, indicating a poor prognosis. Sputum, catheter, and blood cultures are positive for *Pseudomonas aeruginosa*, indicating hematogenous spread. The catheter should be replaced. If the infection cannot be controlled, fosfomycin can be added. The persisting elevated TBIL is related to surgery, biliary tract infection, and obstruction. Percutaneous transhepatic cholangial drainage may be useful.

Doctor Zhu, Chief Physician, MD, Hepatopancreatobiliary Surgery Department

The T-tube is open and the current drug treatments should be continued. There is no indication for a second surgery.

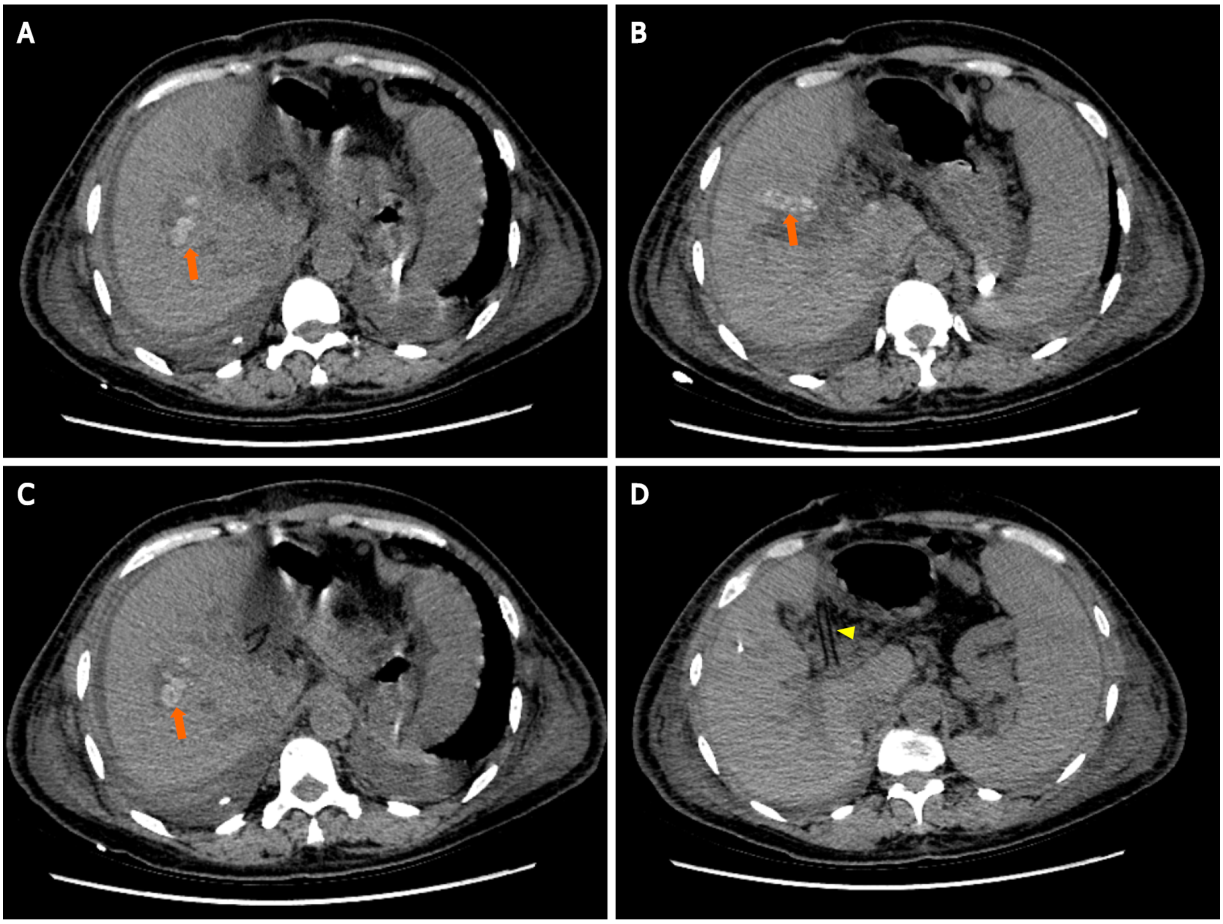

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Figure 4 Postoperative abdominal computed tomography images. A-C: Representative multiple nodular high-density shadows in the right hepatic duct (orange arrows); D: Drainage tube (yellow arrow).

FINAL DIAGNOSIS

Bilateral hepatolithiasis and choledocholithiasis with cholangitis (after partial hepatectomy), subacute liver failure, secondary biliary cirrhosis, splenomegaly, splenic varices, type 1 respiratory failure, severe pneumonia, septicemia (*Pseudomonas aeruginosa*), abdominal infection, anemia, and hypoproteinemia.

TREATMENT

After admission, polyene phosphatidylcholine (465 mg), ademetionine 1,4-butanedisulfonate (1 g), and glycine cysteine sodium chloride (200 mL) were given once a day (QD) as liver-protective therapy. Ceftriaxone sodium and tazobactam sodium (2 g) were given two times a day (BID) for 3 d as anti-infective treatment. On August 6, 2021, hepatectomy of segments II and III, cholangioplasty, left hepaticolithotomy, second biliary duct exploration, choledocholithotomy, T-tube drainage, and accretion lysis were performed. During surgery, stones were palpable in the common bile duct and left lateral lobe of the liver. The liver showed nodular and atrophic changes, which indicated cirrhosis. After surgery, hepatocyte growth-promoting factor (60 μg), acetylcysteine (8 g), and reduced glutathione (1.8 g) were given QD for liver protection. Ambroxol hydrochloride (60 mg) and doxofylline (0.3 g) were given BID to promote expectoration drainage. Imipenem and cilastatin sodium [0.5 g every 8 h (q8h)] and linezolid and glucose [0.6 g every 12 h (q12h)] were given as anti-infective treatment from August 7-10, 2021 and were then switched to meropenem (1 g) and tigecycline (50 mg q8h) from August 11-13, 2021.

On August 10, 2021, the patient developed dyspnea, decreased oxygen saturation, and a continuously increasing level of TBIL. Considering pulmonary infection and liver failure, the patient was transferred to the infectious disease department on August 13, 2021. The anti-infective treatments were changed to meropenem (1 g q8h), teicoplanin (400 mg QD), and voriconazole (0.2 g q12h). On August 14, 2021, the patient developed tachypnea with bilateral moist rales. The arterial PaO_2 dropped to 66.3 mmHg and the $PaCO_2$ increased to 43.9 mmHg. Tracheal intubation was performed, and the patient was transferred to the intensive care unit (ICU). A single dose of methylprednisolone (40 mg) was given, and fiberoptic

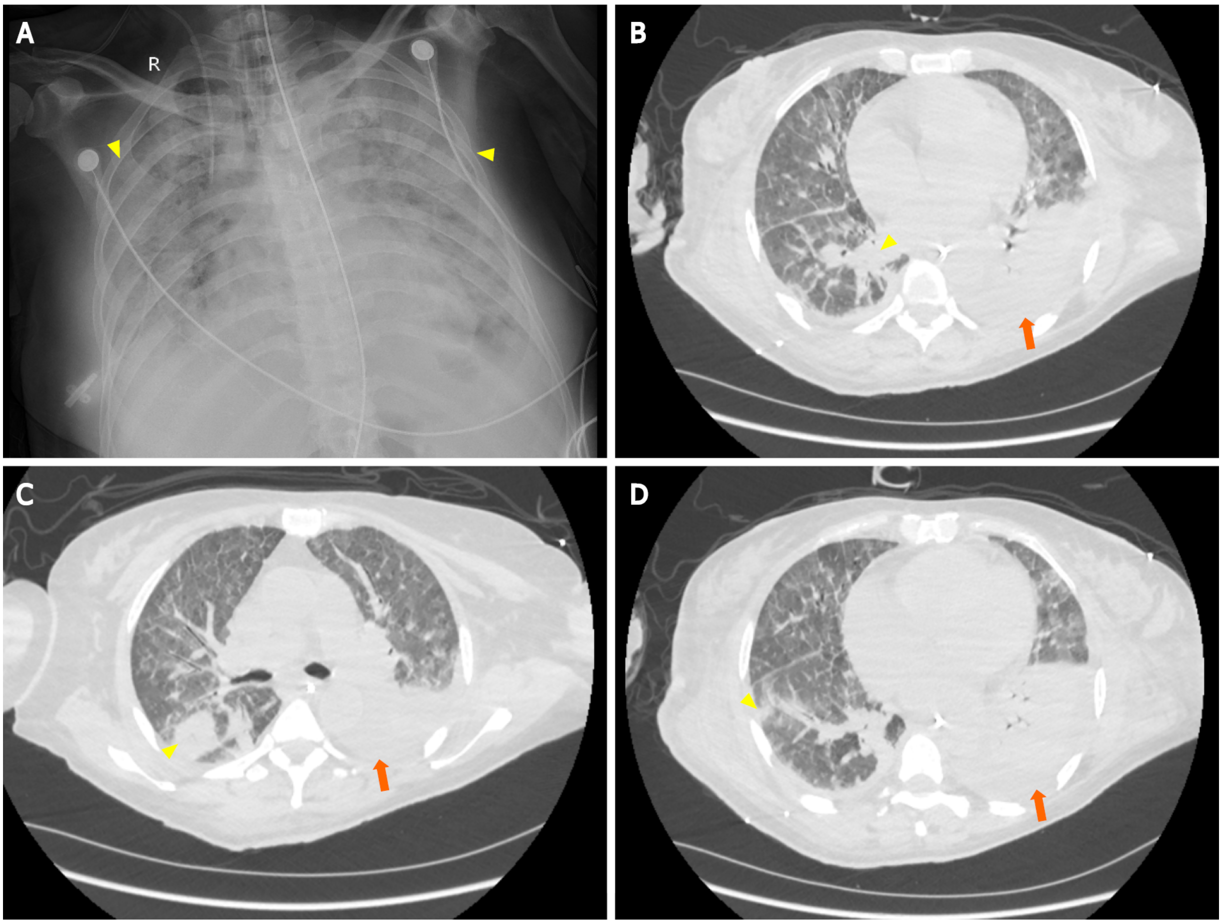

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Figure 5 Postoperative pulmonary imaging. A: Bedside chest X-ray (August 14, 2021) showing bilateral pulmonary diffuse patchy high-density shadows (yellow arrows) and bilateral pleural effusion, indicating bilateral pulmonary infection; B-D: Representative chest computed tomography (August 20, 2021) images showing bilateral pulmonary nodular and patchy shadows (yellow arrows) and left pulmonary atelectasis (orange arrows), indicating pulmonary infection.

bronchoscopy was performed to aspirate sputum. In the ICU, anti-infective treatment included meropenem (1 g q8h) given from August 15-17, 2021, imipenem and cilastatin sodium (0.5 g q8h) given from August 17-22, 2021, piperacillin sodium and tazobactam sodium (4.5 g q6h) given from August 24-28, 2021, amikacin (0.4 g q12h) given from August 24-29, 2021, ceftazidime (1 g q8h) given from August 28 to September 1, 2021, polymyxin B sulfate (75 wu q12h) given from August 29 to September 1, 2021, tigecycline (50 mg q8h) given from August 15 to 23, 2021, vancocin (1000 mg BID) given from August 22 to 30, 2021, voriconazole (0.2 g q12h) given from August 18 to 24, 2021, and micafungin sodium (100 mg QD) given from August 24 to September 1, 2021. Ventilator support was provided, and the patient was given packed red blood cell and fresh frozen plasma transfusions; noradrenaline bitartrate was given to maintain blood pressure.

On August 25, 2021, the patient was successfully extubated and given high flow nasal oxygen. On August 26, 2021, artificial liver support therapy and plasmapheresis were performed. On August 27, 2021, the patient was reintubated because of disturbance of consciousness and decreased oxygen saturation.

OUTCOME AND FOLLOW-UP

Sputum, catheter fluid, and blood cultures were positive for *Pseudomonas aeruginosa*. The patient's TBIL continued to increase after surgery and her coagulation function worsened. Her family elected to discontinue treatment because of severe infection, septicemia, and liver and respiratory failure.

DISCUSSION

Hepatolithiasis is a disease of unknown etiology that seriously impacts patient health and quality of life,

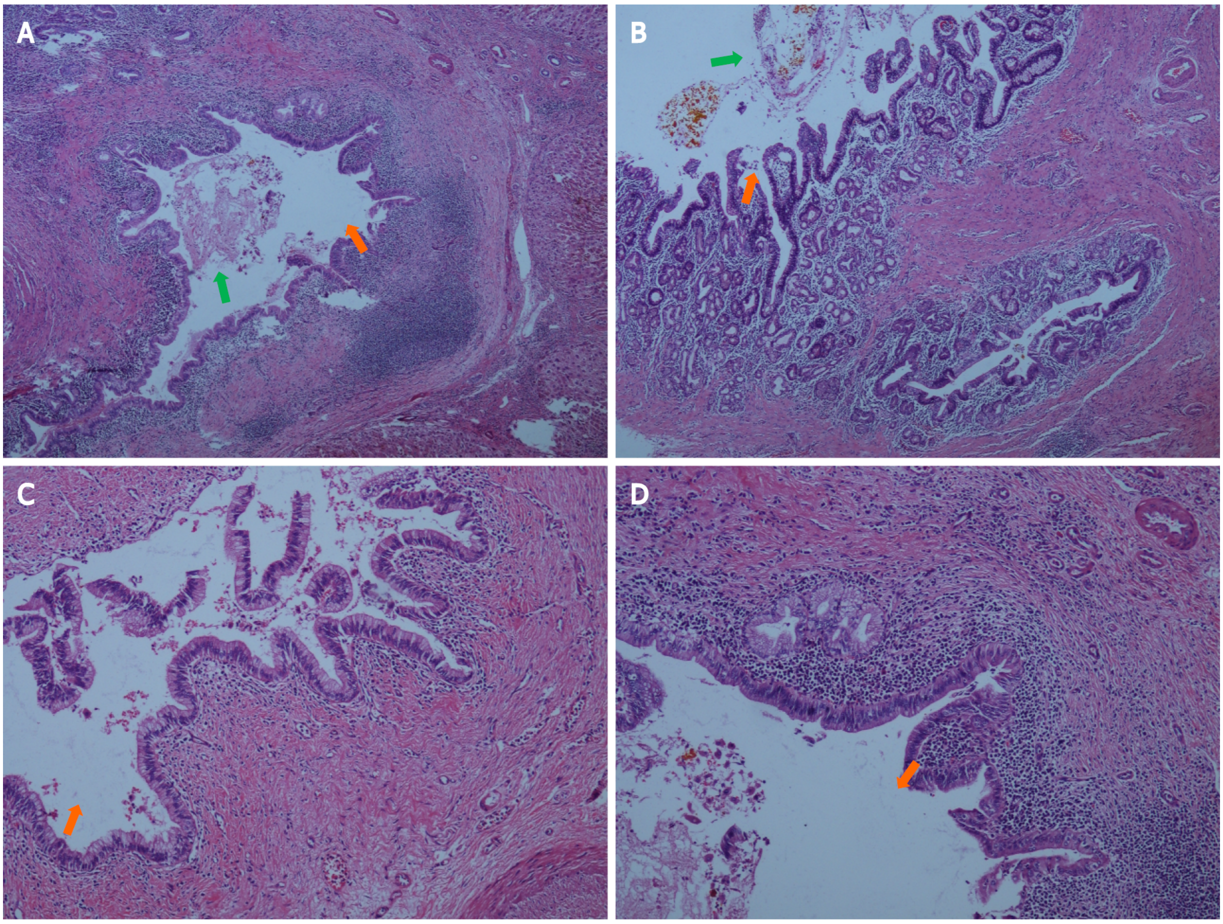

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Figure 6 Histopathological findings of the resected liver (intrahepatic duct). A and B: Representative specimens showing intrahepatic duct dilatation (orange arrows) with stones (green arrows) and inflammatory cell infiltration in bile duct walls (hematoxylin and eosin staining; 40 ×); C and D: Representative specimens showing intrahepatic duct dilatation (orange arrows) with stones and inflammatory cell infiltration in bile duct walls (hematoxylin and eosin staining; 100 ×).

with a reported morbidity of 20%-50% in patients who undergo cholecystectomy[6]. Our patient had undergone cholecystectomy 8 years prior to presentation at our department. Since her autoimmune hepatitis-associated antibodies were not sufficiently elevated to support a diagnosis of autoimmune liver disease, we hypothesize that the etiology of her presenting hepatolithiasis may have been related to her history of cholecystectomy.

Complete stone clearance, restoration of normal bile flow, and excision of diseased hepatic parenchyma are the goals of hepatolithiasis treatment. In the last decade, advances in nonsurgical and surgical treatments have resulted in improvement of the management of the disease, but such nonsurgical treatments as percutaneous transhepatic and peroral cholangioscopic lithotripsy are associated with high rates of residual and recurrent stones[7]. Hepatectomy, mainly segmental hepatectomy, is an effective surgical treatment that can remove stones, diseased bile ducts, and damaged hepatic parenchyma[8]. However, hepatectomy is applied most often to cases of unilobar, particularly left-sided, hepatolithiasis[4]. Hepatolithiasis involving two or more lobes is challenging because diffuse intrahepatic stones in bilateral intrahepatic ducts are difficult to clear, strictures may be present in the remaining liver, and calculus extraction may be incomplete. Hepatectomy for bilateral hepatolithiasis is controversial, as patients may not tolerate resection of multiple liver segments. Therefore, bile duct exploration and choledochoscopic lithotomy combined with a reduced hepatectomy were essential. Some studies have reported resection of the dominantly-affected side, followed by postoperative cholangioscopic lithotomy[9]. Right hepatic lobectomy is usually avoided because of the increased risk involved. Our patient was treated with a left-sided segmental hepatectomy, and stones remaining in the right hepatic duct after surgery can be seen in Figure 4. Bilateral hepatolithiasis deserves to be considered as a distinct disease.

Although imaging evaluation showed that the patient's liver morphology was relatively normal, splenomegaly and splenic varices indirectly indicated portal hypertension. The surgical and pathological findings confirmed secondary biliary cirrhosis. Established liver cirrhosis has been reported in 10%-15% of patients with hepatolithiasis at the initial presentation[10], and secondary biliary cirrhosis has been reported to develop 7 years after the onset of obstruction and 4.5 years after a

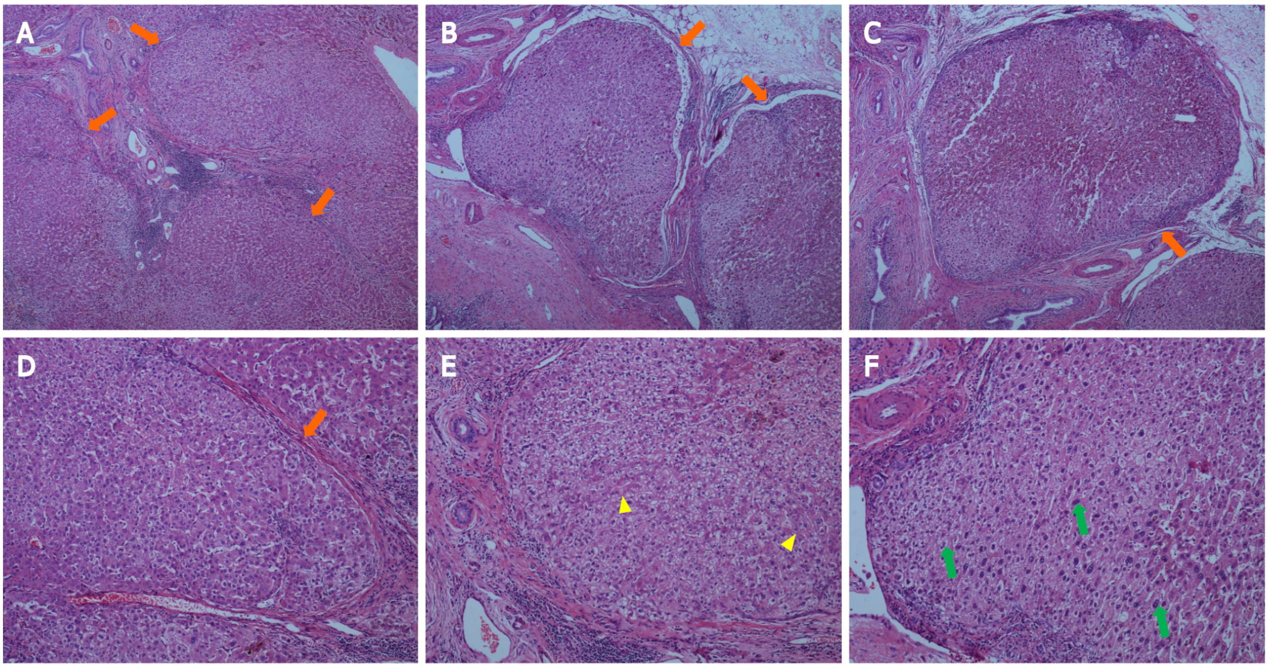

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Figure 7 Histopathological findings in the resected liver (liver parenchyma). A-C: Representative specimens showing proliferation of fibrous tissue in portal tracts dividing the liver parenchyma into irregular regenerative nodules (pseudolobules, orange arrows) that have lost the normal structure, and central veins (hematoxylin and eosin staining; 40 ×); D-F: Representative specimens showing pseudolobules (orange arrow) hepatic cords arranged irregularly, with foci of two layers of cells (yellow arrows), and large, occasionally binucleate cells (green arrows; hematoxylin and eosin staining; 100 ×).

calculous obstruction[11]. Our patient had intermittent abdominal pain with fever for 5 years and her liver function on admission was Child-Pugh class B (*i.e.* decompensated liver cirrhosis), which was consistent with the reported prognosis. Patients with secondary biliary cirrhosis may be prone to postoperative sepsis and at increased risk of postprocedural complications. Previous studies have reported that 10%-30% of patients with cirrhosis developed bacterial infections after abdominal surgery [12], which may have been related to impaired immune defense mechanisms of the liver. As the prognosis is better and the feasibility of aggressive management is greater in patients with Child-Pugh class A than class B or C status, we believe that hepatolithiasis should be managed early, before the development of secondary biliary cirrhosis. Hepatolithiasis combined with secondary biliary cirrhosis was frequently found and we have to pay attention and try to prevent the occurrence of hepatic failure after surgery especially in the jaundiced patient.

There are no widely accepted guidelines for treating patients with terminal hepatolithiasis. According to the classification described by Feng *et al*[13], our patient had Type IIc disease with diffuse stones, biliary cirrhosis, and portal hypertension. Liver transplantation is recommended for such patients[13]. The indications for liver transplantation include end-stage decompensated liver cirrhosis and/or liver failure, compensated cirrhosis or non-cirrhosis in patients with diffusely distributed intrahepatic calculi, and/or multiple hepatobiliary stenoses that cannot be cured by other surgical and nonsurgical procedures[14]. Our patient was suitable for liver transplantation, which has a reported 1-year survival of 100% and 5-year survival of 73%[15]. However, because of the critical shortage of cadaveric livers, grafts are preferentially provided to those with the highest likelihood of death without transplantation. Owing to the limited understanding of patients and doctors about liver transplantation for hepatolithiasis, few patients have received liver transplants[15]. Terminal hepatolithiasis, especially when combined with portal hypertension and previous right upper quadrant surgery, may make the transplantation procedure difficult. Thus, selecting patients for transplantation before they reach end-stage disease is important. However, the imaging before surgery did not show signs of liver cirrhosis and it was until the surgery that surgeons found that the liver showed nodular and atrophic changes indicating cirrhosis. Besides, in China, liver transplantation was mostly for end-stage liver cirrhosis and it was not easy to get access to liver donors since the patient's general conditions were relatively good compared to patients with end-stage liver cirrhosis. Therefore, the surgeons did not discuss liver transplantation with the patient before surgery.

Surgery failed to rescue our patient. One of the reasons was infection. The patient suffered from abdominal infection derived from bile duct and pulmonary infection, resulting in respiratory failure and septicemia. The primary cause of death after hepatectomy is reported to be uncontrollable septicemia [7], and positive bile cultures have been reported in 83.3% of patients with hepatolithiasis[12], which is higher than the incidence of surgical site infections after hepatectomy for hepatocellular carcinoma[12].

Sepsis must thus be effectively controlled before hepatectomy in patients with hepatolithiasis. Another reason for patient death is liver failure. The maximum TBIL of our patient was 10-times higher than the upper limit of normal and her maximum INR was 1.69. The guidelines for diagnosis and treatment of liver failure suggest that patients with a TBIL level of more than 10-times normal and a PTA ≤ 40% or an INR ≥ 1.5 can be diagnosed with liver failure[16]. The reasons for liver failure in our patient were related to liver resection and the abnormal function of the remaining liver.

CONCLUSION

The management of complicated bilateral hepatolithiasis is challenging, and segmental hepatectomy is unable to completely remove all the intrahepatic ductal stones. It is important to effectively control biliary tract infection before surgical procedures. Liver transplantation rather than hepatectomy may be considered as an option in complicated bilateral hepatolithiasis with secondary liver cirrhosis.

FOOTNOTES

Author contributions: Fan WJ reviewed the literature and contributed to manuscript drafting and imaging data interpretation; Zou XJ was responsible for revising the manuscript for important intellectual content; all authors provided approval of the final version for submission and publication.

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CASE REPORT

Surgical timing for primary encapsulating peritoneal sclerosis: A case report and review of literature

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Abstract

BACKGROUND

Primary encapsulating peritoneal sclerosis (EPS) is a rare but devastating disease that causes fibrocollagenous cocoon-like encapsulation of the bowel, resulting in bowel obstruction. The pathogenesis, prevention, and treatment strategies of EPS remain unclear so far. Since most patients are diagnosed during exploratory laparotomy, for the non-surgically diagnosed patients with primary EPS, the surgical timing is also uncertain.

CASE SUMMARY

A 44-year-old female patient was referred to our center on September 6, 2021, with complaints of abdominal distention and bilious vomiting for 2 d. Physical examination revealed that the vital signs were stable, and the abdomen was slightly distended. Computerized tomography scan showed a conglomerate of multiple intestinal loops encapsulated in a thick sac-like membrane, which was surrounded by abdominal ascites. The patient was diagnosed with idiopathic EPS. Recovery was observed after abdominal paracentesis, and the patient was discharged on September 13 after the resumption of a normal diet. This case raised a question: When should an exploratory laparotomy be performed on patients who are non-surgically diagnosed with EPS. As a result, we conducted a review of the literature on the clinical manifestations, intraoperative findings, surgical methods, and therapeutic effects of EPS.

CONCLUSION

Recurrent intestinal obstructions and abdominal mass combined with the imaging of encapsulated bowel are helpful in diagnosing idiopathic EPS. Small intestinal resection should be avoided.

Key Words: Primary encapsulating peritoneal sclerosis; Abdominal cocoon; Intestinal obstruction; Case report

Core Tip: Primary encapsulating peritoneal sclerosis (EPS), also called an abdominal cocoon, is so rare that the etiology, pathogenesis, treatment strategies of primary EPS remain vague. We reported a case of primary EPS and carried out a comprehensive literature analysis. The data indicated for the first time that recurrent intestinal obstructions and abdominal mass combined with the imaging of encapsulated bowel are helpful in diagnosing primary EPS. Surgical treatments are promising, but care should be taken to avoid small intestinal resection. Elective abdominal exploration might decrease complications of patients with primary EPS, but further research is required to substantiate this.

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INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a rare but chronic syndrome, clinically presenting as acute and subacute intestinal obstruction, with abdominal pain, distention, vomiting, and constipation. EPS can be classified as primary (idiopathic) and secondary (cases where causes for the disease have been identified)[1]. Secondary EPS cases are reported to be associated with peritoneal dialysis (PD), tuberculosis, β-adrenergic blocker usage, endometriosis, *etc*[2-5]. With the broader applications of PD, the cases of PD-related EPS have increased up to 0.7%[6]. The pathogenesis, prevention, and treatment strategies of secondary EPS have been well established[7-9]. The term primary EPS, which is also called idiopathic EPS, was first used by Foo *et al*[8] in 1978 to describe EPS cases of unknown origin in young women residing in tropical or subtropical countries. However, primary EPS has since been found to develop in elderly men. The etiology, pathogenesis, and treatment strategies for primary EPS remain vague. This paper reports a patient diagnosed with primary EPS and compiles 63 primary EPS cases reported in the literature.

CASE PRESENTATION

Chief complaints

A 44-year-old female patient was admitted to the emergency department of our institution on September 6, 2021, with complaints of abdominal distention and bilious vomiting for 2 d.

History of present illness

The patient had experienced abdominal distension and bilious vomiting the day before with no obvious precipitating factors. She had no fever, abdominal pain, constipation, and normal menstruation. She was treated with fasting and parenteral nutrition; the patient ceased vomiting, but abdominal distention continued.

History of past illness

She had three episodes of abdominal pain, abdominal distention, and bilious vomiting. The last episode occurred 3 years before, with abdominal distention and massive ascites. The patient recovered after abdominal paracentesis, which indicated bloody ascites. A year ago, she had schizophrenia and took aripiprazole orally (10 mg QD). She had untreated menstrual cramps when she was young, and her menstruation is regular. No weight loss was observed before.

Personal and family history

There was no unremarkable personal or family history.

Physical examination

The patient's vital signs were stable and the abdomen was slightly distended. There was mild

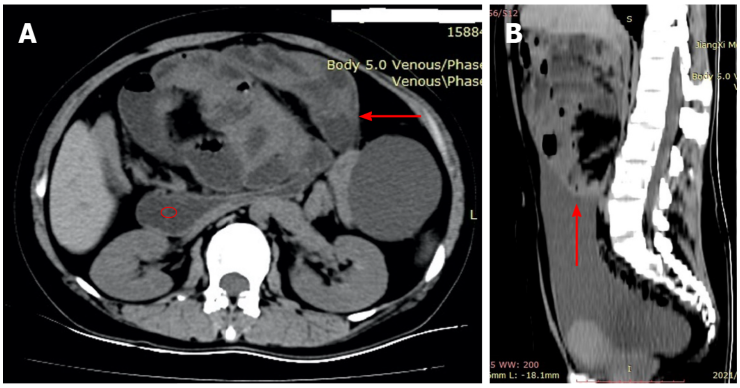

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Figure 1 Computerized tomography of transverse plane and sagittal plane. A: Computerized tomography (CT) of transverse plane: A conglomerate of multiple intestinal loops encapsulated in a thick sac-like membrane (arrow), and dilated duodenum (red cycle); B: CT of sagittal plane: Epigastric mass floating in ascites.

tenderness in the right upper abdomen, but there was no rebound tenderness. A palpable, soft, low mobility mass (6 cm × 8 cm) was detected in the upper right abdomen, and the abdomen ascites sign was positive.

Laboratory examinations

Leukocyte count: 5.66 × 10^9/L, percentage of neutrophils (NEU%): 65.2%; Hemoglobin: 122 g/L; C-reactive protein: 14.3 mg/L; carcinoembryonic antigen: 2.1 ng/mL; and tuberculosis antibody and T.Spot-TB tests were negative.

Imaging examinations

Computerized tomography (CT) scan showed a conglomerate of multiple intestinal loops encapsulated in a thick sac-like membrane, which was surrounded by abdominal ascites (Figure 1). “Gourd sign” (Figure 1A) was also observed in this case, which refers to the expansion of the horizontal part of the duodenum caused by an abdominal cocoon.

FINAL DIAGNOSIS

According to the clinical manifestations of recurrent intestinal obstruction, abdominal mass, and imaging features of encased bowel, this case was clinically diagnosed as primary EPS.

TREATMENT

Laparoscopic exploration was proposed but was not accepted by the patient and her husband. Abdominal drainage was performed for 3 d, and a total of 2200 mL of blood liquid was removed. No carcinoma cells were found in the centrifugal cytology of ascites (Figure 2).

OUTCOME AND FOLLOW-UP

After this, the patient felt well, her abdominal distention was completely relieved, and she was put on a semi-liquid diet. After abdominal ultrasound confirmed the absence of ascites in the abdominal cavity, an abdominal contrast-enhanced CT (CECT) (September 9, 2021) scan was arranged, which revealed that the entire small intestine was dilated, clustered, and wrapped in an enhancing sac, separating the intestine from ascending colon, descending colon, and sigmoid colon (Figure 3). She was discharged on September 13 after resuming a normal diet, with no recurrence of symptoms in the following month.

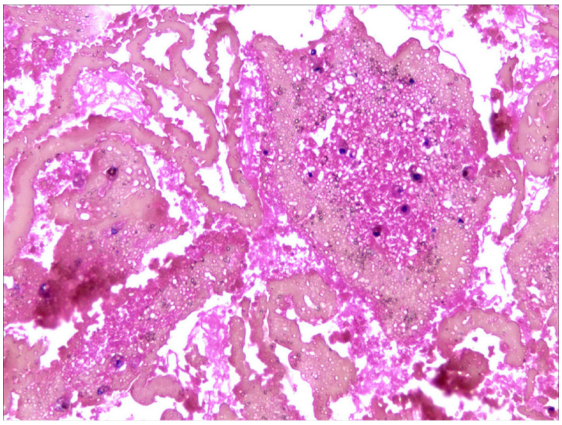

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Figure 2 Exfoliative cytology of ascites (hematoxylin and eosin stain, × 40). A large number of red blood cells, including scattered inflammatory cells.

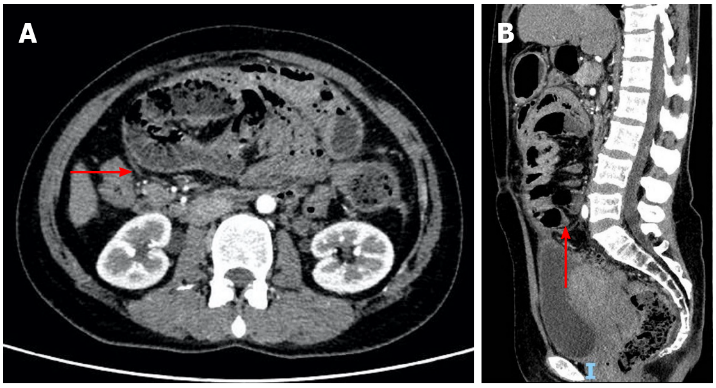

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Figure 3 Contrast-enhanced computerized tomography of transverse plane and sagittal plane. A: Transverse plane; B: Sagittal plane. Intestinal loops were encapsulated in a thick sac-like membrane (arrow).

DISCUSSION

Literature review

A systematic search of the literature, focusing on article titles and abstracts of publications in the English language using the PubMed database, was performed; the publication date of these articles was from January 2004 to September 2021. The search was executed utilizing the following keywords: "abdominal cocoon", "encapsulating peritoneal sclerosis", "sclerosing encapsulating peritonitis", and "peritoneal encapsulation". Manual searches of reference lists of the publications were performed to supplement the electronic search.

Case series without clinical details were excluded. Case reports with features of EPS that might be associated with PD, including abdominal tuberculosis, abdominal surgery, recurrent peritonitis, ventriculoperitoneal or peritoneovenous shunts, liver transplantation, abdominal trauma, beta-blocker treatment (practolol or propranolol), intraperitoneal chemotherapy, endometrioid carcinomas, intraperitoneal povidone-iodine use, liver cirrhosis, carcinomatous peritonitis, fibrogenic foreign material, systemic lupus erythematosus, and parasitic infection, were determined to be secondary EPS and were excluded.

Two investigators independently read the articles. The following information was extracted from the reports: Country (of the author), year (of publication), age/sex (of the patient), major syndrome, past history, major symptoms (of peritonitis and abdominal mass), radiologic tools, ascites characteristics, operations, intraoperative findings, histopathology, curative effect, and follow-up status. A total of 52 reports[10-61] from January 2004 to September 2021 with data of 63 patients was reviewed (Table 1). A total of 14 females with the median age of 38 years (range: 12-64 years) and 49 males with the median age of 45.5 years (range: 7-82 years) were reported; the difference of age between female and male patients was statistically significant (rank-sum test). Recurrent abdominal distention, abdominal pain or colicky pain, nausea, vomiting or bilious vomiting, anal defecation, and dehydration or malnutrition were among the symptoms reported by the patients. Also, 68.25% of the cases reported chronic

Table 1 The information of reviewed cases about primary encapsulating peritoneal sclerosis

Aspects of case description		Male, n = 49	Female, n = 14	Frequency as %, Z, χ^2	
Age		R (7-82), M = 45.5	R (12-64), M = 38	Z = 4.833	
Duration of symptoms	> 2 mo	37	6	68.25	χ^2 = 8.625, P < 0.01
	< 2 mo	3	0	4.76	
	≤ 1 mo	9	8	26.98	
Sign of peritonitis	Not mentioned	12	5	26.98	χ^2 = 0.484, P > 0.5
	Soft	12	4	25.40	
	Tenderness	23	4	42.86	
	Rebound tenderness	2	1	4.76	
Abdominal mass		15	7	34.92	
Ascites		2	3	7.94	
Classification	Not mentioned	2	1	4.76	χ^2 = 9.422, P < 0.01
	Type I	13	2	23.81	
	Type II	26	5	49.21	
	Type III	8	6	22.22	
Lack greater omentum		6	0	9.52	
Operation	Non surgery	2	1	4.76	χ^2 = 12.21, P < 0.01
	Laparotomy	1	4	7.94	
	Dissection + adhesionlysis	39	9	76.19	
	Partial resection	7	0	11.11	
Histopathology (of the membrane)		30	4	53.97	
Curative effect	Not mentioned	4	1	7.94	χ^2 = 0.635, P > 0.5
	Uneventful recover	37	11	76.19	
	Prolonged recover	6	2	12.70	
	Leakage	2	0	3.17	

Dissection: Dissection of membrane; Not mentioned: Not mentioned in the report; Partial resection: Partial resection of small intestine.

symptoms, with the duration of the syndrome being more than 2 mo. Moreover, there were significant differences in the distribution of symptoms between male and female patients, with female patients exhibiting more acute symptoms. There were only 4.76% of the cases with the peritonitis symptom of rebound tenderness. Abdominal mass was palpable in 34.92% of cases, and only five patients (7.94%) were noted with ascites.

The intraoperative findings were analyzed and the cases were divided into the following three types according to the classification of primary EPS[8,9]: Type I: A segment of the small intestine is wrapped by a fibrous capsule; Type II: All intestines are encapsulated by fibers; and Type III: All small intestines and other organs are encapsulated by fibers. Type III and II EPS were more common in females than males, while only three male patients were noted with the absence of greater omentum. Nonoperative treatment was performed in three patients; exploratory surgery was performed in five patients; dissection of membrane and adhesiolysis was performed successfully in 76.19% of patients, and the partial resection of the small intestine was performed only in seven patients (11.11%).

The pathological description data were available for 53% of the cases. Most of the cases were pathologically reported as fibroconnective tissue proliferation with chronic inflammatory infiltration. Most of the patients (76.19%) recovered eventually, except for two patients who developed anastomotic leakage after partial resection of the intestine.

Discussion

The conditions of intestinal membrane encapsulation have been described using a variety of terms. Akbulut[9] emphasized the correct usage of terms, such as peritoneal encapsulation (PE), abdominal cocoon, idiopathic EPS, and secondary EPS. PE is a rare congenital anomaly characterized by an accessory peritoneal membrane derived from the yolk sac peritoneum in the early stages of fetal life [62]; it is not the consequence of chronic inflammation. Unlike PE, EPS is an acquired disease and is associated with chronic peritoneal inflammation that might be provoked by various factors[63]. Depending on the underlying triggering factors and the properties of the fibrocollagenous membrane, EPS can be classified as primary (idiopathic) or secondary[64]. The primary form (EPS of unknown origin) is also known as an abdominal cocoon and was first described by Foo *et al*[8] in 1978.

Primary EPS was thought to be present in tropical and subtropical areas, leading to theories of gynecologic infection or retrograde menstruation as the cause[65]. Although several studies have confirmed the equatorial predilection of primary EPS, men are more vulnerable to EPS than women [66]; however, female patients are younger than men when they develop symptoms.

The diagnosis of EPS was based on clinical manifestations and imaging findings, and most patients were diagnosed during explorative laparotomy. Recurrent intestinal obstructions characterize the clinical manifestation of primary EPS. In a large case series of primary EPS, the average duration of symptoms was 3.9 years before malnourishment symptoms developed[66]. In our study, 68.25% of the patients had a history of recurrent intestinal obstructions for more than 3 mo. While some patients with idiopathic EPS had no symptoms, the majority had abdominal pain, distention, nausea, vomiting or bilious vomiting, constipation, appetite loss, weight loss, dehydration, and malnutrition.

In this study, the physical examination of EPS patients revealed a higher occurrence of mild tenderness (42.86%) compared to rebound tenderness. The abdominal mass was palpable in 34.9% of patients, which is inconsistent with the literature report[8]. This may be due to the difference in case selection methods. Massive ascites was rare and did not seem to indicate a serious condition. There were five patients with massive ascites in the reports reviewed; one case improved by paracentesis, and four cases reported an uneventful recovery after the operation. Bloody ascites was rarer but found in both male (n = 15) and female (n = 21) patients, which questions theories of retrograde menstruation. Therefore, there may be a different cause for the massive bloody ascites in patients with primary EPS.

Blood tests did not report abnormal values, except for some patients with dehydration, electrolyte disorder, and malnutrition. The various imaging tools available for diagnosing EPS are erect abdominal X-ray, ultrasonography, barium meal, and CT or CECT. The air-fluid levels of dilated small bowel of EPS patients are visible in erect abdominal X-rays but are non-specific[28]. Ultrasound may show peritoneal thickening, ascites, and dilated bowel loops enclosed within a membrane; barium meal studies of the small intestine are useful in detecting clumped small bowel loops in the abdomen, which is also known as the cauliflower sign. CT or CECT may be the first choice for preoperative diagnosis of idiopathic EPS by providing the following image features: (1) Thickened jejunal and ileal loops encased in a thick fibrocollagenous membrane[27]; (2) "cauliflower-like" sign[67] or abdominal cystic masses with intestines freely floating in the fluid; and (3) "bottle gourd" sign[29] or dilated duodenum in patients with abdominal cocoon due to jejunal obstruction. Out of these, feature one is more common and specific.

Although the diagnosis of primary EPS is facilitated by the patient`s past history, existing symptoms, physical signs, radiological imaging, and above all, high-level clinical suspicion are major factors contributing to proper detection of the disease[47]. In this study, the preoperative diagnosis rate of primary EPS was low, and most patients were diagnosed in exploratively laparotomy or laparoscopy [11,17].

Presently, the management strategy of secondary EPS associated with PD is well established. However, very few reports suggest the surgical timing for patients who are non-surgically diagnosed with idiopathic EPS. Whether non-surgical management, such as tamoxifen, is efficacious for idiopathic EPS[15]. Célicout *et al*[68] believed non-surgical treatment is required in ascites and subacute intestinal obstruction.

Primary EPS could be categorized into three types according to the extent of bowel encapsulated by the membrane. Type II refers to all types of intestines encapsulated by a membrane and is the most common. In this study, the greater omentum was absent in six male patients[17,18,32,41,56,59], with age ranging from 19 years to 69 years. These cases may be diagnosed as PE or primary EPS, as both are accompanied by embryonic abnormalities[58], such as the absence of greater omentum or greater omentum dysplasia.

Dissection of membrane and adhesiolysis should be performed to all encased intestinal segments by concentrating on the following tips: (1) operate softly and lightly to avoid damaging the bowel and causing iatrogenic bowel perforation[46,54]; (2) resection of the intestine should be performed only when the bowel is nonviable; (3) anastomosis should not be the primary choice as it may increase the incidence of anastomotic leakage[25,47,68]; (4) prophylactic appendectomy is worth recommending because it is difficult to surgically treat acute appendicitis that may occur later[41]; (5) in order to reduce the complication of postoperative adhesive intestinal obstruction, it is recommended that nasointestinal obstruction tube should be installed during the operation[32]; and (6) application of an anti-adhesive substance may help prevent the patients from developing early postoperative small bowel obstruction [41,54].

Thirty-four reports describe the pathological features of the cases. The characteristic histopathological features were fibrocollagenous tissue proliferation, moderate chronic inflammatory infiltrate, and lymphatic endothelial cells[10,14,20]; some cases were accompanied by calcification[30] and hyalinization[36].

Of the 63 cases we reviewed, three patients were discharged after non-surgical treatment, five patients underwent exploratory laparotomy only, while membrane dissection and adhesiolysis were successfully performed on 76.19% of cases. Partial resection of the small bowel was performed for seven cases, two of which developed leakage, resulting in one death[47]. Early postoperative small bowel obstruction[59] was common and difficult to manage, leading to the delayed recovery of eight cases. Total parenteral nutrition with complete gastrointestinal rest was proposed[69], while reoperation was recommended. Other complications, such as poorly healed incision[21], were the cause of the prolonged recovery of one case. However, in general, the surgical effect of primary EPS seems optimistic, which is in contrast with that of secondary EPS associated PD[70].

CONCLUSION

Owing to the uncommon nature of primary EPS, its etiology, pathogenesis, and treatment strategies remain unclear. This paper presents a case of non-surgically diagnosed primary EPS, treated with paracentesis, and her CT scan with and without ascites. Recurrent intestinal obstructions and abdominal mass combined with the imaging of encapsulated bowel help diagnose primary EPS. The surgical effect of excision of membrane and adhesiolysis seems optimistic; however, small intestinal resection should be avoided as it could lead to anastomotic leakage. Elective abdominal exploration might decrease the complications of primary EPS patients with the recurrent syndrome, but further research is required to substantiate this.

FOOTNOTES

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CASE REPORT

Laparoscopic-assisted endoscopic full-thickness resection of a large gastric schwannoma: A case report

Cheng-Hai He, Shi-Hua Lin, Zhen Chen, Wei-Min Li, Chun-Yan Weng, Yun Guo, Guo-Dong Li

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Abstract

BACKGROUND

Schwannomas, also known as neurinomas, are benign tumors derived from Schwann cells. Gastrointestinal schwannomas are rare and are most frequently reported in the stomach. They are usually asymptomatic and are difficult to diagnose preoperatively; however, endoscopy and imaging modalities can provide beneficial preliminary diagnostic data. There are various surgical options for management. Here, we present a case of a large gastric schwannoma (GS) managed by combined laparoscopic and endoscopic surgery.

CASE SUMMARY

A 28-year-old woman presented with a 2-mo history of epigastric discomfort and a feeling of abdominal fullness. On upper gastrointestinal endoscopy and endoscopic ultrasonography, a hypoechogenic submucosal mass was detected in the gastric antrum: It emerged from the muscularis propria and projected intraluminally. Computed tomography showed a nodular lesion (4 cm × 3.5 cm), which exhibited uniform enhancement, on the gastric antrum wall. Based on these findings, a preliminary diagnosis of gastrointestinal stromal tumor was established, with schwannoma as a differential. Considering the large tumor size, we planned to perform endoscopic resection and to convert to laparoscopic treatment, if necessary. Eventually, the patient underwent combined laparoscopic and gastroscopic surgery. Immunohistochemically, the resected specimen showed positivity for S-100 and negativity for desmin, DOG-1, α-smooth muscle actin, CD34, CD117, and p53. The Ki-67 index was 3%, and a final diagnosis of GS was established.

CONCLUSION

Combined laparoscopic and endoscopic surgery is a minimally invasive and effective treatment option for large GSs.

Key Words: Gastric schwannoma; Laparoscopy; Gastroscopy; Immunohistochemical staining; Operation method; Case report

Core Tip: Gastric schwannomas (GSs) do not have specific clinical and endoscopic characteristics. Therefore, preoperative diagnosis may be difficult, and they can be misdiagnosed as gastrointestinal stromal tumors. In addition, while laparoscopic resection is possible, it is difficult to determine the location of intraluminal tumors. In contrast, endoscopic resection is only suitable for small submucosal tumors. Here, we present a case of a GS excised using laparoscopic-gastroscopic cooperative surgery. Additionally, we performed a literature review on computed tomography findings and surgical interventions used in the management of gastrointestinal stromal tumors and GSs.

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INTRODUCTION

Schwannomas are neurogenic tumors that emerge from Schwann cells. The most common site of a gastric schwannoma (GS) is the stomach, followed by the colon and rectum[1]. They usually arise from the muscular layer, with no specific clinical and endoscopic characteristics, and can frequently be misdiagnosed as gastrointestinal stromal tumors (GISTs), which are more common[2].

A GS can be managed by various surgical options, which have their advantages and disadvantages. Here, we report a case of a GS that was resected using combined gastroscopic and laparoscopic surgery.

CASE PRESENTATION

Chief complaints

A 28-year-old woman presented with a 2-mo history of epigastric discomfort and a feeling of abdominal fullness.

History of present illness

Two months before presentation, the patient developed epigastric discomfort, which was accompanied by a sensation of abdominal fullness. She did not experience abdominal pain, melena, and vomiting and exhibited no other symptoms of discomfort.

History of past illness

The patient was a non-smoker and did not drink alcohol. She reported no known food or drug allergies. Additionally, she had no history of blood transfusion or prior surgical procedure.

Personal and family history

The patient reported no significant family history.

Physical examination

Clinical data on admission were as follows: Body temperature, 36 °C; blood pressure, 120/84 mmHg; heart rate, 80 beats/min; and respiratory rate, 16 breaths/min. The abdomen appeared flat and soft, and the patient did not experience any abdominal tenderness or rebound pain.

Laboratory examinations

Routine blood tests, liver and kidney function tests, and electrolyte assay revealed no marked irregularities, and tumor markers were also negative.

Imaging examinations

On upper gastrointestinal (GI) endoscopy and endoscopic ultrasonography (EUS), we detected a hypoechogenic submucosal mass, which arose from the muscularis propria and projected into the lumen, in the gastric antrum (Figure 1). Computed tomography (CT) images revealed a nodular lesion (4.5 cm × 4 cm) showing homogeneous enhancement on the gastric antrum wall (Figure 2).

Initial diagnosis

A working diagnosis of GIST was established, with schwannoma as a differential.

FINAL DIAGNOSIS

Histopathological examination confirmed that the tumor was localized within the gastric muscularis propria. The tumor was well circumscribed and comprised fusiform cells. Immunohistochemically, it showed S-100 (+), 3% Ki-67 index, desmin (-), DOG-1 (-), α-smooth muscle actin (-), CD34 (-), CD117 (-), and P53 (-). Accordingly, a final diagnosis of a GS was established (Figure 3).

TREATMENT

First, endoscopic resection was performed: Endoscopic full-thickness resection (EFTR) was conducted under general anesthesia with endotracheal intubation. A smooth submucosal lesion measuring 5 cm in diameter was observed on the anterior wall of the gastric antrum. We marked the edge of the lesion, injected a solution of methylene blue and saline into the mucosa, and subsequently excised the tumor gradually using a hook knife. Bleeding was minimal and easily controlled with electric hemostatic forceps. Following a successful EFTR, a large full-thickness defect was left on the gastric wall. A supplementary laparoscopic surgery was conducted considering the large defect size and difficulties with endoscopic closure and tumor extraction *via* the esophagus. The patient was placed in a supine position, and a tiny arc-shaped incision was made under the umbilicus. Next, the abdominal cavity was punctured using a pneumoperitoneum (PP) needle and filled with CO_2 gas to generate a peak pressure of 1.59 kPa. The PP needle was then removed. Subsequently, a cannula needle was used to puncture the abdominal cavity. The inner core of the cannula was removed, and the needle was placed into a laparoscope. Two trocar punctures were made on the left and right sides of the abdomen using the open technique. A defect measuring 5.5 cm × 5 cm was detected on the anterior wall of the gastric antrum, approximately 2 cm from the pylorus, and surrounded by small amounts of bloody fluid. The large excised tumor measuring 5 cm × 4 cm dropped into the abdominal cavity and was placed in an extraction pouch, which was subsequently removed *via* the main surgical incision. The edge of the defect on the stomach wall was trimmed using an ultrasonic knife. Subsequently, the wound was closed with a 3-0 slippery thread. Finally, we confirmed the absence of bleeding in the abdominal cavity, extracted the laparoscope, checked for appropriate retrieval of all instruments and gauze, and closed the incision and puncture sites with silk thread.

OUTCOME AND FOLLOW-UP

The patient recovered fully and was discharged on postoperative day 7, and a check-up was performed 3 mo after the surgery. Gastroscopy showed an improvement in the healing of the gastric wall. Figure 4 illustrates the timeline of the clinical course of the patient.

DISCUSSION

GI mesenchymal tumors comprise a wide range of spindle cell tumors, including GISTs, leiomyomas, leiomyosarcomas, and schwannomas[3]. Furthermore, schwannomas are spindle cell mesenchymal tumors that originate from Schwann cells. GSs originate from the gastrointestinal neural plexus. Most GSs are benign, and only a few malignant cases have been reported in the literature[4,5]. Schwannomas are generally asymptomatic in affected patients; however, they may cause abdominal discomfort, pain, or digestive symptoms in some cases. A palpable mass may be detected if the tumor is large and exophytic. Dysphagia and obstipation are possible symptoms when the lesions originate from the

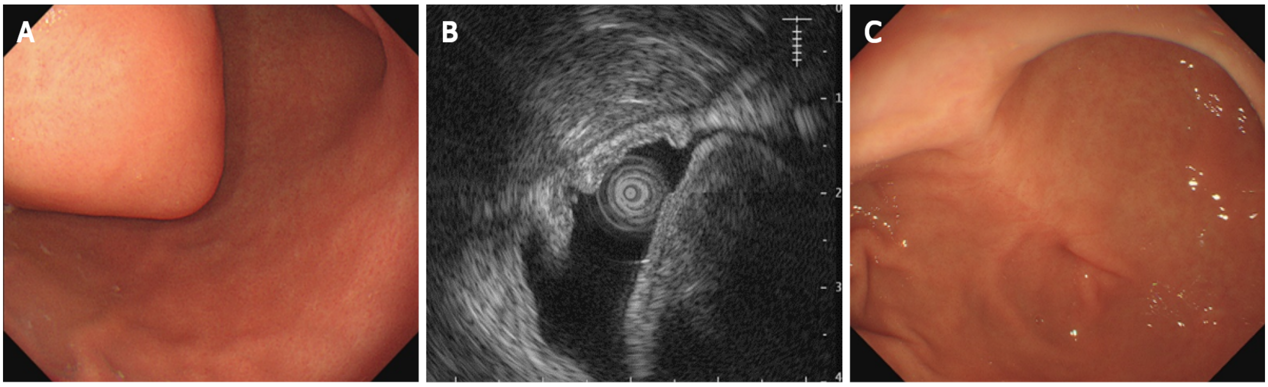

Figure 1 Preoperative endoscopy and endoscopic ultrasonography. A: Upper digestive tract endoscopy showing a submucosal tumor along the greater curvature of the anterior gastric antrum wall; B: Endoscopic ultrasonography showing a mass within the gastric antrum, which originated from the muscularis propria; C: Gastroscopy 3 mo after surgery revealing appropriate incision healing.

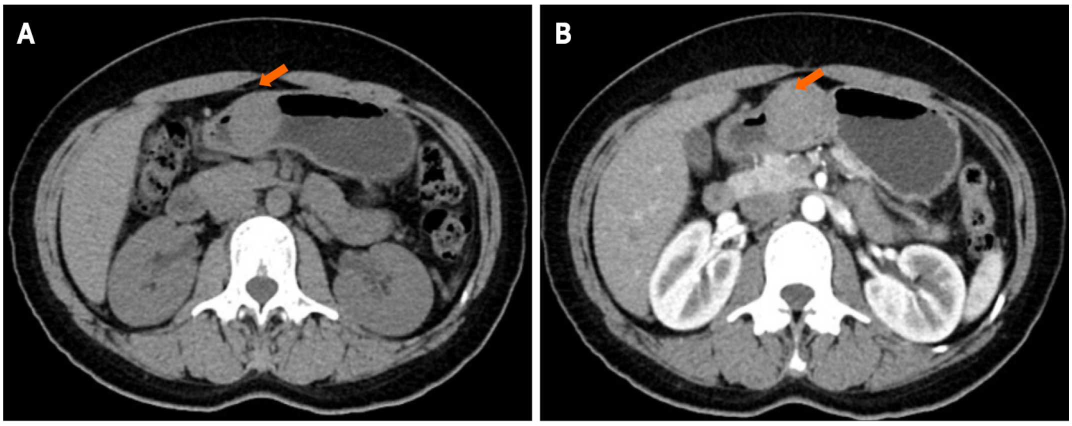

Figure 2 Computed tomography scan. A: Computed tomography showing an oval mass in the antrum of the stomach, with intracavitary growth; B: Enhanced computed tomography shows obvious enhancement of the mass in the arterial phase.

esophagus or rectum, respectively. Bleeding may occur if deep ulcerations are present[6,7].

GISTs are the most prevalent mesenchymal tumors of the GI tract, and 60%–70% of cases occur in the stomach. They are similar to GSs in terms of age of onset, clinical manifestations, and gross and histological appearance; however, the prognoses differ. Generally, schwannomas are mostly benign and have a good prognosis, while 10%–30% of cases of GIST are malignant[3]. Therefore, it is essential to distinguish between a GS and GIST and to develop a targeted treatment plan. The diagnostic workup for gastric tumors mainly includes upper GI endoscopy, CT, magnetic resonance imaging, and intracavitary (endoscopic) ultrasound. On endoscopy, both GS and GIST present as elevated submucosal lesions with a firm consistency. On EUS, a GS usually shows a hypoechogenic lesion originating from the muscularis propria[8]. Reports on EUS assessment show that round shape, definite borders, heterogeneous hypoechogenicity or isoechogenicity, and lack of cystic alteration and calcification are crucial markers for GS diagnosis. In contrast, on EUS, a GIST usually shows a hypoechoic or anechoic and slightly heterogeneous tumor. Hyperechogenicity is a potential sign of malignancy. GISTs are usually observed in the third or fourth layer of the gastric wall and rarely in the second layer[8]. Unlike GISTs, on CT, schwannomas appear to be uniform, significantly contrast-enhancing tumors with no evidence of hemorrhage, necrosis, cystic alteration, or calcification[9]. Despite these differences, establishing accurate preoperative diagnoses of GSs and GISTs is challenging.

In this patient, the tumor was detected on abdominal CT and was initially thought to be a GIST. Gastroscopic and EUS findings were not contradictory; therefore, the tumor was misdiagnosed as a GIST until a correct diagnosis was established based on the tumor's immunohistochemical profile.

A GS rarely presents with specific clinical features and imaging characteristics. Therefore, preoperative diagnosis is challenging, and definitive diagnosis can only be established after careful pathological examination of the resected specimen. Given these challenges, surgical resection is the optimal treatment approach. Local extirpation, wedge resection, and partial, subtotal, or total

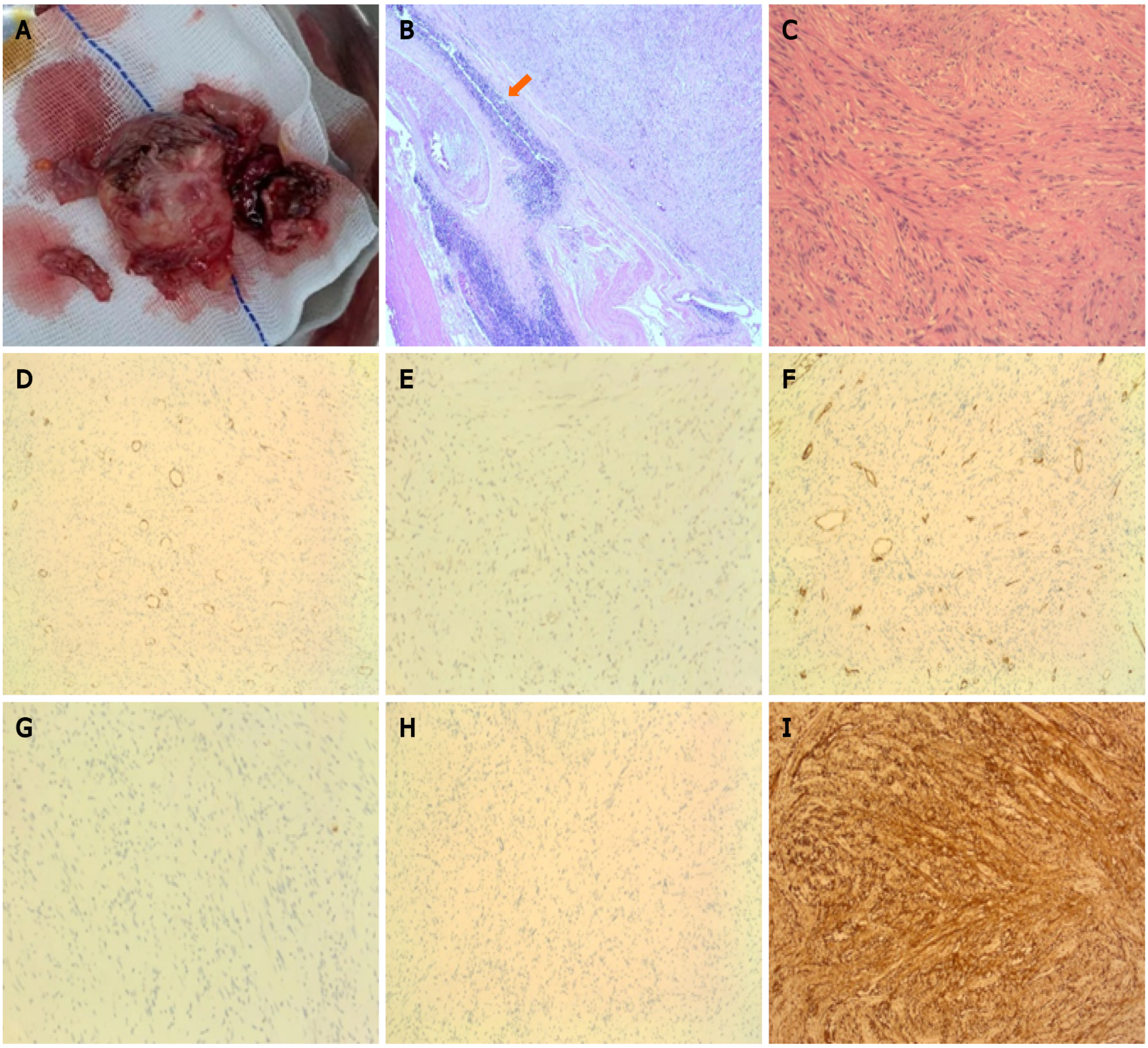

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Figure 3 Specimen after surgery, hematoxylin and eosin-stained pathological sections, and immunohistochemistry. A: The resected tumor; B and C: The tumor comprises intertwined bundles of spindle cells with tapered nuclei; mitotic figures are rare. Lymphocyte infiltration is observed in the tumor tissue, and a characteristic peripheral lymphoid cuff is present (B: 4 × C: 20 ×); D-I: Immunohistochemical staining of the gastric mass confirming a gastric schwannoma with positive staining for S-100 protein (I) and negative staining for α-smooth muscle actin (D), DOG-1 (E), CD34 (F), CD117 (G), and desmin (H).

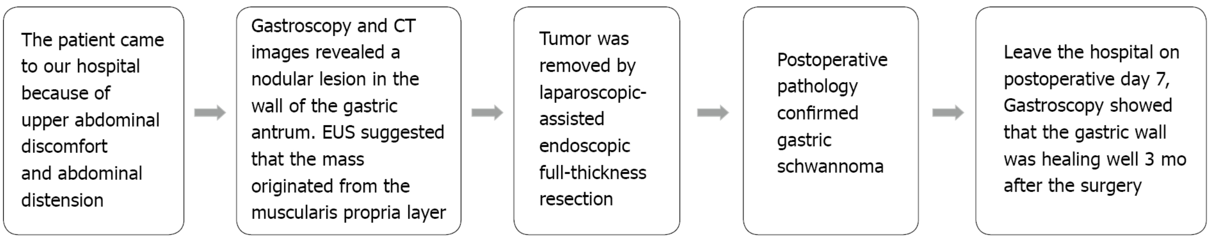

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Figure 4 Timeline of case occurrence. CT: Computed tomography; EUS: Endoscopic ultrasonography.

gastrectomy are all acceptable approaches. Laparoscopic techniques can also be employed[10].

Submucosal gastric tumor therapies have greatly advanced in recent years, thereby enabling a more frequent use of minimally invasive endoscopic techniques, such as snare polypectomy, endoscopic submucosal dissection, and EFTR. Some studies have shown that EFTR is safe and effective for schwannomas and other tumors originating from the muscularis propria[11,12]. However, for larger

Table 1 Literature review of laparoscopic endoscopic cooperative surgery for gastric schwannoma resection

Ref.	Gender	Age (yr)	No. of cases	Tumor size (cm)	Pathology	Treatment	Hospital stay (d)
Eom *et al*[16]	3 Males; 11 Females	Median 61.0 IQR (51.0–66.8)	14	Median 2.6 IQR (2.3–3.7)	9 GISTs, 2 GS, 3 Leiomyomas	LECS	Median 5.0 IQR (4.0– 5.5)
Mahawongkajit *et al*[17]	Female	50	1	2.1	GS	NEWs	NR
Sugiyama *et al*[18]	Female	49	1	1.7	GS	NEWS	5
Matsuda *et al*[19]	47 Males; 53 Females	mean ± SD: 59.8 ± 13.2	100	mean ± SD: 3.09 ± 1.06	75 GISTs; 11 GS; 6 Leiomyomas; 5 Ectopic pancreas; 2 Neuroendocrine tumor; 1 Lymphangioma	LECS	mean ± SD: 8.4 ± 10.2
Mitsui *et al*[15]	Males	58	1	2.4 × 2.3 × 1.9	GS	NEWS	7
Hiki *et al*[13]	7 Females	Range 34–66	7	mean ± SD: 4.6 ± 0.3	6 GISTs 1 GS	LECS	mean ± SD: 7.4 ± 8.1

LECS: Laparoscopy-endoscopy cooperative surgery; NEWS: Non-exposed endoscopic wall-inversion surgery; GISTs: Gastrointestinal stromal tumors; GS: Gastric schwannoma; NR: Not reported; IQR: Interquartile range.

GSs, endoscopic resection should not be indicated without careful consideration because we believe that this could increase the risk of surgery and the incidence of postoperative complications.

Although laparoscopic resection can be used to treat GSs, it is difficult to precisely locate tumors within the gastric lumen with a laparoscope from the serosal surface alone. Consequently, a large portion of the stomach wall may be removed, leading to gastric deformity and outlet obstruction. Laparoscopic endoscopic cooperative surgery (LECS) was first introduced by Hiki *et al*[13] as a surgical intervention for GISTs and is currently classified as "classical LECS." LECS is superior to laparoscopic or robot-assisted wedge resection and partial resection because the gastric serosa resection area is substantially reduced, which lowers the possibility of post-surgical gastric deformity and reduces the negative impact on patients' quality of life[14]. Subsequently, Mitsui *et al*[15] developed another non-exposure technique, known as "non-exposure endoscopic wall-inversion surgery" (NEWS), that can prevent contamination and tumor dissemination into the peritoneal cavity. Only a few studies[13,15-19] have previously reported GS resection using LECS and NEWS (Table 1). Shoji *et al*[20] reported that LECS or NEWS is suitable for submucosal tumors measuring less than 5 cm in diameter. In this case, because the diameter of the gastric tumor reached 5 cm, we considered that endoscopic treatment alone might be complicated by difficulties in closing the gastric wall defect after tumor excision and removing the specimen through the esophagus. Therefore, after discussing with the patient, we decided to remove the tumor endoscopically, and if difficulties arose, laparoscopy would be performed. Accordingly, we could excise the tumor completely without removing a large part of the gastric wall while causing minimal trauma and ensuring safety. The tumor was removed using a gastroscope. The large defect in the gastric wall after tumor resection was difficult to close; therefore, suturing was performed laparoscopically. This combined surgery resulted in complete tumor excision and prevented wound expansion. Although our procedure differed from classical LECS in terms of surgical details, the goal of treatment was still to achieve complete resection of the lesion and avoid the expansion of the incision. Postoperative patient management included gastric acid inhibition, fluid replacement, dietary restriction, and nutritional support. The patient was mobile on postoperative day 1. She recovered completely and was discharged from the hospital 1 wk after surgery. Considering the outcomes of this case, we believe that laparoscopic-assisted endoscopic full-thickness resection can reduce the risk of endoscopic surgery and simultaneously achieve precise resection of lesions, which should be evaluated in future studies.

CONCLUSION

GSs are uncommon and generally mostly benign. Despite advances in endoscopic and imaging techniques, accurate preoperative diagnosis of a GS is difficult to establish. Final diagnosis requires histopathological and immunohistochemical examinations. Surgical resection is the optimal treatment option, and the emergence of techniques, such as EFTR, has greatly increased the possibility of minimally invasive removal of small tumors. For larger GSs, combined laparoscopic and gastroscopic surgery is recommended for tumor resection.

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FOOTNOTES

Author contributions: He CH and Lin SH reviewed the literature and contributed to manuscript drafting; Li GD drafted the manuscript and revised manuscript; Chen Z performed the pathology analyses and interpretation and contributed to manuscript drafting; Li WM and Weng CY analyzed and interpreted the imaging findings; Li GD and Guo Y were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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LETTER TO THE EDITOR

Imaging of acute appendicitis: Advances

Sonay Aydın, Erdal Karavas, Düzgün Can Şenbil

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Abstract

We read with interest the review by Teng *et al*, who summarized the current approach to the diagnosis and treatment of acute appendicitis (AA). Also, the article summarizes the clinical scoring systems very effectively. In one of the previous studies conducted by our research group, we showed that the use of the Alvarado score, ultrasound and C-reactive protein values in combination provides a safe confirmation or exclusion of the diagnosis of AA. Computed tomography is particularly sensitive in detecting periappendiceal abscess, peritonitis and gangrenous changes. Computed tomography is not a good diagnostic tool in pediatric patients because of the ionizing radiation it produces. Ultrasound is a valuable diagnostic tool to differentiate AA from lymphoid hyperplasia. Presence of fluid collection in the periappendiceal and lamina propria thickness less than 1 mm are the most effective parameters in differentiating appendicitis from lymphoid hyperplasia. Although AA is the most common cause of surgical acute abdomen, it remains an important diagnostic and clinical challenge. By combining clinical scoring systems, laboratory data and appropriate imaging methods, diagnostic accuracy and adherence to treatment can be increased. Lymphoid hyperplasia and perforated appendicitis present significant diagnostic challenges in children. Additional ultrasound findings are increasingly defined to differentiate AA from these conditions.

Key Words: Acute appendicitis; Inflammation; Acute abdomen; Perforation

Core Tip: Despite the fact that acute appendicitis is the most common cause of acute abdomen, it remains a diagnostic and clinical challenge. When the ultrasound, Alvarado scoring and C-reactive protein are used in conjunction to diagnose acute appendicitis, the diagnosis can be safely confirmed or ruled out. Computed tomography scans are extremely sensitive in detecting complications from acute appendicitis. Computed tomography scans are especially effective at detecting periappendix abscesses, peritonitis and gangrenous changes. Because of the ionizing radiation it emits, computed tomography is not a good diagnostic tool in pediatric patients. In pediatric patients, ultrasound should be the preferred method.

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TO THE EDITOR

We read with interest the review by Teng *et al*[1], who summarized the current approach to the diagnosis and treatment of acute appendicitis (AA). Also, the article summarizes the clinical scoring systems very effectively.

In one of the published studies of our research group, we have shown that using the Alvarado score, ultrasound (US) and C-reactive protein (CRP) levels in combination enables the confirmation or rejection of AA safely[2]. The Alvarado scoring system is one of the most commonly used methods[1]. Even though the scoring system contains series of laboratory parameters, it does not contain CRP levels. Rather than using the Alvarado system or US alone, combining these methods with CRP levels will increase diagnostic accuracy.

Teng *et al*[1] stated that computerized tomography scans have a well-established role in evaluating AA-related complications. Computed tomography is especially sensitive for detecting periappendiceal abscess, peritonitis and gangrenous changes[1] (Figure 1). Pediatric patients are more likely to develop perforated appendicitis. Imaging is critical in diagnosing perforated appendicitis; clinical differentiation can be challenging, especially in younger children. Computed tomography is not a good diagnostic tool in pediatric patients due to the ionizing radiation it produces. According to our results, US can also be used as an effective diagnostic tool for the detection of pediatric perforated appendicitis cases. The most valuable US parameters are the detection of loculated fluid in the periappendiceal area and fluid collection in all abdominal recesses. When these parameters are combined with CRP levels, diagnostic performance can be improved[3].

Teng *et al*[1] emphasized that AA occurs when the appendiceal orifice is obstructed (for example, by lymphoid hyperplasia or fecaliths), resulting in inflammation. We have demonstrated that, in addition to causing AA, lymphoid hyperplasia can serve as a significant mimicker of AA by forming an incompressible appendix larger than 6 mm in diameter, particularly in pediatric patients. US is a valuable diagnostic tool for differentiating AA from lymphoid hyperplasia. The presence of periappendiceal fluid collection and a lamina propria thickness of less than 1 mm are the most effective parameters for differentiating appendicitis from lymphoid hyperplasia[4] (Figure 2).

The portal vein can be affected from appendiceal inflammation, and thrombosis might occur[1]. In addition to complications, according to our data, portal vein hemodynamic changes can help to confirm AA diagnosis in children. In equivocal cases, detecting an increase in portal vein diameter and/or flow velocity may corroborate other clinical signs of AA[5].

To summarize, AA remains a significant diagnostic and clinical challenge despite being the most common cause of surgical acute abdomen. By combining clinical scoring systems, laboratory data and appropriate imaging methods, diagnostic accuracy and treatment adherence can be increased. Lymphoid hyperplasia and perforated appendicitis present significant diagnostic challenges in children. Additional US findings are increasingly being defined for the purpose of distinguishing AA from these entities.

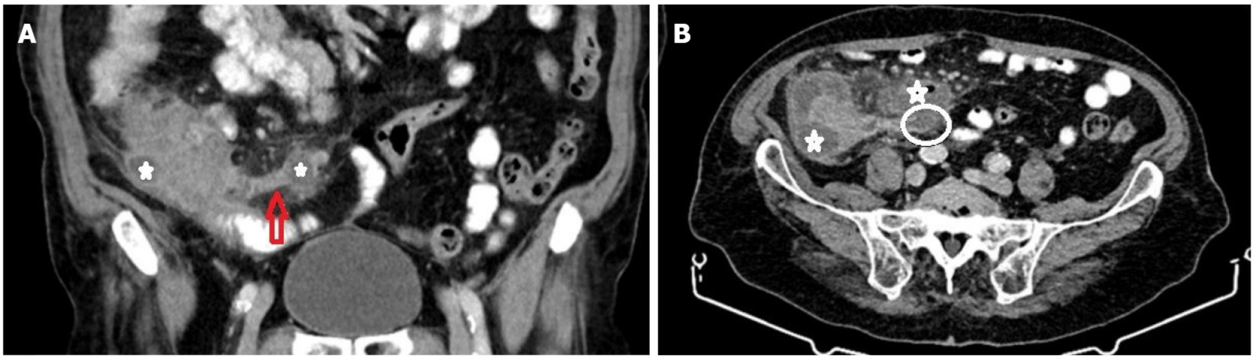

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Figure 1 An 87-yr-old male. Coronal (A) and axial (B) sections are shown. The appendix diameter has increased, and it appears inflamed (red arrow). The distal part of the appendix is perforated (white circle). Abscesses are seen in the periappendiceal and pericecal areas (white star).

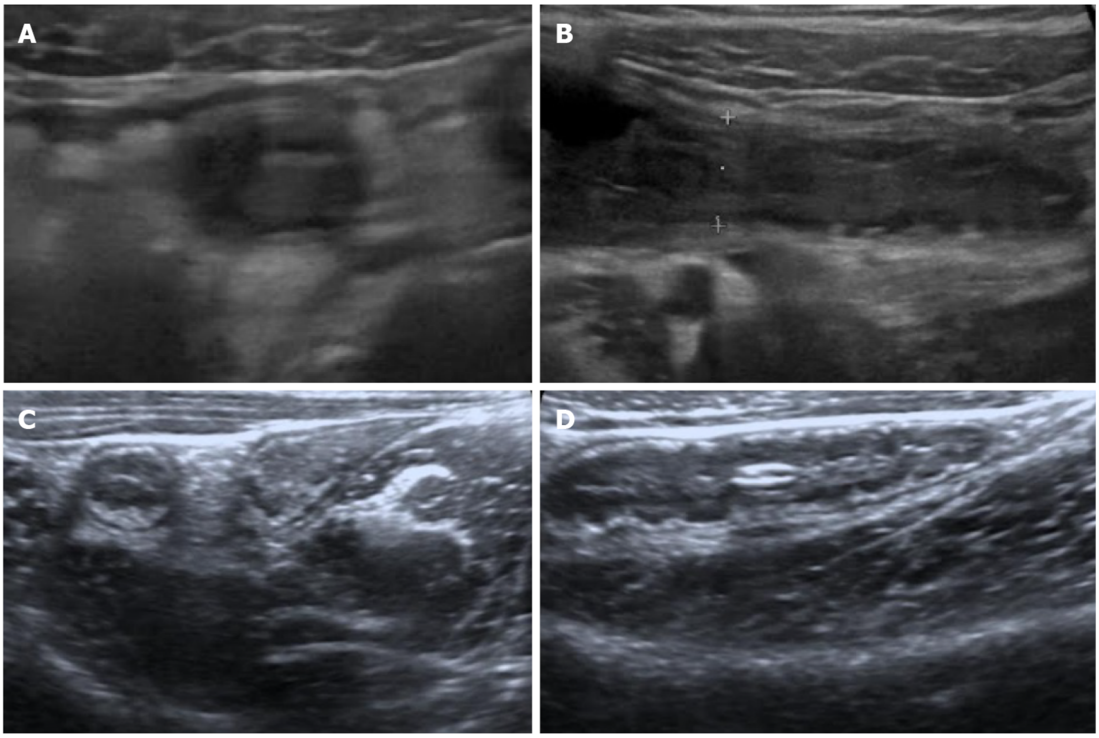

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Figure 2 Acute appendicitis in a 12-yr-old boy. A-B: Sonographic images taken axially (A) and longitudinally (B). The lamina propria is not discernible; C-D: For comparison, axial (C) and longitudinal (D) sonographic images of an 8-year-old girl with lymphoid hyperplasia. Note the prominent and thick lamina propria.

FOOTNOTES

Author contributions: Aydın S put forward the concept; Şenbil DC was responsible for designing; Karavas E provided resources; Aydın S and Karavas E were responsible for supervision, did the literature search and reviewed the manuscript critically; Şenbil DC and Aydın S were responsible for materials and wrote the manuscript; All authors have read and approved the final manuscript.

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