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REVIEW

Gastroesophageal reflux disease in children: What's new right now?

Palittiya Sintusek, Mohamed Mutalib, Nikhil Thapar

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Abstract

Gastroesophageal reflux (GER) in children is very common and refers to the involuntary passage of gastric contents into the esophagus. This is often physiological and managed conservatively. In contrast, GER disease (GERD) is a less common pathologic process causing troublesome symptoms, which may need medical management. Apart from abnormal transient relaxations of the lower esophageal sphincter, other factors that play a role in the pathogenesis of GERD include defects in esophageal mucosal defense, impaired esophageal and gastric motility and clearance, as well as anatomical defects of the lower esophageal reflux barrier such as hiatal hernia. The clinical manifestations of GERD in young children are varied and nonspecific prompting the necessity for careful diagnostic evaluation. Management should be targeted to the underlying aetiopathogenesis and to limit complications of GERD. The following review focuses on up-to-date information regarding of the pathogenesis, diagnostic evaluation and management of GERD in children.

Key Words: Gastroesophageal reflux; Gastroesophageal reflux disease; Children; Infant; Impedance study; Lower esophageal sphincter

Core Tip: Gastroesophageal reflux disease (GERD) is a pathologic process requiring prompt assessment and treatment. The manifestations of GERD, especially in young children vary making it a challenge to diagnose. Combined esophageal pH-MII manometry has increased the diagnostic accuracy of GERD and helped explain its pathogenesis. Medication should be targeted to the underlying GERD pathogenesis, if known, and to minimize complications.

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INTRODUCTION

A combined guideline of the European and the North American Societies for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN and NAPSPGHAN respectively)[1], defined gastroesophageal reflux (GER) as the passage of gastric contents into the esophagus with or without regurgitation and vomiting and GER disease (GERD) where GER leads to troublesome symptoms that affect daily functioning and/or leads to clinical complications within the esophagus or other systems. As the clinical symptoms and signs of GERD are variable and nonspecific especially in infants and young children, it is often difficult to make a diagnosis on the basis of history or physical examination alone. Furthermore, other significant disorders that mimic GERD may need urgent attention and will need to be considered and excluded.

EPIDEMIOLOGY

The prevalence of GERD varies across studies depending on the diagnostic criteria used and the study design. A systematic review published in 2019 demonstrated that the overall pooled prevalence of GERD symptoms from 4 cross-sectional studies, was 26.9% [95% confidence interval (CI) 20.1-33.7, I^2: 6.83][2]; However, the prevalence of GERD in infants, across a number of prospective studies, tends to decrease with time from 25.5%[3] at the age of 1 mo and 26.5%[4] at the age of 6 wk to 7.7%[4] at age 3 mo, 2.6%[4] and 2.9%[3] at the age of 6 mo to only 1.1%[4] and 1.6%[5] at the age of 12 mo. An explanation of this decline is described in the pathogenesis section below. The prevalence of GERD in Asia (8.7%) is comparable to both the United States (8.9%) and Europe (8.3%-32.0%). In children, there are a number of clinical conditions that clearly predispose to the development of GERD, which include corrected esophageal atresia[6], neurological impairment[7,8], prematurity[9-11], and cow's milk protein allergy[12-15]. In corrected esophageal atresia, for example, the prevalence of GERD diagnosed using impedance-pH monitoring and histopathology is high and up to 47.1% and 64.7%, respectively[6].

PATHOPHYSIOLOGY AND REFLUX-ASSOCIATED CONDITIONS

The main pathogenesis of GERD in children, as in adults, is abnormal transient lower esophageal sphincter relaxation (TLESR). Other factors implicated in the pathogenesis of GERD[16] include the anatomy and integrity of the antireflux barrier, as well as those affecting esophageal peristalsis and clearance (Table 1 and Figure 1).

Transient lower esophageal sphincter relaxation

The lower esophageal sphincter (LES) pressure tends to increase in infants with increasing gestational age[17-19]. In normality, LES relaxation follows swallowing or primary peristalsis of the esophagus. However, TLESR or a relaxation of the LES that is not preceded by swallowing can also occur leading to pathologic reflux. TLESR can be stimulated by increasing intraesophageal pressure as a result of crying, gastric distension and respiratory diseases. TLESR can be demonstrated in infants from the gestational age of 28 wks[18,19]. Interestingly, many studies have shown that TLESR do not occur more in patients with GERD compared to healthy persons[18,20]. Patients with GERD are more likely to have acid reflux compared to normal persons, which might explain this finding[21,22]. In addition, the failure of one or more of several protective mechanisms, detailed below, can also contribute to the pathogenesis of

Table 1 Summary of the pathogenesis of gastroesophageal reflux disease

Main underlying mechanism	Associated conditions	Mechanism of GERD
Anatomical defect	Hiatus hernia, immature esophageal anti-relux barrier, *e.g.*, infants, surgical pull up for esophageal atresia	Increased risk of GER
Esophageal or gastric hypomotility/dysmotility	Esophageal disorders associated with dysmotility, *e.g.*, esophageal atresia, achalasia, gastroparesis, cow's milk protein allergy, sleeping, decreased saliva secretion, supine position	Impaired esophageal clearance of refluxate by peristalsis and/or production of neutralizing secretions
Esophageal mucosal defect	Eosinophilic esophagitis, esophageal infection	Impaired esophageal sensation
UES dysfunction	Extraesophageal or respiratory manifestations	Allows refluxate to access airways

GERD: Gastroesophageal reflux disease; UES: Upper esophageal sphincter.

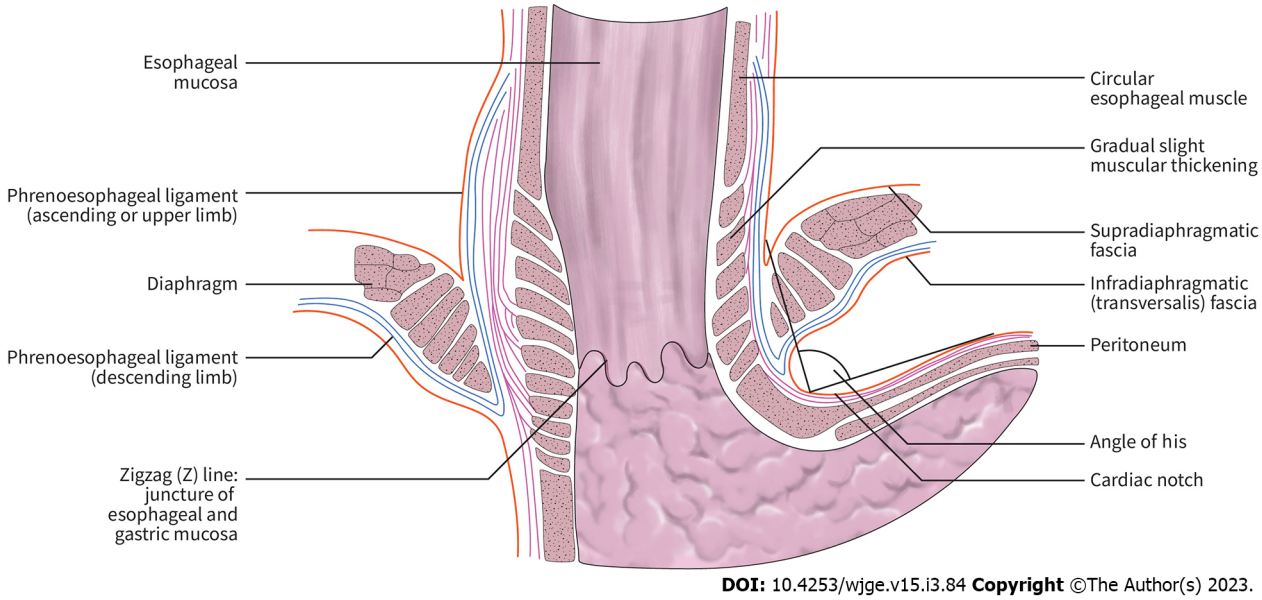

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Figure 1 The anatomical antireflux barrier of the esophagus.

GERD.

The anatomy of antireflux barrier

The antireflux barrier consists of the LES, the diaphragmatic pinchcock and angle of His (Figure 1). The LES a 1-2 cm high pressure zone located at the junction between the esophagus and the stomach and is comprised of intrinsic (lower esophageal muscle fibers) and extrinsic components (oblique sling muscle fibers from the stomach and musculofacial sling from the diaphragm). This is further supported by a short length of intra-abdominal esophagus as well as the angle of His or esophagogastric angle, the acute angle formed between the cardia and abdominal part of LES[23]. This composite anti-reflux barrier acts in normality as a physiologic sphincter between the high stomach (intra-abdominal) pressure compared to the lower pressure in the esophagus (intra-thoracic) and thus to prevent the regurgitation of gastric contents along the pressure gradient into the esophagus.

In infants, alongside TLESRs, underdevelopment of the abdominal part of the LES and angle of His are likely to explain the high prevalence of GERD in the infantile period[24,25]. Where a hiatal hernia is present in patients, the separation of the LES and the crural diaphragm acts to significantly impair the antireflux barrier and contribute to the increase in acid exposure of the esophagus and GERD.

Esophageal peristalsis and clearance

To prevent esophageal mucosal injury from the movement of gastric contents into esophagus after LES relaxation, secondary esophageal peristalsis with clearance of the refluxate back into the stomach is considered a main protective mechanism. Moreover, an upright position can further help volume clearance by gravity. Apart from mechanical clearance, the acid content of any refluxate can be neutralized by both swallowed saliva and esophageal secretions. In infants, volume clearance is less effective due to their mostly recumbent position. During sleep, the reduced frequency of primary and secondary esophageal peristalsis may contribute to precipitate GERD[1,16]. Any disorder that primarily

Table 2 The signs and symptoms of gastroesophageal reflux disease and alarm features of its most significant mimics

Symptoms	Signs	Red flags from other serious conditions that may underlie or mimic GERD
General	**General**	**General**
Irritability	Dental erosion, not dental caries (Figure 2)	Excessive irritability
Failure to thrive	Anemia	Weight loss
Feeding refusal		Fever
Sandifer syndrome		Lethargy
Gastrointestinal	**Gastrointestinal**	**Gastrointestinal**
Recurrent regurgitation	Esophagitis	Onset of regurgitation at > 6 mo of age
Recurrent vomiting	Esophageal stricture	Persistent or progressive regurgitation at > 1 yr of age
Heartburn	Barrett esophagus	Vomiting: Persistent forceful, nocturnal or bilious vomiting
Dysphagia/odynophagia		Hematemesis
Epigastric pain		Marked abdominal distension
Airway	**Airway**	**Neurological**
Difficult to treat wheezing	Apnea	Bulging fontanelle
Unexplained stridor	Recurrent pneumonia	Seizure
Chronic cough	Recurrent otitis media	Macro/microcephaly
Hoarseness of voice		Neurological abnormalities
		Papilledema

GERD: Gastroesophageal reflux disease.

(*e.g.*, esophageal atresia, achalasia) or secondarily (esophagitis) affects oesophageal motility may increase the predisposition to GERD[26-29]. Moreover, delayed gastric emptying or gastroparesis, often a transient phenomenon in children after infection, can cause postprandial reflux from gastric distension stimulating LES relaxation[30].

Others

Interestingly, a postprandial acid pocket phenomenon has been well described by Fletcher *et al*[31] They describe a floating "pocket" of an unbuffered reservoir of gastric acid that may become exposed to the esophagus during LES relaxation. The role of the acid pocket in the pathogenesis of GERD has been reported but limited to adult studies[32,33].

In addition, esophageal mucosal defense may be compromised in a number of conditions such as esophagitis from eosinophilic or other inflammatory diseases as well as infections. A defect in esophageal mucosal defense can lead to esophageal dysmotility and reflux esophagitis can be superimposed. As the esophageal mucosa contains receptors sensitive to acid, temperature and volume, their destruction in severe esophagitis might explain the hyposensitivity with reflux injury in children with Barrett esophagus and corrected esophageal atresia[34]. A high index of suspicion and intensive evaluation and monitoring, including with histopathology of esophagus, are needed in such patients.

In extraesophageal manifestation of GERD, such as upper airway diseases or ENT problems, there are many proposed pathways such as GER induced vagally mediated aspiration or insufficiency of upper esophageal sphincter (UES) function[24,34-38].

CLINICAL MANIFESTATIONS

The manifestations of GERD can vary from an asymptomatic presentation or non-specific symptoms such as irritability in infants, frequent vomiting, failure to thrive, unexplained anemia, difficult to treat respiratory symptoms through to more specific ones such as heartburn in older children. However, a high index of suspicion or the presence of alarm features, may require early investigation to either exclude other mimickers or confirm the diagnosis of GERD (Table 2).

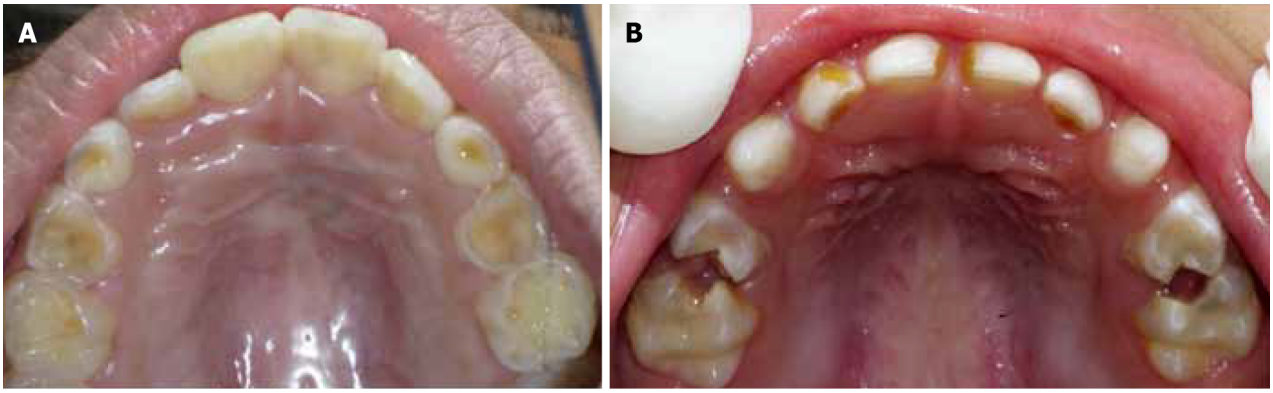

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Figure 2 Characteristics of dental erosion in a child with corrected esophageal atresia compared to dental caries in a healthy child. A: Characteristics of dental erosion on the occlusal and palatal surface of deciduous teeth; B: Characteristics of dental caries on deciduous teeth.

INVESTIGATION

There has been no single gold standard tool to diagnose GERD in children. In practice, therapeutic trials of medication and follow-up can be considered in older children with a typical presentation of GERD such as heartburn but these may not reliable in infants[39]. If there is no response after an 8-week trial of PPI or in the presence of alarm features, investigations are necessary to confirm or rule out GERD. The major limitation of all diagnostic tools is that the normal values for each parameter are not well established in infants and children. A number of investigations have been used to distinguish GERD from other worrisome disorders that mimic GERD.

Ultrasound

Ultrasound has high sensitivity and positive predictive value for GERD as it can assess both the anatomy of the esophagus and real-time reflux. It is a non-invasive tool with some evidence-based studies supporting its fair sensitivity (76%-100%) and specificity (50%-100%) compared to pH studies [40-43]. A study noted the presence of a shorter abdominal esophageal length, increased cervical and abdominal esophageal wall thickness, diameter and angle of His in Thai children diagnosed with GERD (n = 22, median age of 1.6 years) compared with healthy children (n = 23), however, these differences failed to reach statistical significance[44] (Figure 3). Moreover, the reliability of the test depends on the individual experience of the radiologist[45].

Barium (contrast) swallow and upper gastrointestinal studies

Barium (contrast) swallow and upper gastrointestinal studies (meal ± follow through) are used to evaluate anatomical abnormalities of esophagus, stomach and proximal small bowel such as tracheoesophageal fistula, achalasia, hiatus hernia, midgut malrotation ± intermittent volvulus. Furthermore, the barium study can roughly evaluate the transit time of esophagus and stomach but lacks standardized protocols and normal values. Although, episodes of reflux are commonly observed during these procedures, there is poor correlation with an abnormal reflux index from a 24-h pH study[46]. Overall, such contrast studies are neither sensitive nor specific tests for GER or GERD and should not be used for diagnosis.

Endoscopy

Endoscopy is generally utilized where esophagitis is suspected in patients with significant clinical issues such as recurrent vomiting, unexplained anemia, hematemesis, positive stool occult blood or high-risk groups (corrected esophageal atresia, eosinophilic esophagitis, immunocompromised hosts that are prone to have esophageal infection). Eosinophilic esophagitis and eosinophilic gastrointestinal disease can present with symptoms and signs similar to that of GERD and its diagnosis requires histopathology of esophageal tissue (Figure 4). Clinicians should be aware that severe esophagitis in GERD rarely presents with pain[34] and there is a poor correlation between the severity of symptoms and presence or severity of esophagitis. In children with extraesophageal symptoms such as cough and wheezing, up to one third had microscopic esophagitis[47], suggesting endoscopy may also have a role in children with extraesophageal symptoms.

pH-monitoring, combined MII-pH monitoring test and combined Video-MII-pH monitoring test

The pH-monitoring test has largely been replaced with MII-pH monitoring that can provide more data not only of acid reflux but also of other types (weakly acid, nonacid, liquid or air) as well as the

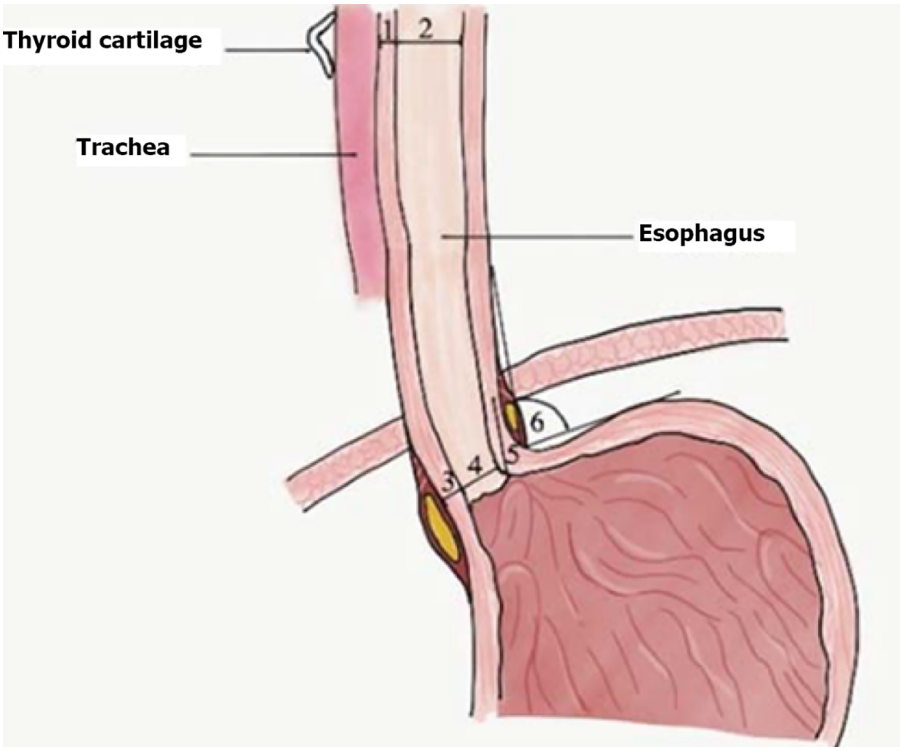

Figure 3 Landmarks of the esophagus and stomach measured by ultrasonography in the study of Charoenwat *et al*[44]. 1: Cervical esophageal thickness; 2: Cervical esophageal diameter; 3: Abdominal esophageal thickness; 4: Abdominal esophageal diameter; 5: Abdominal esophageal length; 6: Angle of His. Citation: Charoenwat B, Sintusek P, Chaijitraruch N, Mahayosnond A, Suksri S, Patcharatrakul T, Chongsrisawat V. Transcutaneous esophageal ultrasonography in children with suspected gastroesophageal reflux disease. *J Med Asso Thai* 2018; 101: S1-S745[44]. Copyright ©The Authors 2018. Published by Medical Association of Thailand. The authors have obtained the permission for Medical Association of Thailand (Supplementary material).

proximal extent of reflux (Figure 5). However, pH-monitoring does retain value especially with regards to wireless pH recording, that minimizes disruption of patients during monitoring and allows for prolonged assessment of up to 5 days[48,49]. Similar to other diagnostic tools for GERD in children, there remains a lack of normal values hence the results of the test should be interpreted with caution. The most recent combined ESPGHAN- NAPSPGHAN guidelines recommend using the MII-pH study to correlate persistent troublesome symptoms with reflux episodes[1]. Recently, researchers have reported enhancements of the technique such as the use of combined VDO-MII-pH studies (Figure 6) in high-risk children with corrected esophageal atresia. Many children with corrected esophageal atresia may develop reflux esophagitis without specific symptoms or signs, however, Maholarnkij *et al*[6] found a trend of specific symptom that associated with reflux by using real-time Video recording and MII-pH monitoring. In this study, vomiting, irritability or unexplained crying and cough were the most common symptoms associated with reflux during combined Video-MII-pH monitoring. Hence, this novel tool might help the clinicians to diagnose GERD by increasing the symptom association index from MII-pH monitoring.

Oropharyngeal pH monitoring

UES dysfunction is thought to represent a major factor underlying the pathogenesis of the extraesophageal symptoms of GERD. Oropharyngeal pH monitoring should, in theory, detect abnormal acid reflux in this area and thus the cause of such symptoms. However, studies to date report conflicting results regarding the correlation of oropharyngeal pH monitoring and full-column reflux episodes detected by pH-impedance monitoring[50-56]. These studies were limited by small numbers of participants as well as equipment available to measure the pH above the LES and at the UES in children. The linkage of acid reflux from below the LES to that above the UES may have been impacted by the longer frequency used to detect acid in the proximally implanted Dx-pH probe (every 0.50 s) compared to the distal MII-pH recording (every 0.02 s)[52]. There is no connection between oropharyngeal pH events and pH-impedance events, according to a systematic review in adults[53]. Moreover, there were no significant differences in oropharyngeal acid exposure between PPI responders, partial responders and nonresponders in adult patients with laryngeal symptoms[54-56].

Esophageal manometry and esophageal manometry with pH-MII monitoring

Esophageal manometry can help clarify the role of esophageal dysmotility leading to ineffective esophageal clearance in the pathophysiology of reflux. It is, however, an invasive test that relies on

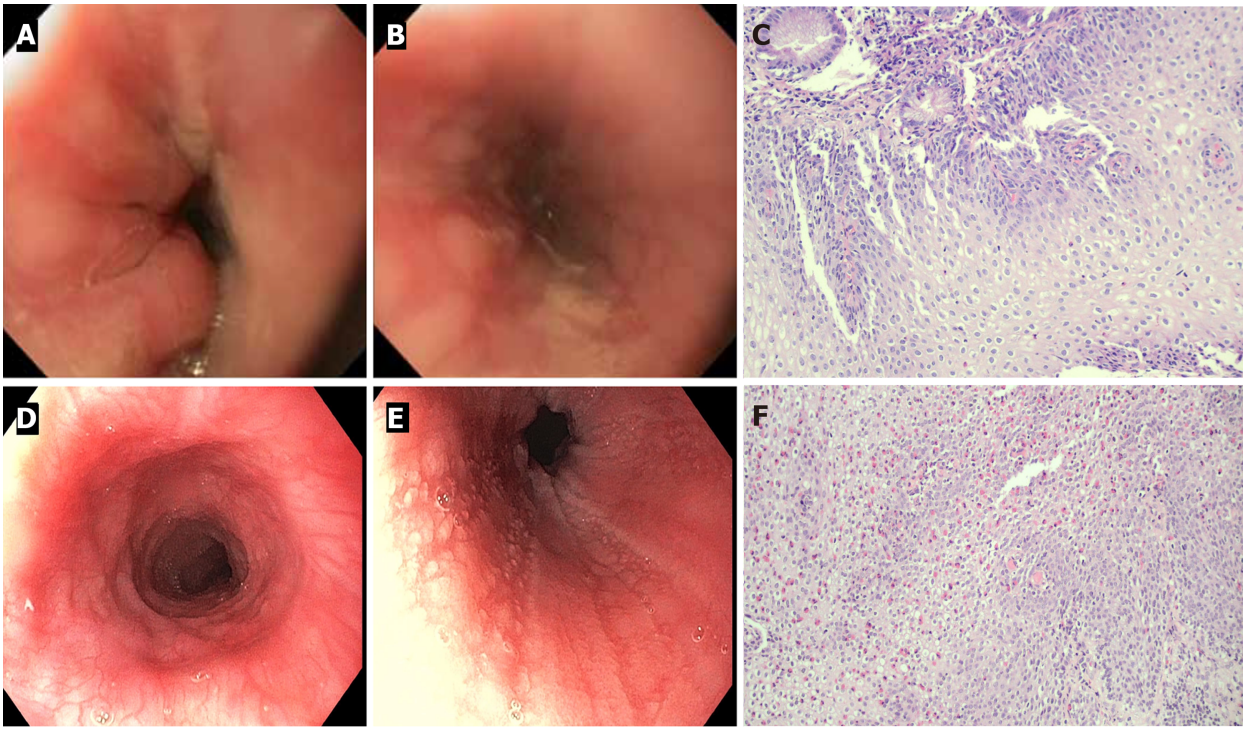

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Figure 4 The endoscopic and histologic findings of reflux esophagitis and eosinophilic esophagitis. A and B : Endoscopic finding of reflux esophagitis shows mucosal breaks and healing mucosal damage; C: Histopathology section (× 20) showing basal cell hyperplasia, elongation of the lamina propria papillae and scattered eosinophilic infiltration; D and E: Endoscopic findings of eosinophilic esophagitis showing ringed esophagus, linear furrows and whitish papules; F: Histopathology section (× 20) showing numerous eosinophils diffusely infiltrating the squamous epithelium (peak eosinophilic count = 40 cells/HPF). The squamous epithelium reveals spongiosis. Eosinophilic microabscesses and eosinophil degranulation are also noted.

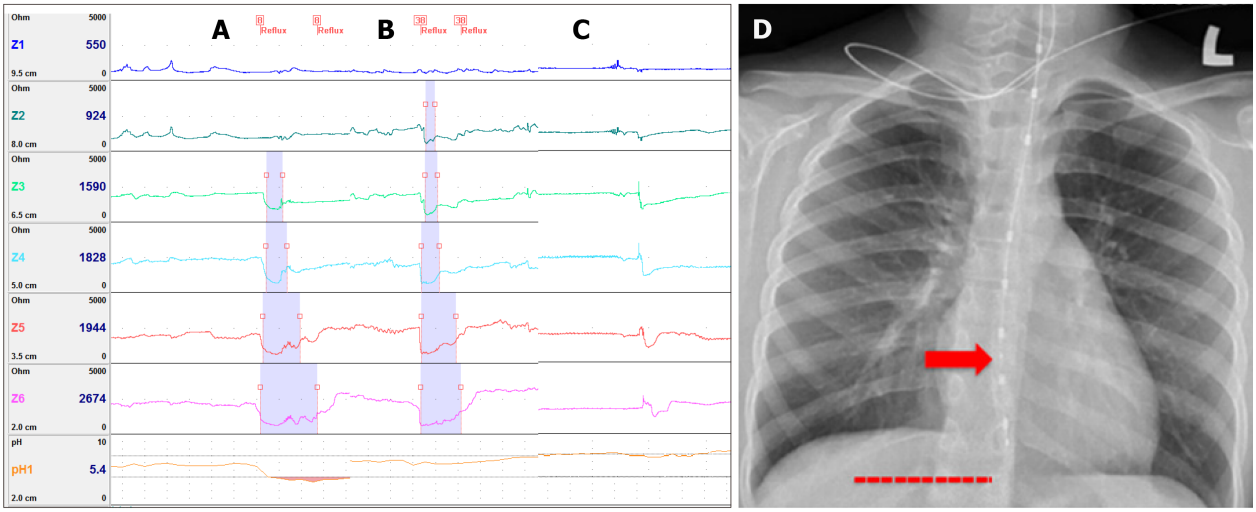

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Figure 5 Tracing from MII-pH study and correct position of MII-pH probe on chest radiography. A: Acid reflux (impedance changes up to 7.5 cm above the pH sensor, which shows a drop in pH); B: Non-acid reflux (impedance changes up to 9 cm above the pH sensor, without a pH drop); C: Swallow shown by impedance changes; D: Chest X-ray showing proper position of the pH sensor (arrow) of the MII-pH probe 2 vertebral bodies above the diaphragm (dotted line).

cooperation from children undergoing the studies[57-59].

In a study by van Lennep *et al*[60], even though esophageal manometry with or without 24-h pH impedance study was successfully completed in children (> 90%), complete interpretation is limited in children under the age of 4.

Esophageal manometry with pH-MII monitoring has a potential role in the assessment of extraesophageal symptoms such as aspiration pneumonia from esophageal stasis[1], or to improve the cough-reflux correlation[61].

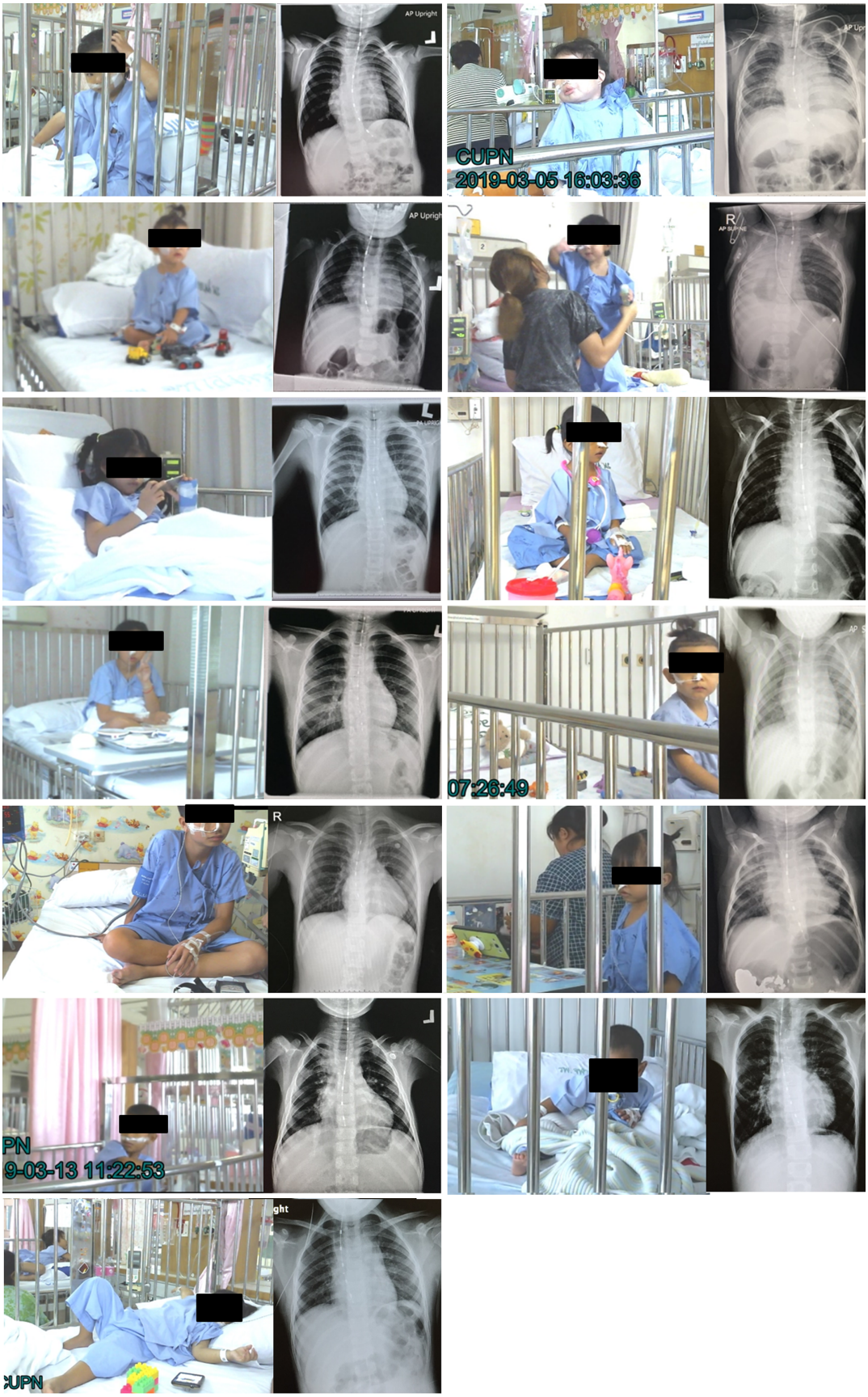

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Figure 6 Children after corrected esophageal atresia who underwent Video-MII-pH monitoring.

Electrogastrography

Electrogastrography (EGG) is a noninvasive test to study the electrophysiology of stomach, and in turn

assess for the presence of gastroparesis or gastric hypomotility as potential pathogenic factors for GERD [59,62]. Studies suggest significantly higher pooled prevalences of EGG abnormalities in GERD patients compared to healthy adults[63] and children[64]. However, the protocol and techniques for EGG studies are quite variable between centers.

Biomarkers

Due to the limitations of current investigative procedures used to diagnose extraesophageal manifestations of GERD, biomarkers have been proposed for use in diagnosing this type of GERD. Studies have suggested using of pepsin, lipid-laden macrophages and, bilirubin[65-71]. However, their diagnostic efficacy has not been established, and most call for invasive procedures like bronchoscopy to get the necessary samples, which restricts their application.

Therapeutic trial: PPI or transpyloric feeding

Studies to support the role of diagnostic trials of PPI and transpyloric feeding in children are scarce[72, 73]. Trials of transpyloric feeding to confirm GERD are not specific given improvements in symptoms of vomiting or feeding intolerance may also be seen in mimickers of GERD such as severe gastroparesis [74].

TREATMENT

In GER, non-pharmacological treatments and close follow-up are often sufficient whilst in GERD more therapeutic options are usually needed with careful consideration of treatments that balance optimal symptom resolution with predictable side effects.

Non-pharmacological treatment

Non-pharmacological treatments are recommended in infants suspected of GER and include the following.

Head and body position after meals: So far there is no recommendation for prone, right lateral position in infants as it may increase the risk of sudden infant death syndrome[34]. One study has demonstrated the effectiveness of a supine 40 degree anti-Trendelenburg position using a "Multicare-AR Bed" in decreasing symptoms and acid reflux detected with MII-pH monitoring[75]. However, a retrospective study demonstrated more reflux episodes in the upright position compared to the supine position in children and infants, probably as a result of frequent TLESRs while they were awake[76]. Nocturnal reflux has, however, been associated with prolonged esophageal acid exposure due to decreasing esophageal clearance from gravity, which may support the rationale of upright head position after feeding in infants.

Diet: Extensively hydrolysed protein or amino acid formulas should be considered in infants suspected of GERD. Nonspecific signs and symptoms, however, provide a challenge for the diagnosis of cow's milk protein allergy (CMPA). The Cow Milk Symptom Score (CoMiSS) might be used to evaluate infants before and after treatment of CMPA, but it is not considered as a diagnostic tool[77]. If there is no clinical improvement after a 4-8 wk trial of dietary cow's milk protein exclusion, CMPA is unlikely. Recently CoMiSS was modified in which a score of more than 10 (previously more than 12) in infants supported a diagnosis of CMPA[78]. The stool pattern was also changed from the Bristol Stool Scale to the Brussels Infant and Toddlers Stool Scale as a more user-friendly tool for non-toilet trained children. The updated CoMiss score is shown in Table 3.

Thickened formula use is associated with a significant decrease of visual regurgitation but not of acid reflux monitored by MII-pH[34]. Hence, thickening products have been recommended for use in infants with GER[1]. However, there has been rising concern about the safety of thickeners; for example inorganic arsenic in rice cereal[1], and the risk of necrotizing enterocolitis from xanthum gum and carob bean[79,80]. Moreover, rice cereal can be digested by amylase in breast milk limiting its use with breast milk.

Pharmacological treatments

If GERD symptoms in infants and children are not resolved with non-pharmacological treatment, medication can be considered. The most common medications include drugs that promote esophageal and gastric motility, tighten the LES, and acid suppressants to reduce esophageal mucosal injury (Table 4).

Acid suppressant agents: Proton pump inhibitors (PPI)[81,82] and H_2-receptor antagonists (H_2RA)[83] are used as the gold standard of GERD treatment[1]. PPIs are more effective than H_2RAs for acid suppression[84] and there is no tachyphylaxis with prolonged used. However, they may not be effective in non-acid or weakly acid reflux and their prolonged use can cause side effects especially increased rates of respiratory and gastrointestinal infection[85-88]. In addition, some H_2RAs were withdrawn from

Table 3 Updated version of the Cow's Milk-related Symptom Score (CoMiSS) used to evaluate children suspected of cow's milk protein allergy

Symptom	Characteristics and frequency	Score
Crying assessed by parents and without any obvious cause ≥ 1 wk, and not related to infection	≤ 1 h/d	0
	1.0-1.5 h/d	1
	1.5-2.0 h/d	2
	2-3 h/d	3
	3-4 h/d	4
	4-5 h/d	5
	≥ 5 h/d	6
Regurgitation ≥ 1 wk	0-2 episodes/d	0
	3-5 episodes (volume < 5 mL)/d	1
	> 5 episodes of volume > 5 mL	2
	> 5 episodes (volume < 50% of feeds)/d	3
	Small volume and happens > 30 min after each feed	4
	Regurgitation of ≥ 50% volume of a feed in ≥ 50% of total feeds	5
	Regurgitation of the complete feed after each feeding	6
Stool: Brussels Infant and Toddlers Stool Scale (BITSS); no change ≥ 1 wk	Hard stools	4
	Formed stools	0
	Loose stools not related to infection	4
	Watery stools not related to infection	6
Skin symptoms not related to infection	Atopic eczema ≥ 1/wk	
	Absent	0
	Mild	1
	Moderate	2
	Severe	3
	Acute urticaria/angioedema that directly related to cow's milk	
	No	0
	Yes	1
Respiratory symptoms not related to infection ≥ 1 wk	No respiratory symptoms	0
	Slight symptoms	1
	Mild symptoms	2
	Severe symptoms	3

the market because of the increased risk of malignancy from nitrosamine contamination[89]. It should also be noted that acid suppression has potential effects on the integrity of gut microbiota[90] with worsening of GI symptoms, although the concomitant use of probiotics have been suggested to mitigate this issue[91-93].

Prokinetic agents: The effectiveness of prokinetic agents was evidenced in adult populations but much less so in children. Common prokinetics used in infants and children include domperidone[94], metoclopramide[95] and erythromycin. Domperidone and metoclopramide act as $5HT_4$ agonists in the stomach and gut while erythromycin stimulates motilin receptors in the antral area of stomach[96]. These medications are therefore believed to be useful in children and infants who have GERD secondary to gastroparesis and to speed up upper GI transit time. Limitations for the use of domperidone and metoclopramide include significant potential side effects of QT prolongation[97] and extrapyramidal symptoms[98], respectively. When administered for a prolonged period, erythromycin

Table 4 Summarizes the drugs used in infants and children with gastroesophageal reflux disease[1-5] (for guidance only, prior to use please refer to local formulary and guidelines for accuracy and appropriate doses)

Medication	Dose	Adverse effect	Approved age (FDA indicated)
PPI[1]			
Omeprazole	1-4 mg/kg/d od	Diarrhea, abdominal pain, flatulence, headache, enteric infection, respiratory infection, rebound hypersecretion	> 1 yr old
Lansoprazole	0.7-2 mg/kg/d od	[1]Esomeprazole: Tarry stool, darkened urine	> 1 yr old
Esomeprazole	3-5 kg: 2.5 mg od > 5-7 kg: 5 mg od > 7.5 kg, < 20 kg: 10 mg od 20 kg: 20 mg od	[1]Rabeprazole: Light-colored stool	> 1 mo old
Pantoprazole	1-2 mg/kg/d od		> 5 yr old
Rabeprazole	0.5-1.0 mg/kg/d od		> 1 yr old
Pro-motility			
Metoclopramide	0.4-0.9 mg/kg/d tid	Extrapyramidal side effect (1%), diarrhea, drowsiness	> 1 yr old
Domperidone	0.8-0.9 mg/kg/d tid	Dry mouth, QT prolongation (rare) Abdominal pain, diarrhea, (rare) HPS in infants, QT prolongation (rare)	> 12 yr old
Erythromycin	5 mg/kg/dose qid	Dizziness, diarrhea, dry mouth	All ages
Baclofen	0.5 mg/kg/d tid		All ages
Esophageal mucosal protection			
Alginate antacid		Flatulence, diarrhea, nausea and vomiting	Younger than 12 yr of age is not generally recommended
Magnesium alginate plus simethicone	Infant: 1-2 mL/kg/dose after feeding		
Sodium alginate (225.00 mg sodium alginate, 87.25 mg magnesium alginate per sachet)	Child: 2.5-5.0 mL oral tid after meal		
Sucralfate (sucrose, polyaluminium hydroxide)	40-80 mg/kg/d qid	Constipation, aluminum toxicity in long-term use	In adult
Esoxx (sodium hyaluronate, sodium chondroitin sulfate, poloxamer 407, povidone K30, xylitol, potassium sorbate, sodium benzoate, red grape aroma, purified water) (10 mL/sachet)	1-2 sachet/d after main meal and bedtime	No serious adverse effect because of the poor absorption, however, no data of long-term adverse effect	In Italy, it is approval for adolescents age > 12 yr old
Probiotics			
Lactobacillus reuteri DSM 17938	> 1 × 10^8 colony-forming units/d od	None	All ages

[1]Dose depend on metabolizer *via* cytochrome P2C19. FDA; od; bid; tid; qid.
PPI: Proton pump inhibitor.

can potentially cause tachyphylaxis[99]. There is little available information on other prokinetic drugs such as mosapride, itopride, prucalopride and renzapride in children. Another prokinetic agent with direct effects on the LES is baclofen. Baclofen is a gamma-aminobutyric acid (GABA)-B receptor agonist and appear to act by reducing TLESRs. Baclofen has also been shown to accelerate gastric emptying[100-103]. However, the adverse effects of dyspepsia, drowsiness and dizziness[104] can limit its use in infants and children.

Alginate antacids: Since the late 1990s, compound alginate preparations were changed to become

aluminum-free and safe for infants. A Cochrane review in 2014 indicated moderate evidence of this agent for the improvement of GER in infants in short term follow-up[105-108]. Alginate antacids act by creating a barrier and appear effective for rapid symptom resolution regardless of the stimulus (acid, pepsin, bile, or mixed)[109]. Evidence for their use in GERD is limited[110].

Esophageal mucosal protectants: Sucralfate is a well-known mucosal protective drug that is composed of sucrose sulfate and aluminum hydroxide. It acts by inhibiting peptic digestion, providing mucosal protection and stimulating tissue growth and healing[111]. Recently, the novel medical device, Esoxx™, was developed and mainly composed of two mucopolysaccharides, mixed to a mucoadhesive gelling agent and a viscosity regulator compound to form a mucoadhesive formulation. It adheres to the esophageal mucosa and act as barrier against refluxed gastric content[112-115]. However, Esoxx™ was originally developed for use in adults[114,116], and there is a rising concern about applying it in children[117]. A recent publication has demonstrated the efficacy and safety of Esoxx™ in adolescents [118] but the data in younger children is scarce.

Probiotics: Because of the safety profiles of probiotics, this agent has been used worldwide in infants and children for many purposes such as acute diarrhea, colic, and regurgitation. A large RCT study in 589 term infants demonstrated significant efficacy of Lactobacillus reuteri DSM 17938 in preventing colic. In the same RCT, the author also demonstrated the efficacy of this probiotic in decreasing the mean number of regurgitations per day[119]. Hence, probiotics are prescribed widely in clinical practice to prevent or treat GER. However, in GERD, there has been no strong evidence for their use and further research is warranted.

Post-pyloric feeding, Surgery and therapeutic endoscopic management

These are reserved for a minority of children suffering severe GERD non responsive to medical treatments.

Transpyloric feeding is often considered in GERD that might subside with time for example; in severe gastroparesis from medications such as opioids, preterm infants[72,73] or from critical illness such as children in intensive care units[120]. There is, however, increasing data supporting its use as a viable alternative therapeutic strategy to surgery (*fundoplication*) even for high-risk patients, such as those with neurological impairment, given their similar overall efficacy and rates of complications[121,122]. For transpyloric feeding recurrent tube dislodgement provides one of most common complications.

In the highest risk patients especially those with severe neurodisability and life-threatening complications of GERD, open surgical or laparoscopic *fundoplication* has traditionally been considered the therapy of choice[123-126].

They are, however, associated with a significant need for redo-fundoplication and concurrent medication use in the most difficult to treat patients[34]. In addition, transoral incisionless fundoplication (TIF) procedures have been increasingly performed in patients with severe GERD[127-130]. Even though the recurrence rate in long term follow-up in children with severe neurological impairment was high[131], the complications from TIF were minimal[132]. As a result, some selective cases with GERD might benefit from this low-risk procedure.

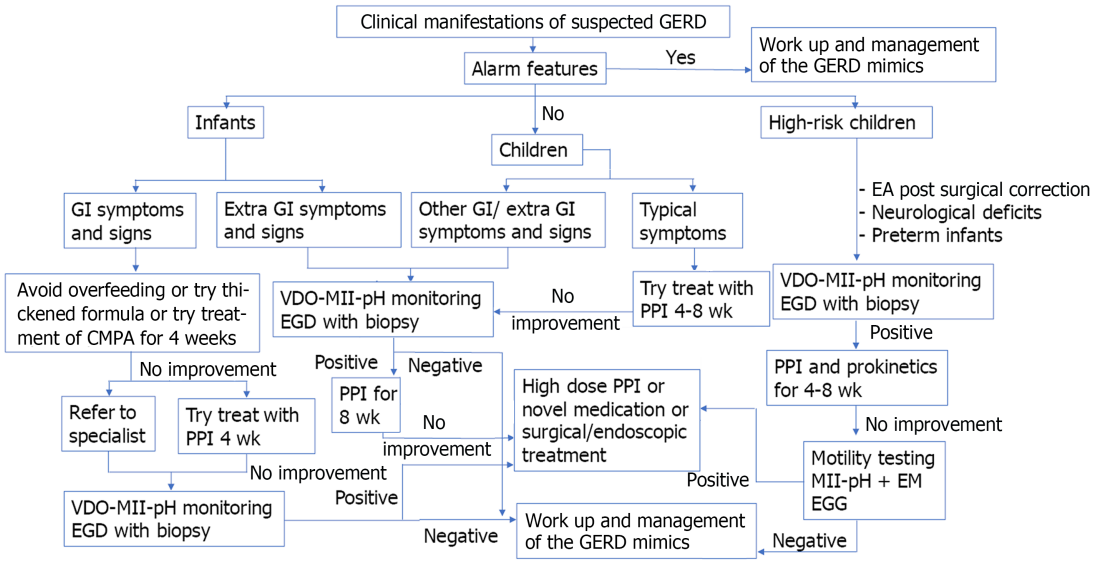
CONCLUSION

The recognition, diagnosis and treatment of GERD, especially in young children remains challenging. It requires to be differentiated from GER as well as GERD mimics, which is best approached using careful clinical assessment, especially in high-risk groups, paying attention to alarm features and the selective use of investigations, where necessary. There remains, however a lack of a gold standard tool for the diagnosis of GERD. Management should aim to target underlying aetiopathology and minimize complications. These may be managed through a variety of non-pharmacological and pharmacological strategies with surgery limited to very selected indications. Further studies to optimize the diagnosis and management of GERD are still needed. Table 5 summarize the updated diagnostic investigations and treatments for children with suspected GERD and Figure 7 proposes the steps of diagnosis and management in children with suspected GERD.

Table 5 Summarizes the updated diagnostic investigations and treatments for children with suspected GERD

Novel diagnosis tools	Treatment
Combined Video-MII-pH monitoring test to increase the detection of symptom associated reflux	**Non-pharmacological treatment**
	Supine 40-degree anti-Trendelenburg position
	Using the updated Cow Milk Symptom Score (CoMiSS) before and after therapeutic trial for CMPA
Esophageal manometry with pH-MII monitoring	**Pharmacological treatment**
	Novel prokinetics ex. mosapride, itopride, prucalopride and renzapride
Electrogastrography	Alginate antacid
	Esophageal mucosal protection: sucralfate, EsoxxTM
	Probiotics
Therapeutic trial with transpyloric feeding	**Endoscopic treatment**
	Transoral incisionless fundoplication

CMPA: Cow's milk protein allergy; CoMiSS: Cow Milk Symptom Score.



DOI: 10.4253/wjge.v15.i3.84

Figure 7 Proposed steps in the diagnosis and management of children with suspected GERD. GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor; EGG: Electrogastrography; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; EM: Esophageal manometry; EA: Esophageal atresia; MII-Ph: Multichannel intraluminal impedance-pH study.

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FOOTNOTES

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MINIREVIEWS

Endoscopic techniques for gastric neuroendocrine tumors: An update

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Abstract

Gastric neuroendocrine neoplasms (gNENs) are a rare type of gastric neoplasm, even if their frequency is increasing according to the latest epidemiologic revisions of the main registries worldwide. They are divided into three main subtypes, with different pathogeneses, biological behaviors, and clinical characteristics. GNEN heterogeneity poses challenges, therefore these neoplasms require different management strategies. Update the knowledge on the endoscopic treatment options to manage g-NENs. This manuscript is a narrative review of the literature. In recent years, many advances have been made not only in the knowledge of both the pathogenesis and the molecular profiling of gNENs but also in the endoscopic expertise towards innovative treatment options, which proved to be less aggressive without losing the capa-bility of being radical. The endoscopic approach is increasingly applied in the field of gastrointestinal (GI) luminal neoplasms, and this is true not only for adenocarcinomas but also for gNENs. In particular, different techniques have been described for the endoscopic removal of suspected lesions, ranging from classical polypectomy (cold or hot snare) to endoscopic mucosal resection (both with "*en bloc*" or piecemeal technique), endoscopic submucosal dissection, and endoscopic full-thickness resection. GNENs comprise different subtypes of neoplasms with distinct management and prognosis. New endoscopic techniques offer a wide variety of approaches for GI localized neoplasms, which demonstrated to be appropriate and effective also in the case of gNENs. Correct evaluation of size, site,

morphology, and clinical context allows the choice of tailored therapy in order to guarantee a definitive treatment.

Key Words: Stomach neoplasm; Neuroendocrine tumors; Endoscopy; Endoscopic mucosal resection; Endoscopic submucosal dissection

Core Tip: Gastric neuroendocrine neoplasms (gNENs) are a rare form of gastric neoplasia, although their incidence is increasing worldwide according to recent epidemiological reviews of large registries. The heterogeneity of gNENs poses a challenge, and therefore these neoplasms require different treatment strategies. Among the possible treatment options, the endoscopic approach is increasingly used and progressively improved, with different techniques available, ranging from classical polypectomy (cold or hot snare) to endoscopic mucosal resection (both with "*en bloc*" and piecemeal techniques), endoscopic submucosal dissection and endoscopic full-thickness resection. In this manuscript, we have summarized all new endoscopic techniques for the treatment of gastric neuroendocrine tumors.

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INTRODUCTION

Gastric neuroendocrine neoplasms (gNENs) are heterogeneous tumors whose incidence has increased rapidly recently due to improved recognition and awareness of neuroendocrine neoplasms as distinct tumor types[1]. Representing approximately 1%-2% of all gastrointestinal (GI) malignancies[2], they are still a rare type of tumor, even if they constitute the most frequent localization of digestive NENs, accounting for 20% of all enteric neuroendocrine tumors in selected countries, followed by rectal NENs [3-5]. In addition to the European Neuroendocrine Tumors Society (ENETS) grading system that all NENs follow, based on the degree of differentiation and the Ki67 index (*i.e.*, well-differentiated G1, G2 and G3, and poorly differentiated G3 neoplasms), gNENs are also divided into three main clinical types with different etiology and pathophysiology, as well as different prognosis and treatment strategy[6]: Type 1 gNENs are associated with chronic autoimmune atrophic gastritis (CAAG); type 2 gNENs are associated with gastrinoma/MEN-1 syndrome; in contrast; type 3 gNENs are not associated with any related pathology because they are usually sporadic[3,7]. Type 1 tumors represent the majority of gNENs and account for approximately 70%-80%[8]; they are usually detected through an upper GI endoscopy, and they mainly appear as small, multiple, located in the gastric body or fundus. They are composed of enterochromaffin-like (ECL) cells, that are usually confined to the mucosal or submucosal layers of the gastric wall[6] (Figure 1A-C); as for their etiopathogenesis, they are known to be an epiphenomenon of hypergastrinemia due to CAAG[9,10], while the role of PPI is more controversial [11]. Patients with CAAG, therefore, have an increased incidence of gNENs[12], and for this reason, they should undergo endoscopic surveillance with a variable interval[13].

Since type 1 gNENs are associated with a risk of metastasis of less than 5%, a conservative approach based on endoscopic resection (ER) and follow-up is preferred to surgery for small neoplasms greater than 5 mm in diameter and not infiltrating the muscularis propria[14,15], although there is no evidence of a significant superiority of ER over surveillance alone in terms of prognosis and recurrence in case of these small lesions[16]. According to ENETS guidelines, a EUS staging is recommended for lesions > 10 mm to determine the exact depth of tumor infiltration, its size and echogenicity, to assess loco-regional lymph node involvement, and thus to confirm the appropriateness of ER[17,18]. Nevertheless, the accuracy of EUS in staging submucosal lesions appears to be only 45% when compared with the histologic diagnosis after complete ER[19]. Therefore, accurate staging is often not possible until the lesion has been removed, as histology remains the gold standard for determining tumor differentiation, infiltration of the deep resection margins, and lymphatic vessel invasion[9].

Type 2 gNENs represent the smallest proportion of all gNENs, accounting for only 5%-6% of them; like type 1 neoplasms, they arise from ECL cells, and they are often small, multiple, and polypoid. They also represent an epiphenomenon of the trophic effect induced by hypergastrinemia on the gastric mucosa, but in this case hypergastrinemia is due to preexisting gastro-entero-pancreatic gastrinoma; type 2 gNENs are therefore associated with Zollinger-Ellison Syndrome (ZES), particularly in the

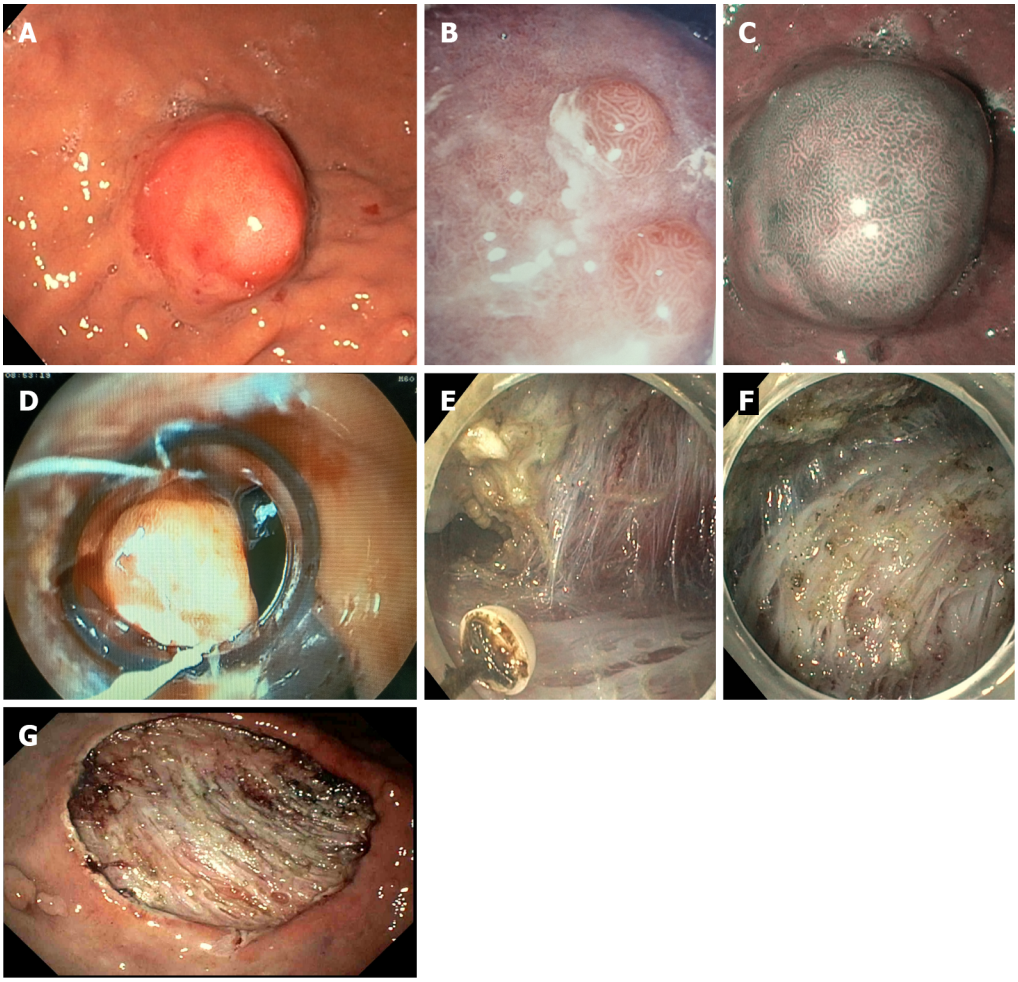

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Figure 1 Gastrointestinal endoscopy. A and B: White light endoscopic aspect of gastric neuroendocrine neoplasms; C: Chromoendoscopic blue light endoscopic aspect of gastric neuroendocrine neoplasms; D: Cap band endoscopic mucosal resection of a gastric neuroendocrine neoplasm; E-G: Endoscopic submucosal dissection of a gastric neuroendocrine neoplasm.

context of multiple endocrine neoplasia type 1 (MEN-1) syndrome[6]. To date, there is no complete agreement among international guidelines regarding the timing of endoscopic surveillance of gNEN in patients diagnosed with gastrinoma[20-22]. Although approximately 10%-30% of cases are diagnosed at a metastatic stage, type 2 gNENs are relatively benign tumors[23], and therefore, the same therapeutic approach is taken as for type 1 gNENs[17,24], even if the definitive treatment is removal/treatment of primary gastrinoma; for this purpose, EUS is useful to detect the associated primary duodenal/pancreatic lesion[16].

Type 3 gNENs, which account for approximately 14%-25% of all gNENs, are usually larger, sporadic single lesions, with a greater tendency to infiltrate and metastasize[14]. They are not associated with hypergastrinemia. Because of their aggressiveness, surgery represents the therapeutic strategy of choice, with total or subtotal gastrectomy together with lymphadenectomy being the standard treatment, as for gastric adenocarcinoma. ER may be a reasonable alternative only in selected cases of small (< 10 mm) G1/G2 (Ki-67 < 5%) type 3 gNENs that have been completely endoscopically resected (R0) and that have no risk factors for metastatic disease[25,26].

Different endoscopic techniques have been described to approach gNENs, and the majority of them proved to be radical[27]. Conventional approaches, such as polypectomy and traditional endoscopic mucosal resection (EMR) with mucosal lifting and hot snare resection, have recently been compared with new techniques, such as modified EMR, endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR), which are more invasive options, but with higher radicality rates. The rationale behind this shift trend towards new techniques lies in the increasingly clear evidence of the existence of well-differentiated gNENs that are already metastatic at the diagnosis.

AIM

This narrative review aims to describe in detail various proposed techniques for gNENs resection, even including latest technical tips.

METHODS

This manuscript is a narrative review of the literature. We performed a systematic research in PubMed, Medline and Embase databases using the terms "gastric neuroendocrine neoplasms" and "endoscopy" or "endoscopic treatment", and we selected original articles, with English written abstract available.

RESULTS

Excisional biopsy and polypectomy

Epidemiologically, most detected gNENs lesions are < 10 mm in diameter[9], so that the most common and simple endoscopic treatment, especially when they are < 5 mm, is excisional biopsy, which has an overall diagnostic, staging, and therapeutic role[28]. For lesions > 5 mm, endoscopic treatment should be performed if a therapeutic goal R0 can be achieved, and it can be performed with polypectomy or with more technically demanding endoscopic procedures, such as EMR, ESD, or EFTR[29].

Cold snare polypectomy

Cold snare polypectomy is a simple procedure in which the lesion is resected with a snare[29]. The endoscopist advances the snare sheath, opens the snare, and encircles the polyp; then, the nurse slowly closes the snare until the lesion is trimmed, capturing 1-2 mm of normal tissue around the polyp. This technique can be performed without lifting the polyp. However, cold snare polypectomy can be performed also with fluid injection into the submucosal layer (*e.g.*, saline), to lift the gNEN and then cut with the snare using the same technique. In this second option, more normal tissue around the lesion can be captured to achieve a R0 resection. However, in this case, single-layer snares are preferable to conventional ones, because of their higher mechanical cutting power[30]. Cold snare polypectomy provides margins without coagulation artifacts[31]. Potential complications with this technique include bleeding, which is usually controlled by applying clips after the incision, or perforation, which is very rare[32,33].

Hot snare polypectomy

Hot snare polypectomy is very similar to the cold snare technique[29], but in this case the snare not only cuts mechanically, but it also applies electrocoagulation when it is completely closed around the lesion. In this way, even larger lesions can be removed *en bloc*. Hot snare polypectomy is mostly used for lesions > 10 mm, pedunculated, or for flat lesions, which are actually very rare among NENs.

EMR

Traditional EMR: EMR is the technical term for the snare resection after an appropriate lifting of the lesion. There are many solutions that can be injected into the submucosal layer to obtain it; glycerol and saline solution are most used. For the resection of larger (> 10 mm) or flat lesions, EMR, as mentioned earlier, has a lower rate of incomplete resection, compared with cold or hot snare polypectomy[29]. The aim of EMR in gNENs is the *en bloc* R0 resection. However, although some studies show that EMR can achieve a high percentage of free resection margins in the smallest and most superficial lesions, conventional EMR sometimes cannot provide effective R0 resection, because many lesions already have submucosal involvement at the time of detection[9].

Anchored EMR: Anchored EMR is a very similar technique to conventional EMR: After lifting the submucosal layer, the endoscopist places the snare tip on the normal tissue surrounding the lesion and performs a small incision using the electrocoagulation. The tip of the snare is then inserted into the small incision and thus anchored into the tissue, and this allows the rest of the snare to open more stably around the lesion, better guaranteeing *en bloc* resection[34,35].

Cap band EMR: Cap band EMR is a technique mainly used for esophageal or cardial lesions[36]. After aspirating the lesion into the transparent cap of a band ligation set (DuetteTM Multi-band Mucosectomy Device®, Cook Medical, Bloomington, IN, United States), an elastic band is placed around the base of the lesion. Resection can then be performed with an appropriate snare closed below the mucosectomy band [37] (Figure 1D). The DuetteTM Multi-band Mucosectomy Device allows the *en bloc* EMR of small lesions. For larger lesions, this system allows only piece-meal resections, which limits the pathologist's capability to evaluate the lateral margins[36].

A recent study compared traditional EMR with cap-band EMR for removal of gastric submucosal lesions, including some gNEN, and showed a similar *en bloc* resection rate, which was 97% for conventional saline- mucosectomy, and 100% for cap band mucosectomy technique[38].

Under-water EMR: Under-water EMR is performed without lifting the lesion with any solution, but using the ability of water to lift the lesion[39]. Filling the lumen with water, it allows the lesion to be lifted[40]. The complications are comparable to those of conventional EMR[39]. This technique has been shown to be more effective than traditional EMR for *en bloc* resection of colonic lesions[41], including rectal NENs[42]. However, to date, only a few cases of underwater EMR in gNENs have been described [43].

Overall, EMR is a safe, cost-effective, and technically simple procedure. However, its major limitation is associated to the size of the lesion, which often forces the endoscopist to perform a piece-meal resection, especially for lesions larger than 10 mm in diameter, with the risk of a lower rate of radical excision. According to recent studies, complete resection is achieved with EMR in 52%-84% of cases[44, 45]. Nevertheless, there is limited evidence to date on the role of piece-meal resection in NENs. In a study that included 14 gNENs between 10-20 mm, treated with EMR, complete resection was not achieved in six cases. However, no recurrence occurred in any of them after 5-year follow-up[46]. Moreover, EMR often removes an amount of submucosal tissue insufficient to accurately define lymphatic vessel invasion, making an accurate histopathologic assessment impossible[46,47]. In addition, it should be considered that neuroendocrine tumors are usually not confined to the mucosa but they frequently invade the submucosal layer[48,49].

In case of incomplete resection, a second endoscopic procedure is more difficult due to fibrosis, with a higher risk of perforation. Hybrid techniques such as EMR/ESD or ESD alone, can better achieve R0 resection in larger lesions.

Endoscopic submucosal dissection

This technique, developed in Japan about 20 years ago for the endoscopic treatment of early gastric cancer, allows *en bloc* ER, regardless of tumor size, including the submucosal layer underneath the lesion, thus increasing the chance of histologically complete resection[50]. In addition, examination of a substantial amount of submucosal tissue allows accurate determination of lymphatic invasion and histologic grading, which may guide subsequent therapeutic decisions[47,51]. ESD is technically more demanding than EMR and it is associated with longer procedure times and higher risk of complications (bleeding and perforation). It consists of a delineating a circumferential excision zone around the lesion by using an electrocauterization knife, followed by the creation of a cushion under the lesion by the injecting of a viscous solution, and thus performing a dissection underneath the submucosal layer under direct visualization[46,52] (Figure 1D-G).

In 2012, an initial study by Chen *et al*[51] about the role of ESD in the management of gNENs examined 33 cases, including 22 type 1 and 11 type 3 gNENs. Histopathologic examination revealed a 100% complete resection rate, with horizontal and vertical negative margins and no lymphovascular invasions in all cases. Only one patient experienced delayed bleeding which could be controlled endoscopically, and no perforation was reported. Additional surgery was indicated for type 3 gNENs larger than 10 mm (7 cases), but only one patient agreed to undergo surgery. During a median follow-up of 28.9 months, two local recurrences occurred both of which were successfully treated by ESD. No lymph node metastases (LNM), or distant metastases were observed in any patient[51].

Two studies have examined the efficacy of ESD compared with EMR in the treatment of type 1 gNENs. The first was a small study of 13 lesions by Sato *et al*[53], that found a superiority of ESD in achieving complete resection with 100% negative horizontal and vertical margins, whereas positive vertical margins occurred in 66.7% of cases in the EMR group. A subsequent retrospective study by Kim *et al*[47] performed on 87 small lesions (< 10 mm in diameter) confirmed these results: The histological rate of complete resection was higher in the ESD group (94.9%) than in the EMR group (83.3%), mainly because the vertical margins were significantly less affected in patients who underwent ESD (2.6% *vs* 16.7%, $P = 0.038$). This is explained as EMR removes less submucosal tissue than ESD and for larger lesions only piece-meal resection is possible with higher risk of incomplete resection. Regarding safety, the bleeding rate was similar in both groups, but perforation occurred in one patient in the ESD group; all complications were successfully managed endoscopically[47]. Despite these findings, pooled data analysis of a recent systematic review by Panzuto *et al*[54] aiming at determining the best endoscopic technique (ESD, EMR, or polypectomy) in the management of type 1 gNENs did not show clear superiority of ESD over EMR in terms of efficacy and safety, with similar complete resection rates (97.4% and 92.3%, respectively) and complication rates (11.7% and 5.4%, respectively). Nevertheless, ESD demonstrated a lower risk of recurrence.

Regarding type 3 gNENs, studies reporting ESD are mainly focused on finding a proper indication for ER. In 2013, Kwon *et al*[23] retrospectively collected data from 50 patients with type 3 gNENs less than 20 mm in size, who were endoscopically treated by EMR (41 patients) or ESD (9 patients). Complete pathologic resection was achieved in 80.4% of all cases. ESD showed a lower complete resection rate than EMR (66.7% and 85.4%, respectively), probably due to larger average size of lesions in the ESD group. Lymphovascular invasion associated with larger tumor size was observed in 3 cases,

although no statistical significance was found; all 3 patients subsequently underwent surgical resection. In the remaining patients, no local or distant recurrence was observed during the median follow-up period of 46 mo, even in the case of incomplete resection. This study concluded that ER should be considered as initial treatment for type 3 gNENs smaller than 20 mm and confined to the submucosal layer[23]. However, another South Korean study by Min *et al*[55] reported that type 3 G2 and G3 gNENs had aggressive features with frequent metastases regardless of tumor size and depth of invasion. In this study only one patient had a LNM 68 mo after a complete ESD of a type 3 G1 gNEN of 19 mm, so the authors suggested that only for type 3 G1 gNENs no larger than 15 mm surgical wedge resection or ER (EMR or ESD) can be considered as a valid option in the absence of lymphovascular invasion[55]. A 2020 Japanese multicenter retrospective study analyzed data from 144 patients with type 3 gNENs who underwent primary surgical (81) or ER (63 in total, 53 treated by ESD, 10 treated by EMR). In the second group, 15 patients required additional surgery because of lymphovascular invasion, positive vertical margin, and/or G2 grading; of the remaining patients only one developed LNM and liver metastases during a median follow-up of 32 mo. In this study, LNM occurred in 16.1% of cases and was observed in one patient with a 6 mm type 3 G1 gNEN. Given the risk of LNM, authors concluded that gastrectomy with lymph node dissection is recommended for all type 3 gNENs, even for small low grading tumors; however, given the overall and recurrence-free survival superior to 90%, ER for type 3 G1 gNENs ≤ 10 mm in size confined to submucosa could be an alternative therapeutic option despite the risk of LNM [56]. Conversely, Li *et al*[57] published a retrospective study reporting 33 ER (ESD and EMR) of G1-G2 type 3 gNENs, with no local recurrence, LNM or distant metastases during a median follow-up period of 36 mo, and concluded that ER is safe and effective for G1-G2 type 3 gNENs confined to the submucosa and smaller than 20 mm. However, as mentioned before, no one of these studies was aimed to demonstrate the efficacy of ESD in this setting or its superiority over EMR, and therefore further studies are needed. Furthermore, no randomized controlled trials comparing EMR and ESD in gNENs resection are to date available[58]. Data from a Chinese retrospective study analyzing efficacy and safety of different endoscopic techniques on any GI NEN, proved ESD to have a higher pathological complete resection rate compared to EMR[59].

EFTR

EFTR, performed with the application of an over-the-scope-clip (OVESCO®, Tübingen, Germany), has been shown to be feasible, effective, and safe for small colorectal subepithelial tumors[60]. A multicenter retrospective study has shown that EFTR could be a rapid, effective, and safe alternative for the removal of rectal NEN < 20 mm[61]. Several studies investigated the role of EFTR in the management of gastric subepithelial tumors, but to date very few data are available on gNENs[62-67]. In the RESET trial, three gNENs with a size of < 15 mm were removed by using the gastric EFTR device, and R0 resection was obtained in all cases; no recurrence was detected at 3-mo follow up[67]. Anyway, further prospective, or controlled studies are needed to clarify whether EFTR has a standardized role in the treatment of gNEN.

Table 1 summarizes key information regarding the possible endoscopic therapeutic approaches for the different types of gNENs.

Endoscopic surveillance

Endoscopic surveillance after endoscopic treatment of gNENs has never been validated in prospective studies[68,69], so it is mainly based on histology. If resection margins are positive or indeterminate, the patient should undergo gastroscopy after 3-6 mo. If macroscopic residual disease is detected, a second and more aggressive endoscopic treatment is recommended. Otherwise, taking a biopsy from the scar is suggested[70].

After R0 ER of type 1 gNEN, follow-up with an upper GI endoscopy is recommended every 6-12 mo in the first three years, and annually thereafter; after ER of type 2 or 3 gNENs, annually follow-up is suggested[70]. According to an Italian prospective study, a specific timing has also been proposed for type 1 gNENs based on the tumor recurrence rate[71].

CONCLUSION

GNENs include different subtypes of neoplasms with distinct management and prognoses. After proper evaluation of size, site, morphology, and clinical context, different endoscopic techniques have been shown to be appropriate to treat GI localized neoplasms. To simplify, small lesions, especially when < 5 mm, can be radically resected by excisional biopsy or, if pedunculated, by polypectomy (cold or hot snare); > 5 mm type 1 and 2 (G1, G2, and G3) gNENs, and for type 3 (G1), if confined to the submucosal layer and without LNM or distant metastases, the therapeutic goal of R0 could be achieved by both modified EMR techniques (anchored, cap band and under-water EMR) and ESD; ESD might be preferred over EMR for larger lesions, > 10 mm in diameter, but no randomized controlled trials are yet available to confirm this. Larger type 3 G2/G3 gNENs should undergo surgery. Endoscopic ultrasound might achieve a more standardized role in the therapeutic diagram of gastric neuroendocrine lesions. Further randomized, controlled head-to-head studies with homogeneous and stratified patients are

Table 1 Endoscopic therapeutic approaches for the different types of well-differentiated gastric neuroendocrine neoplasms

	Type 1 gNENs (any grade)	Type 2 gNENs (any grade)	Type 3 gNENs (G1)	Type 3 gNENs (G2, G3)
Endoscopic presentation	Small, located in the gastric body or fundus, associated with CAAG	Small, multiple lesions, associated with gastrinoma (MEN1)	Larger, infiltrative, sporadic, single lesions	Larger, infiltrative, sporadic, single lesions
Risk of metastases	< 5%	10%-30%	50%-90%	50%-90%
Suggested resection technique	< 5 mm: Endoscopic surveillance *vs* excisional biopsy	< 5 mm: Endoscopic surveillance *vs* excisional biopsy	< 5 mm: Excisional biopsy *vs* polypectomy	Surgery (regardless of the size)
	5-10 mm: Polypectomy *vs* EMR (traditional or modified) *vs* ESD (ESD lower risk of recurrence)	5-10 mm: Polypectomy *vs* EMR (traditional or modified) *vs* ESD (ESD lower risk of recurrence)	5-10 mm: Modified EMR *vs* ESD (no randomized trials)	
	> 10 mm: EUS (to make sure it is confined to the submucosal layer, without LNM) + modified EMR *vs* ESD (no randomized trials)	> 10 mm: EUS (to make sure it is confined to the submucosal layer, without LNM) + modified EMR *vs* ESD (no randomized trials)	> 10 mm: Surgery *vs* EUS + ESD (possible role of EFTR)	

In case of incomplete resection: hybrid endoscopic mucosal resection/endoscopic submucosal (ESD) or ESD. CAAG: Chronic atrophic autoimmune gastritis; EFTR: Endoscopic full-thickness resection; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; EUS: Endoscopic ultrasound; gNENs: Gastric neuroendocrine neoplasms; LNM: Lymph node metastases; MEN: Multiple endocrine neoplasia.

needed.

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FOOTNOTES

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MINIREVIEWS

Endoscopic advances in the management of gastric cancer and premalignant gastric conditions

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Abstract

Gastric cancer is the fifth most common cancer and in 2018, it was the third most common cause of cancer-related deaths worldwide. Endoscopic advances continue to be made for the diagnosis and management of both early gastric cancer and premalignant gastric conditions. In this review, we discuss the epidemiology and risk factors of gastric cancer and emphasize the differences in early *vs* late-stage gastric cancer outcomes. We then discuss endoscopic advances in the diagnosis of early gastric cancer and premalignant gastric lesions. This includes the implementation of different imaging modalities such as narrow-band imaging, chromoendoscopy, confocal laser endomicroscopy, and other experimental techniques. We also discuss the use of endoscopic ultrasound in the diagnosis and staging of early gastric cancer. We then discuss the endoscopic advances made in the treatment of these conditions, including endoscopic mucosal resection, endoscopic submucosal dissection, and hybrid techniques such as laparoscopic endoscopic cooperative surgery. Finally, we comment on the current suggested recommendations for surveillance of both gastric cancer and its premalignant conditions.

Key Words: Gastric cancer; Premalignant gastric conditions; Endoscopy; Narrow-band imaging; Endoscopic mucosal resection; Endoscopic submucosal dissection; Gastric cancer surveillance

Core Tip: Consider screening for gastric cancer in appropriate patient populations, as early gastric cancer outcomes are associated with improved survival. Use of different imaging modalities during endoscopy such as narrow-band imaging may improve detection of gastric cancer and premalignant gastric conditions. Endoscopic mucosal resection and submucosal dissection have shown favorable long-term outcomes. While there are no established evidence-based gastric cancer surveillance guidelines in the United States, other studies have suggested annual surveillance after gastric cancer resection. Endoscopic surveillance of premalignant gastric conditions may be considered, with closer intervals in patients with evidence of dysplasia.

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INTRODUCTION

Globally, gastric cancer is the fifth most common cancer, with an estimated 1 million new cases annually [1-3]. In 2020, it was the fourth most common cause of cancer-related deaths worldwide[1-3]. In recent years, many endoscopic advances have been made for both the diagnosis and therapy of gastric cancer. In this article, we review the endoscopic tools used for the diagnosis and treatment of gastric cancer and premalignant gastric conditions. First, we discuss briefly the epidemiology of gastric cancer and outline the differences in outcomes for early-stage *vs* late-stage gastric cancer. We then review the endoscopic approaches in the diagnosis and treatment of gastric cancer and premalignant conditions. Finally, we review the current guidelines for endoscopic surveillance of gastric cancer and premalignant conditions.

Epidemiology, risk factors, and high-risk populations

According to the International Agency for Research on Cancer GLOBOCAN project, there were over 1 million new cases of gastric cancer and 768793 deaths from gastric cancer in 2020[4]. The majority of cases of gastric cancer are found in East Asia such as Japan and Korea, as well as Eastern Europe and South America. It is also more highly associated with the male sex, as well as with increasing age[1]. Other risk factors include low socio-economic status, cigarette smoking, alcohol use, pernicious anemia, and autoimmune gastritis[5]. Obesity and gastroesophageal reflux disease are associated with an increased risk of specifically gastric cardia cancer[2].

Infection with *Helicobacter pylori* (*H. pylori*) is a significant cause of gastric cancer[6]. Chronic infection may lead to inflammatory mucosal changes including atrophic gastritis and ultimately intestinal metaplasia[7]. The risk of gastric cancer in patients with *H. pylori* may also be increased with salted food intake, as there is thought to be a synergistic effect. Treatment of *H. pylori* may reduce the risk of the development of gastric cancer, and earlier treatment of this infection has been associated with risk reduction of gastric cancer[1].

Early vs late-stage gastric cancer outcomes

Overall, outcomes for gastric cancer are poor, especially in advanced stages[7,8]. Correa's cascade describes the development from atrophic gastritis to intestinal metaplasia, dysplasia, and ultimately invasive gastric adenocarcinoma[9]. Each step in this cascade offers an opportunity to screen and perform surveillance in order to arrest the development of gastric cancer. The implementation of gastric cancer screening programs in countries with a high incidence of gastric cancer such as Japan and South Korea has demonstrated that earlier diagnosis leads to improved survival[7]. The biennial screening program in South Korea has led to an increase in the diagnosis of early gastric cancer from 39% to 73%, as well as an increase in 5-year survival from 46% to 75%[6]. The difference in survival between early and late stage gastric cancer emphasizes the importance of early diagnosis and treatment.

ENDOSCOPIC ADVANCES IN THE DIAGNOSIS OF EARLY GASTRIC CANCER AND PREMALIGNANT GASTRIC LESIONS

White-light endoscopy

Conventional endoscopic evaluation of the stomach is performed with white-light endoscopy. When performing endoscopy with white-light imaging, it is recommended to take sufficient time to observe the stomach. Prior studies have demonstrated that endoscopists who took more time to observe the

stomach closely detected a greater number of early gastric cancer lesions[10]. The use of defoaming agents such as simethicone to wash the stomach during evaluation may also improve visibility of the stomach lining[10]. The sensitivity of white-light endoscopy for detecting gastric cancer and premalignant lesions has been reported to be anywhere between 30%-70%[11-13]. Additionally, there are now suggested standard mapping protocols in place in order to carefully examine the entire gastric mucosa and ensure that no areas were not viewed under white-light endoscopy[14]. In recent years, other methods of endoscopic visualization have been developed in hopes of improving the diagnosis of gastric cancer.

Chromoendoscopy

In chromoendoscopy, indigo carmine or a similar stain is applied topically to the mucosa to help improve identification of gastric cancer or premalignant gastric lesions. Early prospective studies suggest that the use of chromoendoscopy aids in the diagnosis of gastric neoplasia compared to conventional endoscopy[15]. Prior meta-analysis of the diagnostic efficacy of chromoendoscopy suggests that there is an increased diagnostic efficacy and detection of early gastric cancer and premalignant gastric conditions, with a sensitivity of 90% and specificity of 82%[16]. However, it is important to note that no randomized controlled trials have yet been performed to evaluate chromoendoscopy.

Narrow-band imaging

In narrow-band imaging (NBI), wavelengths of light used for visualization are limited to a specific band. This allows for improved visualization of the architecture of the mucosa[14,17]. NBI is now used as part of a diagnostic algorithm known as magnifying endoscopy simple diagnostic algorithm for early gastric cancer for classifying early gastric cancer. With the use of NBI, the lesion is evaluated for a demarcation line (DL). If a DL is present, the lesion is then evaluated for an irregular microvascular pattern (IMVP) and an irregular micro surface pattern (IMSP). If the lesion has either an IMVP or IMSP, the diagnosis of early gastric cancer is made[18].

The data for NBI in the diagnostic efficacy and detection of gastric cancer and premalignant gastric lesions is variable. For gastric cancer specifically, there does not appear to be a significant difference in diagnostic yield[19]. However, prior studies indicate that NBI may improve detection of premalignant lesions such as intestinal metaplasia. One randomized controlled trial revealed that non-magnifying NBI had a significantly higher detection rate than white-light endoscopy in the diagnosis of intestinal metaplasia, but not gastric cancer[20]. In a systematic review of ten studies (eight prospective studies and two retrospective studies), NBI appeared to significantly increase the detection of intestinal metaplasia[21,22]. Use of NBI should thus be considered in high risk populations to evaluate for premalignant gastric lesions.

Confocal laser endomicroscopy

Confocal laser endomicroscopy is an endoscopic technique that uses a low-power laser to obtain very high magnification of the mucosal layer of the gastrointestinal tract. Prior studies including meta-analyses evaluating the diagnostic value of confocal laser endomicroscopy suggest that CLE provides high sensitivity and specificity for the diagnosis of gastric cancer[23,24]. CLE also appears to have a high sensitivity and specificity in the diagnosis of premalignant gastric lesions. A meta-analysis of four studies including 218 patients and 579 lesions evaluating CLE for the diagnosis of intestinal metaplasia showed a pooled sensitivity of 97% and specificity of 94%[23].

Other experimental imaging techniques

Flexible spectral imaging color enhancement (FICE) is another technique with the potential to detect early gastric cancer. In FICE, a narrow bandwidth is obtained from a white-light image without optical filters. This allows for the possible visualization of laminar structures and blood flow in the gastrointestinal mucosa that has been altered by inflammation or malignancy, which will appear as high contrast compared to normal mucosa[25]. Prior studies have suggested that FICE is helpful in distinguishing between non-neoplastic and neoplastic lesions of the stomach[26]. However, FICE is limited in visualization of the mucosal microvasculature of the tumor surface, and visualization may need to be supplemented with additional imaging techniques[25].

Artificial intelligence is a growing field in gastroenterology and has shown efficacy in the detection of many different gastrointestinal lesions. Initial studies of neural networks generated from endoscopic images under both white-light endoscopy and NBI show high sensitivity for both methods in detecting lesions[27,28]. Real-time artificial intelligence detection of gastric lesions has yet to be studied.

Endoscopic ultrasound

Endoscopic ultrasound (EUS) allows for assessment of the depth of gastric cancer as it is able to distinctly identify the layers of the stomach[29]. Ultrasound can be achieved using the linear or radial transducers on the endoscope or with a through-the-scope ultrasound catheter probe. The five layers of the gastric wall are identified by their alternating hyperechoic and hypoechoic appearance[29]. EUS therefore is utilized to determine the T category of staging according to the TNM classification. A query

of the Surveillance, Epidemiology, and End Results-Medicare claims database performed in 2016 suggested that patients who underwent EUS were more likely to receive National Comprehensive Cancer Network recommended care such as perioperative chemotherapy[30]. Prior meta-analysis of 54 clinical studies suggests that EUS is successfully able to differentiate T1 and T2 stages from T3 and T4 stages, with reported sensitivity of 86% and specificity of 91%[31]. Specifically, EUS has been reported to distinguish T1 from more advanced stages with a sensitivity of 83% and specificity of 96%[31]. However, there was significant heterogeneity among the studies included, with some studies using older TNM classification systems. Factors that appear to decrease EUS accuracy include larger cancer diameter, ulceration, undifferentiated histology, and proximal location[31,32]. Further studies are needed to evaluate the staging accuracy of EUS based on the updated TNM classification system.

EUS is also a modality to help determine nodal involvement of gastric cancer. Larger size of the node, sharp margins, and hypoechoic pattern may help endosonographers determine lymph node involvement. Prior meta-analysis suggests that the sensitivity and specificity of EUS for the assessment of nodal involvement is less than for the T category of staging, with only 69% sensitivity and 84% specificity[29,31]. Similar to T category of staging, there was a large heterogeneity of studies included.

ENDOSCOPIC ADVANCES IN TREATMENT OF GASTRIC CANCER AND PREMALIGNANT GASTRIC LESIONS

Prior studies have shown that patients diagnosed with early gastric cancer who did not undergo resection, whether endoscopic or surgical, had a greater 5-year risk for progression to the advanced stage[33,34]. Current guidelines established for the therapy of early gastric cancer recommend resection once the diagnosis has been established[33,34]. Traditional criteria for endoscopic resection of early gastric cancer included adenocarcinoma that was 2 cm or less in diameter without ulceration or lymph node or vascular involvement[35,36]. More recently, this criteria has been expanded as additional studies have shown favorable long term outcomes of endoscopic resection in early gastric cancer, especially with the advances made in endoscopic submucosal dissection (ESD)[35,36]. In fact, multiple studies have now found 5-year survival rates to be nearly 100%[34].

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) is a procedure where a submucosal injection is used to lift the lesion, followed by resection of the lesion using snare. This technique allows for safe removal of intramucosal cancers that are 2 cm or less in diameter[37]. EMR has proven to be an effective treatment for early gastric cancer in terms of long-term outcomes. In one prior study in Japan with 479 cases of gastric cancer treated with EMR, there were no gastric cancer-related deaths during a median follow up period of 38 mo[38]. Notably, the rates of complete resection with EMR decrease with larger lesions with prior studies demonstrating complete resection rates as low as 20%-30% in lesions greater than 2 cm[39].

ESD

ESD is a technique in which the submucosal layer is injected to lift the lesion. Following injection, careful dissection of the submucosal layer from the muscular layer is performed using through-the-scope endoscopic knives, until the entire lesion is completely removed[40] (Figure 1). More recently, tools including various endoscopic knives and hemostatic forceps have been developed in order to perform quicker, more secure, and more precise incisions[38,39,41]. ESD has been shown to be more effective at complete resection of larger gastric cancer lesions[34]. In a meta-analysis of 18 observational studies, ESD proved to have a greater incidence of complete and curative resection compared to patients who underwent EMR[42]. ESD also has been associated with a lower risk of recurrence compared to EMR.

Endoscopic vs surgical resection

There are no randomized trials yet comparing endoscopic and surgical management of early gastric cancer, though several studies report favorable outcomes in endoscopic resection. Endoscopic resection has been associated with fewer complications and an improved quality of life when compared to surgical resection[43,44], likely because endoscopic resection allows for preservation of the stomach. Notably, studies also suggest that the recurrence rates are significantly higher with endoscopic resection than surgical resection[45].

Hybrid techniques

A more recently developed technique for removal of early gastric cancer lesions is laparoscopic endoscopic cooperative surgery (LECS). LECS involves endoscopic mucosal or submucosal dissection with laparoscopic seromuscular resection, with the intention to preserve as much of the normal stomach as possible[45,46]. LECS was initially used for the removal of submucosal tumors, but more recently has been studied for the removal of early gastric cancer[47,48]. It is important to note that with all types of

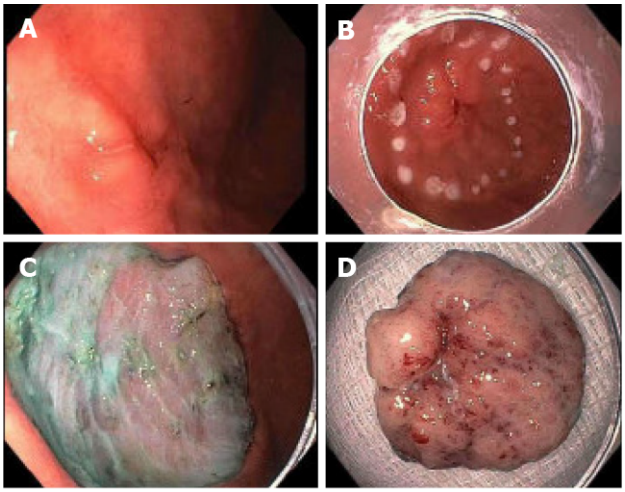

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Figure 1 Endoscopic submucosal dissection of a type 0-IIc lesion found in the antrum. A: Lesion noted in the antrum; B: Lesion marked for endoscopic submucosal dissection (ESD); C: Lesion removed successfully with ESD; D: Removed specimen, pathology returned as well-differentiated adenocarcinoma with no evidence of malignancy at the margins and no lymph node invasion (courtesy of Dr. Makoto Nishimura).

LECS, laparoscopic peri-gastric lymph node dissection is also performed[46].

ENDOSCOPIC SURVEILLANCE

Surveillance of gastric cancer

At present, there are no established evidence-based gastric cancer surveillance guidelines in the United States. Patients with gastric cancer that was treated with resection continue to have a risk for metachronous gastric cancer. Prior studies report an incidence of metachronous gastric cancer of 3 to 4 percent per year[49]. Japanese guidelines suggest annual or biannual endoscopic surveillance. Other studies have recommended earlier follow-up of 3 mo after resection, followed by gradual spacing to 6 mo and then a year if no lesion identified[49].

Surveillance of premalignant gastric conditions

Premalignant gastric conditions include atrophic gastritis and intestinal metaplasia. There are various guidelines for the surveillance of these premalignant conditions. The European Society of Gastrointestinal Endoscopy suggests surveillance intervals depending on the degree and extent of the premalignant lesion[50]. However, the American Gastroenterological Association suggests against endoscopic surveillance in patients with gastric intestinal metaplasia in the general population, and elective surveillance for those with a higher risk of gastric cancer, including family history, certain ethnic minorities, or extensive premalignant conditions[51]. In Japan, patients with atrophic gastritis are recommended to have surveillance endoscopy at 1-2 year intervals[52].

Prior studies report varying rates of progression of dysplastic lesions to gastric cancer, ranging anywhere from 0% to 73% per year[53]. This is in part due to the difference between specific populations such as Asian populations, who appear to have a greater risk of progression. A prior cohort of patients with dysplastic lesions showed progression from high grade dysplasia to gastric cancer in 25% of patients, and progression from low grade dysplasia to gastric cancer in 7% of patients[54]. Based on the current evidence, the International Consensus Project from 2012 has proposed that patients with intestinal metaplasia should be offered endoscopic surveillance every 3 years, while patients with low grade dysplasia should have surveillance imaging every 12 mo. Those with high grade dysplasia are recommended to have surveillance every 6 mo[54].

CONCLUSION

Over recent years, many endoscopic advances have been made for the diagnosis and treatment of gastric cancer lesions. Further studies to enhance visualization and diagnosis of early-stage gastric cancer tumors as well as different techniques for removal should be encouraged.

FOOTNOTES

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MINIREVIEWS

Endoscopic ultrasound guided biliary drainage in surgically altered anatomy: A comprehensive review of various approaches

Sridhar Sundaram, Aditya Kale

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred modality for drainage of the obstructed biliary tree. In patients with surgically altered anatomy, ERCP using standard techniques may not be feasible. Enteroscope assisted ERCP is usually employed with variable success rate. With advent of endoscopic ultrasound (EUS), biliary drainage procedures in patients with biliary obstruction and surgically altered anatomy is safe and effective. In this narrative review, we discuss role of EUS guided biliary drainage in patients with altered anatomy and the various approaches used in patients with benign and malignant biliary obstruction.

Key Words: Endoscopic ultrasound guided biliary drainage; Surgically altered anatomy; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound; Stents; Intervention

Core Tip: Endoscopic retrograde cholangiopancreatography is the mainstay for biliary drainage in benign and malignant biliary obstruction. Surgically altered anatomy poses a significant challenge to successful endoscopic retrograde cholangiopancreatography (ERCP). Enteroscopy assisted ERCP may need to be performed in this situation with variable rates of success. On the other hand, Endoscopic ultrasound guided biliary drainage represents a potential alternative to enteroscopy assisted ERCP. In patients with benign biliary obstruction, endoscopic ultrasound (EUS) guided rendezvous is the primary option for accessing the bile duct and ensuring clinical success of ERCP. In malignant obstruction, EUS guided antegrade intervention or transmural stent placement are options. EUS-BD ensures technical and clinical success is higher than 90% in expert hands.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred method for biliary drainage. Although quiet successful in normal anatomy, it challenging to perform ERCP in patients with surgically altered anatomy[1]. Even with the use of single or double balloon enteroscope, when standard duodenoscope fails to reach papilla, it is technically difficult to bring papilla en-face for cannulation[1]. Cannulation using existing ERCP equipment is also challenging. Traditional alternative for biliary drainage was percutaneous transhepatic biliary drainage (PTBD) however, with development in endoscopic ultrasound (EUS) it has become possible to visualise and get access to biliary tree by various approaches using linear array echoendoscopes[2]. With better echoendoscopes with wide working channel it has become possible to perform EUS guided biliary interventions not only for malignant diseases but also for benign cases even in patients with surgically altered anatomy[3,4]. In this review we will cover role of EUS biliary drainage (EUS-BD) in patients with surgically altered anatomy (SAA), various approaches, methods, their advantages and disadvantages.

SURGICALLY ALTERED ANATOMY AND EUS GUIDED APPROACH TO BILIARY TREE FOR DRAINAGE

Surgically altered anatomy (SAA) can be divided into two distinct types. Type 1 when duodenum is still in continuity with gastric remnant and standard duodenoscope can be passed till Ampulla of Vater to perform ERCP. Type II is one in which stomach remnant or stomach itself is not in continuity with duodenum and there is need of enteroscope or colonoscope to reach the ampulla causing difficulties. Examples of type I include sleeve gastrectomy and Billroth I type anatomy while type II SAA includes partial gastrectomy with Billroth II reconstruction or gastrojejunostomy (GJ) without gastric resection, Whipple anatomy, Roux-en-Y gastric bypass, and Roux-en-Y heapticojejunostomy[5] (Figure 1).

Sleeve gastrectomy

In this procedure the greater curvature of the stomach is resected, and the remnant stomach is kept in continuity with the small bowel. Duodenoscope can be passed through gastric sleeve to reach Ampulla of Vater and ERCP can be performed using standard accessories. In case of failed ERCP procedure, EUS guided access to bile duct is possible through duodenum and segment 2 or 3 radicals can be accessed from remnant stomach for antegrade approach[3,5,6].

Billroth I gastrectomy

In this procedure, antrectomy is performed followed by an end-to-end anastomosis between the remnant stomach and the duodenum. Since duodenum is in continuity with stomach remnant ERCP can be performed using duodenoscope from major papilla. As in sleeve gastrectomy EUS guided access to bile duct is possible through duodenum and segment 2 or 3 biliary radicals can be accessed through gastric remnant[3,5,6].

Partial gastrectomy with Billroth II reconstruction and gastrojejunostomy

Partial gastrectomy with gastrojejunostomy is commonly performed for gastric cancer while gastrojejunostomy is performed for complications of peptic ulcer disease like gastric outlet obstruction. In both

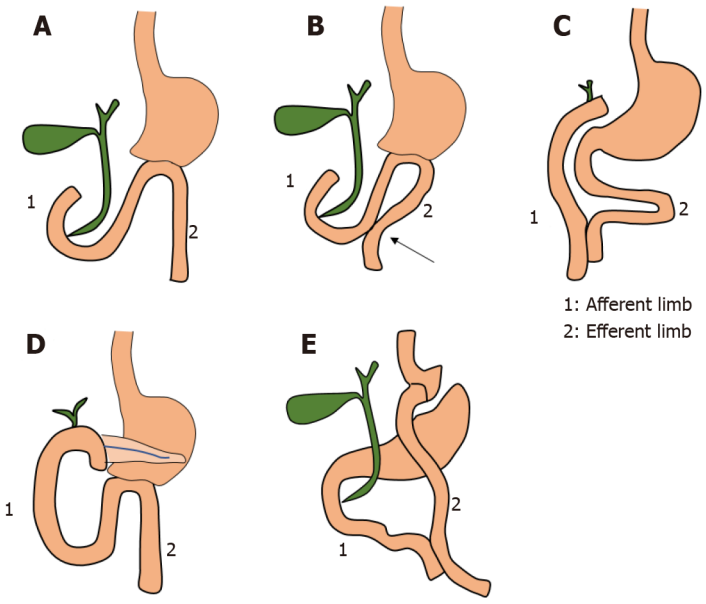

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Figure 1 Graphical representation of surgical altered anatomy. A: Billroth II anatomy; B: Billroth II anatomy with Braun anastomosis; C: Roux-en-Y Hepaticojejunostomy; D: Post-Whipple surgery anatomy; E: Roux-en-Y Gastric Bypass anatomy.

cases afferent limb of variable length is in continuity with duodenum and efferent limb is connected to small bowel. Approach to the papilla is through the afferent limb. Success of cannulation depends on length of afferent limb, angulation of anastomosis and position of papilla. EUS guided approach to biliary tree is through segment 2 or 3 biliary radicles which can be accessed through gastric remnant[3,5,6]. If there is difficulty inserting an e-ERCP scope in Billroth-II anatomy, switching to Interventional EUS without straining is a reasonable option.

Roux-en-Y gastric bypass

In this procedure, the stomach is divided into small proximal pouch and large distal pouch which is in continuity with duodenum. Small bowel is divided into two limbs one is biliopancreatic which is formed by duodenum and proximal jejunum, while Roux limb is formed by small bowel distal to division and anastomosed with gastric pouch as gastojejunostomy (GJ). Enteroscope assisted ERCP is possible, however with a low success rate[7,8]. Papilla can be accessed in up to 84% cases with successful cannulation achieved in 94%. This rate is lower than other surgically altered anatomy[9]. EUS guided approach to biliary tree is through segment 2 or 3 biliary radicles which can be accessed through gastric remnant[3,5,6].

Whipple procedure

This surgery is performed for periampullary carcinoma and pancreatic head carcinoma. It consists of removal of the pancreatic head, distal stomach, duodenum, proximal jejunum, distal common bile duct, and gallbladder. Reconstruction is done by creating a pancreaticojejunostomy (PJ), choledochojejunostomy (CJ), and GJ. EUS guided approach to biliary tree is possible through segment 2 or 3 biliary radicles which can be accessed through gastric remnant[3,5,6].

EUS GUIDED BILIARY DRAINAGE PROCEDURES

EUS guided biliary drainage can be performed by three approaches: EUS-rendezvous (EUS-RV), transluminal and EUS-guided antegrade approaches. These procedures are performed using CO_2 insufflator, under general anaesthesia or conscious sedation after administration of prophylactic antibiotics[3,5,6,10]. No previous studies have assess the comparative need based on surgical altered anatomy.

EUS-rendezvous (EUS-RV)

This procedure should only be attempted in the SAA cases where papilla is accessible using duodenoscope or balloon assisted enteroscope. Dilated biliary tree can be accessed using stomach from where segment 2 or 3 ducts can be accessed or dilated bile duct can be accessed from first part of duodenum (D1) as in EUS guided choledochoduodenostomy (EUS-CDS). Guidewire is then passed across dilated

biliary tree through the papilla, where it is captured using duodenoscope or enteroscope after careful exchange of endoscopes to avoid slippage of guide-wire[3,5,6,10]. EUS-RV is the preferred technique in benign biliary obstruction (Figure 2).

Transluminal

It involves creation of fistula between part of biliary tree and lumen of gastrointestinal tract. This can be between bile duct and duodenum as in EUS-CDS or segment 2 or 3 ducts and stomach or gastric remnant as in EUS-HGS. Puncture of common bile duct or segment 2 and 3 radicals is made from duodenum or stomach respectively. Guidewire is passed deep inside biliary tree. After guidewire insertion fistula is created using cystotome across which self- expandable metal stent (SEMS) can be placed (Figure 3). In cases of total gastrostomy with jejunum anastomosed to oesophagus transluminal drainage can be performed from afferent jejunal limb and creation of choledocho-jejunostomy or hepaticojejunostomy[3,5,6,10].

EUS guided antegrade approaches

Approach to biliary tree is from segment 2 or 3 biliary radicals of left lobe of liver. Guidewire is negotiated across the stricture or anastomotic site and stent is placed across the stricture or papilla in antegrade fashion (Figure 4). In case of choledocholithiasis balloon dilatation of sphincter or anastomotic stricture in antegrade fashion can be performed and stones can be pushed into the small intestine using balloon catheter[3,5,6,10,11].

EUS directed transgastric ERCP (EDGE) procedure

Using linear array echoendoscope gastric remnant is identified. Puncture is taken using 19G FNA needle. Contrast-saline is injected to confirm the position. Electrocautery enhanced lumen opposing metal stent (LAMS) is placed across the fistula. Balloon dilatation of the stent is carried out to 18 mm and ERCP is performed by passing the scope across the stent from gastric pouch to gastric remnant which is in continuity with duodenum. ERCP can be performed using standard duodenoscope and accessories through papilla[12]. ERCP can be performed immediately after LAMS placement or after 4 weeks once fistula is mature. If performed immediately then chances of LAMS dislodgement are high and require fixation of LAMS using sutures[5]. LAMS can be removed once biliary intervention is completed. Fistula is allowed to close by secondary intention and closure is confirmed at 8 wk by oral contrast study or endoscopy. In case of failure of fistula to close over the scope clip or suturing can be performed.

APPLICATION OF EUS GUIDED BILIARY DRAINAGE TECHNIQUES IN SURGICALLY ALTERED ANATOMY

In patients with surgically altered anatomy approach to EUS guided biliary drainage depends on access to papilla. In case of sleeve gastrectomy stomach remnant is in continuity with the duodenum and ampulla is accessible. Hence in case of failed conventional ERCP, EUS guided rendezvous and transluminal procedures like EUS-CDS can be performed as in native anatomy[5]. However in cases where access to papilla is not possible or difficult *e.g.* Billroth II gastrectomy, Roux-en-Y reconstruction, rendezvous procedure is not possible. In these cases antegrade approaches by puncturing segment II or III duct or transluminal approaches like hepaticogastrostomy (EUS-HGS) or hepaticojejunostomy (EUS-HJ), in cases of accessible afferent limb, need to be performed. Multiple procedures can also be combined together, especially for benign indications like choledocholithiasis[3,5,6,10,11]. Table 1 gives a summary of surgically altered anatomy with approach to biliary tree and EUS guided biliary drainage procedures.

SUCCESS AND COMPLICATIONS OF EUS BILIARY DRAINAGE PROCEDURES IN PATIENTS WITH SURGICALLY ALTERED ANATOMY

Antegrade drainage procedures

Initial studies with antegrade drainage procedures showed lower success rate of about 67% however recent studies showed shown clinical and technical success rate of more than 90%[13-21]. In a large series of EUS guided antegrade stent placement (n = 54) including patients with surgically altered anatomy, technical success was 88.7% with clinical success of 95.7%[22]. Complication rate has also reduced from 70% to 10% with increasing expertise and use of different techniques[13-23]. Mukai *et al* [21] had used two staged technique to tackle choledocholithiasis with > 90% clinical and technical rate. At first, EUS HGS was performed with placement of covered SEMS followed by interventions to remove stone using cholangioscope and lithotripsy devices after maturation of the fistulous tract.

Table 1 shows surgically altered anatomy, approach to biliary tree and endoscopic ultrasound guided biliary drainage procedures

No	Surgically altered anatomy	Approach to biliary tree	EUS biliary drainage procedure
1	Sleeve gastrectomy	From duodenum bile duct can be punctured; From Segment 2 or 3 ducts	Transmural: EUS CD, Rendezvous procedure; Transmural: EUS HGS, Antegrade drainage procedure
2	Billroth-I gastrectomy	From duodenum bile duct can be punctured; From segment 2 or 3 ducts	Transmural: EUS CD, Rendezvous procedure; Transmural: EUS HGS, Antegrade drainage procedure
3	Billroth-II gastrectomy	From segment 2 or 3 ducts	Transmural: EUS HGS, Antegrade drainage procedure
4	Roux-en-Y gastric bypass	From segment 2 or 3 ducts	Transmural: EUS HGS, Antegrade drainage procedure; EDGE procedure
5	Whipple's procedure	From segment 2 or 3 ducts	Transmural: EUS HGS, Antegrade drainage procedure
6	Roux-en-Y hepatojejunostomy	From segment 2 or 3 ducts	Transmural: EUS HGS, Antegrade drainage procedure

CD: Choledochduodenostomy; HGS: Hepaticogastrostomy; EUS: Endoscopic ultrasound.

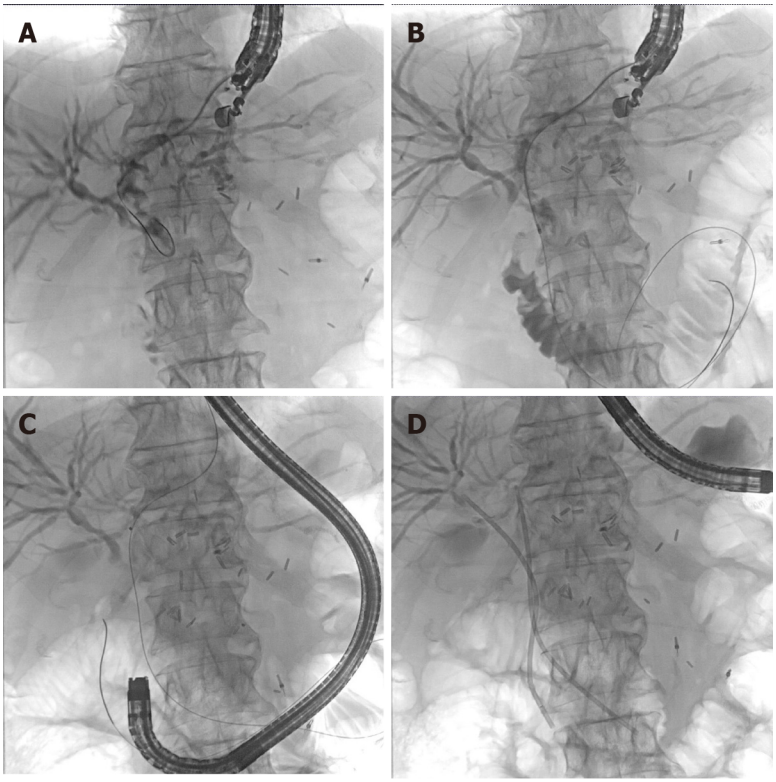

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Figure 2 Endoscopic ultrasound guided transhepatic rendezvous in a case of carcinoma stomach post distal gastrectomy with intraoperative bile duct injury. A: Puncture and passage of wire from segment II in left hepatic duct with proximal common bile duct stricture; B: Guide-wire passed across the papilla after tract was dilated with cystotome; C: Scope changed to upper gastrointestinal (GI) endoscope and passed till the level of the papilla; D: Bilateral plastic stent placement using upper GI endoscope.

Transmural drainage procedures (EUS-HG, EUS-CD and EUS-rendezvous)

Huang *et al*[2] in their study showed that clinical and technical success rate of transmural drainage procedures (EUS-HG, EUS-CD, EUS-rendezvous) in patients with surgically altered anatomy is 93.3% and 84.9%. Minaga *et al*[23] also noted similar success rate. Complication rate was 8%-9% in both studies. Haemorrhage, cholangitis, bile leak were complications noted in both studies[2,23].

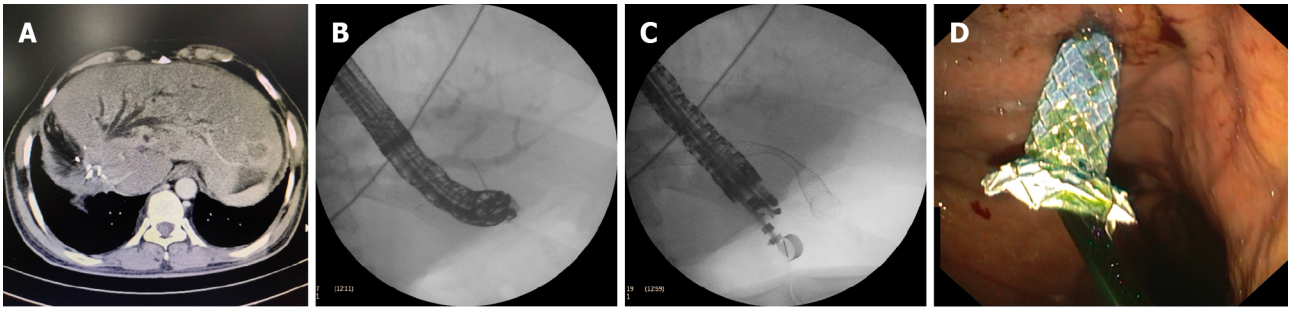

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Figure 3 Endoscopic ultrasound guided Hepaticogastrostomy in case of right hepatectomy with extrahepatic biliary tract excision with left hepatiojejunostomy with stenosis with new onset recurrence in left lobe. A: Computed tomography scan showing dilated left intrahepatic biliary radicles with hypodense lesion in segment II; B: Puncture from segment III with 19G FNA needle; C: Covered self- expandable metal stent (SEMS) placed across the hepaticogastrostomy tract; D: Endoscopic view of SEMS protruding in the proximal stomach with drainage of bile.

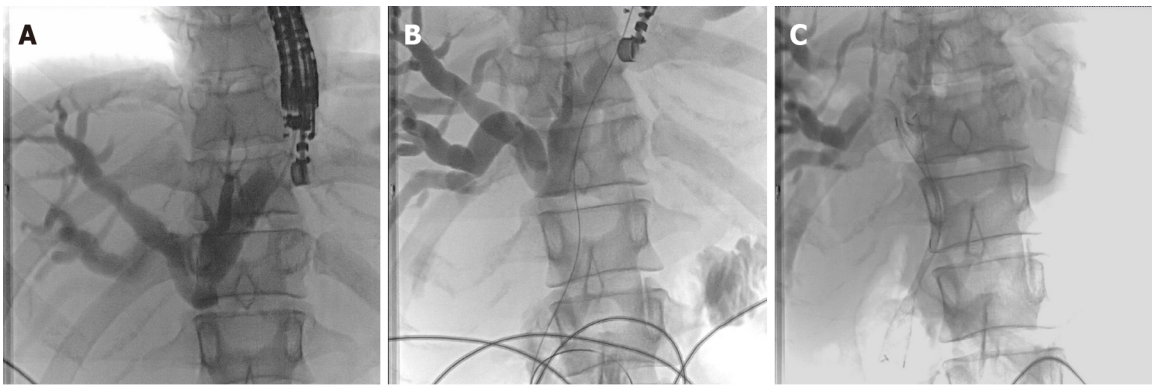

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Figure 4 Endoscopic ultrasound guided antegrade self- expandable metal stent placement in a patient post subtotal gastrectomy with recurrence in portocaval lymph node with proximal common bile duct obstruction with inaccessible papilla. A: Puncture into segment II radicle with 19G FNA needle; B: Cholangiogram showing Bismuth type I block; C: Self- expandable metal stent placement across the papilla with drainage of contrast.

OUTCOMES OF EDGE PROCEDURE (EUS DIRECT TRANS-GASTRIC ERCP)

Kedia *et al*[24] compared laparoscopy assisted ERCP with EDGE procedure in Roux-en-Y Gastric Bypass (RYGB) and found similar technical success (EDGE 96.5% *vs* LA-ERCP 97.7%), number of ERCP procedures needed to achieve clinical resolution (EDGE 1.2 *vs* LA-ERCP 1.02) and adverse event rate (EDGE, 24%, 7/29 and LA-ERCP, 19%, 8/43). However total procedure time (73 *vs* 184 min) and length of hospital stay (0.8 *vs* 2.65 d) was significantly shorter for EDGE compared to LA-ERCP. Bukhari *et al* [25] in their study comparing EDGE procedure to enteroscope assisted ERCP (e-ERCP) for RYGB found that technical success rate was significantly higher in the EDGE versus the e-ERCP group (100% *vs* 60.0%, $P < 0.001$). EDGE was associated with shorter procedure time Total procedure time was significantly shorter in patients who underwent EDGE (49.8 min *vs* 90.7 min, $P < 0.001$). Resource utilisation with length of hospitalization was shorter in the EUS-GG group (1 *vs* 10.5 d, $P = 0.02$) with similar rate of adverse events. While EDGE appears to have upper hand in biliary drainage, this study had a small sample size and was retrospective in nature. Also procedures in this study was performed in expert hands making the results less generalisable. Limb length often decides success in e-ERCP, with length less than 150 cm associated with higher success[26].

ENTEROSCOPE ASSISTED ERCP VS EUS GUIDED BILIARY DRAINAGE IN PATIENTS WITH SAA

An international comparative study involving 98 patients (49-EUS BD group and 49 enteroscope assisted ERCP group), technical success was achieved in 98% patients in the EUS-BD group as compared to 65.3% patients in the e-ERCP group (OR 12.48, $P = 0.001$) and clinical success in 88% of patients in EUS-BD group as compared to 59.1% in the e-ERCP group (OR 2.83, $P = 0.03$). EUS BD had

significantly shorter procedural time (55 min *vs* 95 min, $P < 0.0001$). AEs occurred in the EUS-BD group (20% *vs* 4%, $P = 0.01$) which were of mild/moderate severity. Both complications in e-ERCP group were pancreatitis, while patients in EUS-BD group had cholangitis, sepsis, bleeding and pneumoperitoneum, all of which were self-limiting. Length of stay was significantly longer in the EUS-BD group (6.6 d *vs* 2.4 d, $P < 0.0001$)[16]. Based on this result EUS BD can be an alternative to enteroscope assisted ERCP in patients with surgically altered anatomy. No previous studies have assessed impact of choice of procedure on quality of life or activities of daily living.

PERCUTANEOUS TRANSHEPATIC BILIARY DRAINAGE *VS* EUS GUIDED BILIARY DRAINAGE IN PATIENTS WITH SAA

Iwashita *et al*[27] in their study comparing EUS guided antegrade biliary stenting and PTBD in patients with surgically altered anatomy and malignant biliary obstruction. The technical, clinical, and internalization success rates in the EUS-ABS and PTBD groups were 97.1% *vs* 96.6% ($P = 1.00$), 97.1% *vs* 93.1% ($P = 0.586$), and 97.1% *vs* 75.9% ($P = 0.01$), respectively. The adverse event rate was 11.4% *vs* 27.6% ($P = 0.119$). No significant long-term difference was seen in time to recurrent biliary obstruction and survival [28]. EUS guided antegrade biliary stenting is evolving and comparable to PTBD with lesser adverse events in EUS guided antegrade stenting group[27].

ADVANCES IN EUS BILIARY DRAINAGE APPROACHES AND TECHNIQUES IN SAA

Right hepatic duct approach for EUS guided biliary drainage

EUS guided approach to intrahepatic biliary ducts is usually from the left lobe segment 2 or 3 intrahepatic ducts. Alternatively right intrahepatic duct can be approached through the duodenal bulb. Park *et al*[28] presented study of 6 patients where right intrahepatic ducts were approached under EUS guidance. Three had altered anatomy. Two underwent successful anastomotic site stricture dilatation and one patient had failed procedure.

EUS directed transenteric ERCP (EDGE) in non-Roux-en-Y gastric bypass

This procedure can be performed in patients with non-Roux-en-Y surgically altered anatomy. Bilioenteric limb is distended with water instillation by upper gastrointestinal (GI) scope or placement of nasobiliary drain or through PTBD catheter. Using echoendoscope distended small bowl loop is localised. Doppler signal is applied to see avascular plane for puncture for puncture. Distance between two loops is confirmed to be less than 1cm and puncture is taken. Electrocautery enhanced lumen opposing stents is placed between two loops. This is similar to an EUS guided Gastroenterostomy where the same steps of catheter passage, distension of small bowel loop, localisation of loop and use of cautery enhanced LAMS for puncture are done. ERCP is performed by passing the therapeutic upper GI scope through the LAMS after maturation of fistulous tract. Non-electrocautery enhanced LAMS can also be used. In a previous study by Ichkhanian *et al*[29] involving eighteen patients, post-Whipple (10/18) and Roux-en-Y hepaticojejunostomy (6/18) were the most common anatomical alterations. Technical success rate of EUS-guided lumen-apposing metal stent (LAMS) placement was 100% and of ERCP was 94.44% (17/18). Minor adverse event in the form of abdominal pain was noted in only 1 patient. Although procedure appears promising very nearly 100% success rate further large studies are required to prove its utility. Table 2 summarises the different studies of EUS guided intervention in patients with SAA.

OUR APPROACH TO A PATIENT WITH BILIARY OBSTRUCTION WITH SURGICALLY ALTERED ANATOMY

Figure 5 describes algorithm for EUS guided management of biliary obstructions in patients with surgically altered anatomy. Choice of biliary drainage procedure in patients with SAA depends on surgical procedure performed, expertise and equipments available at the center, interventional radiology and surgical back up available. In sleeve gastrectomy and Billroth I reconstruction where duodenum is continuity with gastric remnant and papilla is accessible to standard duodenoscope, ERCP can be attempted as in native anatomy. In case of failed ERCP, if EUS guided approach is planned then it depends on procedure indication. For benign indications EUS-RV and antegrade approaches can be attempted to pass guidewire across the papilla and further procedure can be completed with duodenoscope. In case of malignant distal biliary obstruction where preoperative biliary drainage is required EUS-RV and EUS-antegrade approaches and stenting can be performed which doesn't significantly alter anatomy and allows surgical resection of tumour along with stent. In cases where palliative biliary

Table 2 Summarises current literature regarding technical and clinical success of different endoscopic ultrasound guided biliary drainage procedures in surgically altered anatomy

Serial No.	Ref.	EUS BD procedure	Surgically altered anatomy	Indication	No. of cases	Success rate (Technical and clinical)	Complications
1	Weilert *et al*[13], 2011	Antegrade approach	RY gastric bypass	Choledocholithiasis (CDL)	6	TS-67%; CS-NA	Liver hematoma- 1 case
2	Iwashita *et al*[14], 2013	Antegrade approach	RY gastrojejunostomy, Whipple's	CDL, Malignant biliary obstruction (MBO)	6	TS-100%; CS-NA	Mild pancreatitis-2
3	Itoi *et al* [15], 2014	Antegrade approach	RY, Gastric bypass, Billroth reconstruction	CDL, MBO	5	TS-60%; CS-NA	Nil
4	Khashab *et al*[16], 2016	Antegrade approach	RY reconstruction, RYGB, Whipple, B-II	CDL, MBO	49	TS-98%; CS-88%	20%
5	Miranda-García *et al* [17], 2016	Antegrade approach	Biliary enteric anastomosis (details N/A)	Anastomotic stricture	7	TS-57%; CA-100%	70% Bleeding, stent migration
6	Iwashita *et al*[18], 2016	Antegrade approach	GR with RY-19; GR with BII-3; GR with jejunal interposition-2; PD-4; BDR with HJ-1	CDL	29	79%	17% Bile peritonitis, cholecystitis, elevated CRP
7	James *et al* [19], 2018	Antegrade approach	RYGB, RY, B-II reconstruction, Whipple	Benign biliary stricture	20	TS-95%; CS-95%	15% Abdominal pain, mild pancreatitis, mild cholangitis
8	Hosmer *et al*[20], 2018	Antegrade approach	RYGB, RY	CDL	9	TS-100%; CS-NA	11% Cholangitis
9	Mukai *et al* [21], 2019	Antegrade approach	RY, RYGB, Whipple, B-II	Benign biliary stricture, CDL	48	TS-91.9%; CS-91.9%	8.1% Biliary peritonitis
10	Huang *et al* [2], 2020	Transmural drainage; EUV RV-8; EUS-HG = 14; EUS-CD-11	Billroth I, Billroth II, RYGB, RYHJ Roux-en-Y choledochoje-junostomy	MBO	33	TS-93.3%; CS-84.9%	9.09% Haemorrhage, cholangitis
11	Minaga *et al*[23], 2020	Transmural stenting -24; Antegrade stenting-2; Combination of transmural and antegrade-14	Gastrectomy with RY, Billroth-II, Pancreaticoduodenectomy, RYHJ	MBO	40	TS-100%; CS-95%	15% Bile leak, biliary peritonitis, pneumoperitoneum

CDL: Choledocholithiasis; CS: Clinical success; CRP: C Rectaive protein; EUS: Endoscopic ultrasound; MBO: Malignant biliary obstruction; RY: Roux-en-Y; RYGB: Roux-en-Y gastric bypass; RYHJ: Roux-en-Y hepaticojejunostomy; TS: Technical success.

drainage is planned EUS-RV or EUS-antegrade approach or EUS-CDS or EUS-HGS can be utilised depending. In case of inaccessible papilla with RYGB, EDGE procedure can be used with success. If EDGE procedure is not feasible then EUS-HGS is the option. For Whipple's, Billroth II reconstruction, Roux-en-Y hepaticojejunostomy, EUS guided antegrade interventions, EUS-HGS guided interventions can be performed for both benign and malignant biliary indications. For malignant hilar obstructions with surgically altered anatomy multiple procedures may be required including percutaneous biliary drainage to drain right side hepatic ducts.

CONCLUSION

EUS guided biliary interventions are feasible in surgically altered anatomy for benign as well as malignant indications. EUS-BD equals PTBD and scores over enteroscope assisted ERCP in terms of success rate in patients with biliary obstruction and surgically altered anatomy. With advent of newer devices like LAMS these techniques will develop further and has potential to be 'primary modality' for biliary drainage in patients with biliary obstruction and surgically altered anatomy.

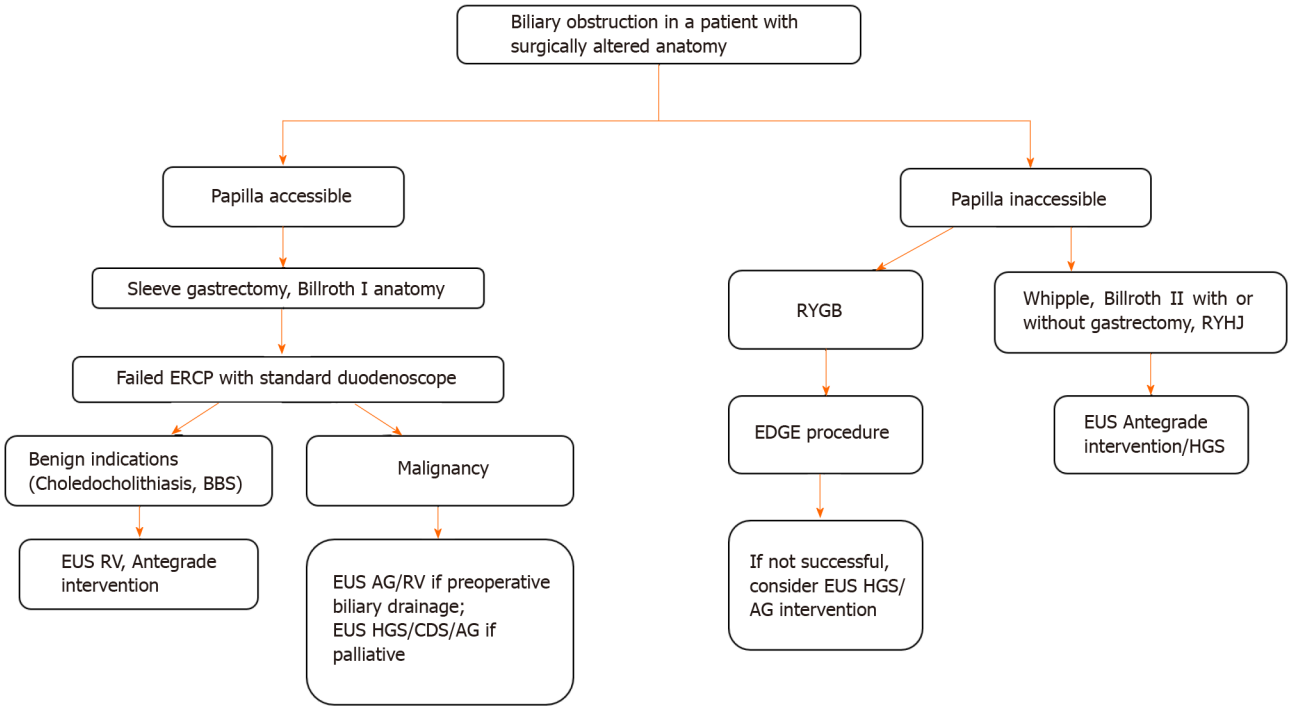

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Figure 5 Algorithm for endoscopic ultrasound guided intervention in patients with surgically altered anatomy. AG: Antegrade stenting; BBS: Benign biliary stricture; CDS: Choledochoduodenostomy; EUS RV: Endoscopic ultrasound rendezvous; HGS: Hepaticogastrostomy; EDGE: Endoscopic Ultrasound Directed Transgastric ERCP; RYHJ: Roux-en-Y hepaticojejunostomy; RYGB: Roux-en-Y gastric bypass.

FOOTNOTES

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MINIREVIEWS

Quality of bowel preparation in patients with inflammatory bowel disease undergoing colonoscopy: What factors to consider?

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Abstract

An adequate bowel preparation in patients with inflammatory bowel disease (IBD) is a prerequisite for successful colonoscopy for screening, diagnosis, and surveillance. Several bowel preparation formulations are available, both high- and low-volume based on polyethylene glycol. Generally, low-volume formulations are also based on several compounds such as magnesium citrate preparations with sodium picosulphate, oral sulphate solution, and oral sodium phosphate-based solutions. Targeted studies on the quality of bowel preparation prior to colonoscopy in the IBD population are still required, with current evidence from existing studies being inconclusive. New frontiers are also moving towards the use of alternatives to anterograde ones, using preparations based on retrograde colonic lavage.

Key Words: Bowel preparation; Colonoscopy; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Artificial intelligence

Core Tip: Obtaining adequate bowel preparation is challenging when treating a patient with inflammatory bowel disease (IBD) undergoing colonoscopy. Colonoscopy has multidimensional value ranging from diagnosis to disease surveillance and cancer screening. Although numerous data are available on bowel preparations in the general population, it is still unclear which preparation is the best for both efficacy and safety in patients with IBD. In addition, the factors that increase the risk of suboptimal preparation in IBD patients remain unclear.

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INTRODUCTION

Adequate bowel preparation is crucial for successful colonoscopy in diagnostic, therapeutic, and screening indications; however, it remains one of the main challenges in patients undergoing colonoscopy[1,2]. Thus, several requirements were identified for managing this issue, including improving the palatability and tolerability of bowel preparation products and adopting a tailored, patient focused approach by taking into account the patient's choice of product[1]. Management of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), requires regular endoscopic surveillance. In patients with IBD, endoscopic procedures are indicated for initial diagnosis, monitoring of disease activity, evaluation of therapeutic response, and cancer screening[3]. The latter indication is significant as patients with IBD are at an increased risk of developing colorectal cancer[4]. In addition, a proportion of patients with IBD undergo surgical intervention and therefore require postoperative endoscopic re-evaluation to identify any postsurgical recurrence, especially in CD [5].

Emerging evidence has emphasised "treat-to-target" approaches in the management of IBD by defining specific treatment goals and punctuating the timing of evaluation. Assessment of these uses standardised endoscopic scores, the calculation of which requires adequate bowel preparation in all regions of the colon and last ileum that can be explored by colonoscopy and ileocolonoscopy[6,7]. However, especially in IBD patients, there is a need to weigh up the safety of intestinal preparations, especially under severe disease activity conditions[8]. Although rare, significant adverse events associated with bowel preparation, such as mucosal inflammation[9], intestinal perforations[10], and ischaemic colitis[11], have been reported.

The purpose of the present review is to provide an overview of the current available evidence on bowel preparation formulations, specifically evaluated in IBD, to determine the factors of successful and unsuccessful bowel preparation in patients with IBD, and to provide clues on the appropriate choice of formulation for IBD patients.

TYPE OF BOWEL PREPARATIONS STUDIED IN IBD

Several bowel preparations are available for patients undergoing colonoscopies. They can be categorized into high-volume (volume of at least 3 L), isosmotic, polyethylene glycol (PEG) formulations, and low-volume (volume less than 3 L, but with the addition of osmotically active adjuvants such as ascorbic-acid, citrate, and bisacodyl) PEG[12]. There are also osmotically active, non-PEG, low-volume solutions. Examples include magnesium citrate preparations or other preparations based on sodium picosulphate, oral sulphate, and oral sodium phosphate[12]. However, they have a high potential risk of adverse events due to their osmotic properties.

There are currently no studies that provide a definitive and detailed overview of the application of various bowel preparations available to patients with IBD. Table 1 summarises the bowel preparation regimens studied specifically for IBD patients. Case reports of patients with IBD and the relevant adverse events associated with bowel preparation are shown in Table 2.

Bowel preparation studied in IBD: Origins

An early trial in 1982 focused on evaluating bowel preparation in patients with UC who underwent colonoscopy for dysplasia screening[13]. The study compared two bowel preparation products, castor oil (30 mL) and senna tablets (75 mg sennosides). However, the authors highlighted post-colonoscopy complaints (particularly complaints that were more common with senna tablets) and many UC flare-ups

Table 1 Anterograde and retrograde bowel preparation regimens studied in patients with inflammatory bowel disease

Ref.	Year	Design	*n*	IBD	Bowel preparation	Split dosing considered	Low fiber diet considered	Main result (success), %	Post-colonoscopy IBD flare-up rate, % (days after colonoscopy)	Severe AEs
Gould *et al*[13]	1982	CT	23	UC: 23	Castor oil 30 mL	-	YES	82.6	26 (14-21 d)	NO
Gould *et al*[13]	1982	CT	23	UC: 23	Sennosides 75 mg	-	YES	86.9	48 (14-21 d)	NO
Lazzaroni *et al*[15]	1993	CT	48	UC: 26; CD: 23	4 L PEG-ELS plus placebo	YES	-	96	-	NO
Lazzaroni *et al*[15]	1993	CT	57	UC: 35; CD: 21	4 L PEG-ELS plus simethicone	YES	-	96	-	NO
Manes *et al*[53]	2015	CT	106	UC: 106	2 L PEG plus bisacodyl	YES	YES	83	-	NO
Manes *et al*[53]	2015	CT	105	UC: 105	4 L PEG-ELS	YES	YES	77.1	-	NO
Kim *et al* [22]	2017	CT	53	UC: 53	4 L PEG-ELS	YES	YES	96.2	5.7 (7 d); 1.9 (28 d)	NO
Kim *et al* [22]	2017	CT	56	UC: 56	2 L PEG plus ascorbate	YES	YES	92.9	3.6 (7 d); 1.8 (28 d)	NO
Briot *et al* [31]	2019	nCT Prospective		UC: 21; CD: 57; Unspecified IBD: 2	Picosulphate-based regimen	YES	YES	78.4	0	NO
Bezzio *et al*[39]	2020	nCTProspective	189	UC: 63; CD: 63	2 L PEG-ELS plus simethicone	YES	-	UC: 89.8; CD: 86.2	-	NO
Maida *et al*[25]	2021	nCT Retrospective	185	UC: 95; CD: 90	1 L PEG plus ascorbate solution	YES	YES	92.9	-	NO
Mohsen *et al*[30]	2021	CT	61	-	2 L Sodium; picosulphate, magnesium citrate PEG	YES	YES	89.5	-	NO
Mohsen *et al*[30]	2021	CT	64	-	2 L PEG plus ascorbate solution	YES	YES		-	NO
Neri *et al* [29]	2021	nCT Prospective	103	UC: 47; CD: 56	1 L PEG-ELS	YES	YES	85.4	-	NO
Kim *et al* [32]	2022	nCT Prospective	52	UC: 35; CD: 17	2 L PEG plus ascorbate	YES	YES	98.1	0 (7 and 28 d)	NO
Kim *et al* [32]	2022	nCT Prospective	55	UC: 37; CD: 18	Novel oral sulphate tablets	YES	YES	98.1	3,63 (7 and 28 d)	NO
Gajera *et al*[51]	2022	nCT Retrospective	318	UC: 182; CD: 104; Unspecified IBD: 28	Colonic lavage	Not applicable	YES	97	-	NO

IBD: Inflammatory bowel disease; PEG: Polyethylene glycol; ELS: Electrolyte lavage solution; UC: Ulcerative colitis; CD: Crohn's disease; CT: Clinical trial; nCT: Non-clinical trial.

in several cases requiring steroid treatment. In this study, they targeted patients with UC with inactive or presumably mild disease activity. The efficacy rate shown with both preparations exceeded 80%. In any case, to date, such preparations are insupportable and fall into disuse, especially given the abundant availability of new generation products with better safety margins.

Table 2 Case reports on patients with known inflammatory bowel disease and relevant adverse events related to bowel preparation

Ref.	Bowel preparation	Age	IBD	Gender	AE	Comorbidity	IBD therapy	Outcome
Loraine *et al* [34]	Sodium picosulphate/magnesium oxide/citric acid	73	CD	F	Shock	Severe COPD, hypertension, dyslipidemia, cardiomyopathy, diverticular disease	Azathioprine	Dead
Gonlusen *et al*[35]	Sodium picosulphate	56	CD	F	Acute renal failure	GERD, healed gastric ulcer, endometriosis, mitral valve prolapse, migraine	None	Favourable

IBD: Inflammatory bowel disease; CD: Crohn's disease; F: Female; AE: Adverse event; COPD: Chronic obstructive pulmonary disease; GERD: Gastroesophageal reflux disease.

High- and low-volume plus adjuvant preparations of polyethylene glycol in patients with IBD

PEG-based preparations were first introduced in 1980 by Davis *et al*[14] as an alternative to traditional laxatives. Several studies have examined high-volume PEG preparations in patients with IBD. In general, these formulations have been studied alone or in comparison to a control group of other solutions such as low-volume solutions.

An early Italian study[15] evaluated the efficacy of simethicone in addition to a 4 L PEG Electrolyte Lavage Solution (ELS). A high efficacy rate of 96% was shown in the group taking only 4 L PEG-ELS (considering at least acceptable preparation). In contrast, preparation was adequate and excellent in 50% and 27% of IBD participants, respectively. The authors defined the preparation as excellent in the absence of formed stools and the presence of low fluid content. The preparation was defined as adequate in the absence of formed stools and the moderate presence of clear fluid. Regarding the safety profile, the preparation showed poor tolerability in only 14% of participants with no serious adverse events and the main complaint was abdominal bloating.

However, two subsequent studies compared high-volume and low-volume PEG solutions with bisacodyl and ascorbic acid adjuvants.

Bisacodyl is a diphenylmethane compound. It has an extrinsic laxative action owing to its dual prokinetic and secretion properties after conversion to an intestinally active metabolite. It has shown comparable properties in some intestinal motility parameters to other drugs such as prucalopride, linaclotide, and tegaserod[16].

In a noninferiority study with 211 participants, Kastenberg *et al*[17] compared a high-volume 4 L PEG-ELS solution with a low-volume solution (2 L PEG) with bisacodyl adjuvant at 5 mg, and concluded a noninferiority of the latter over the former. They focused exclusively on patients with UC. Patients had a free choice of a split or non-split regimen, but nonetheless were instructed to eat a low fibre diet for the 3 d prior to preparation. Bisacodyl was administered by patients in the afternoon of the day before the procedure, and only after the procedure was initiated. Colon cleansing was assessed using the Ottawa scale[17]. The efficacy rate was higher in the low-volume group (83%), compared with 77.1% in the high-volume group, but the difference was not significant. In addition, the presence of bubbles was significantly worse in the low-volume group. Disease activity and the type of administration (split or not) did not influence patient compliance. In terms of safety, severe adverse reactions were not observed in both solutions. The low-volume PEG preparation with bisacodyl in this study, showed greater potential in avoiding gastrointestinal disorders associated with bowel preparation, including bloating, cramping, anal irritation, nausea, and vomiting.

In any case, the use of bisacodyl at high dosages > 5 mg should be avoided[18]. Cases of ischaemic colitis after bisacodyl use have been reported. Two cases were reported after using 15 mg bisacodyl in two women over 50 years of age with ischaemic colitis. In both cases, the patients were discharged without adverse outcomes; however, in one of the two cases, haemodynamic deterioration was experienced[19]. They were not IBD patients; however, in the latter patients, bisacodyl dosing must be weighed carefully. Certainly, such preparations should be evaluated with extreme caution in elderly patients with cardiovascular and ischaemic colitis risk factors[20] and even more so in patients with coexisting IBD.

Neurointestinal reactions are further rare but serious adverse reactions. In some studies, the use of bisacodyl as a laxative induced changes in colonic redundancy and colonic dilatation with loss of haustral markings. This is likely to have been caused by neuronal or colonic muscle damage[21]. In addition, *in vitro* evidence in rat bladder epithelium, suggests that bisacodyl has the potential to induce proliferative epithelial injury[21]. However, such evidence is still experimental and does not definitively impose a contraindication for this product. Moreover, the contraindication for bisacodyl in patients with advanced congestive heart failure should also be considered[18].

A subsequent study by Kim *et al*[22] investigated the low-volume solution adjuvant ascorbic acid, and compared this with classic high-volume 4 L PEG-ELS. As in the previous study, the authors exclusively targeted 109 patients with inactive UC. In addition, in this study, patients were given a free choice

between a split and non-split regimen, and were advised to eat a fibre-free diet for 2 d before the endoscopic examination. Bowel preparation quality was assessed with the Boston Bowel Preparation Scale (BBSP)[23] and a score of equal to or greater than 6 defined a successful preparation. The authors also assessed possible disease recurrence 4 wk after the endoscopic procedure using the Simple Clinical Colitis Activity Index[24], with a cut-off greater than 4 defined as recurrence. In both groups, the split regimen was the most widely used, and more than 90% of patients in both groups achieved an effective preparation. The safety profile was slightly worse in the 4 L PEG group, but not significantly different from that of the low-volume preparation. However, patients treated with 4 L PEG experienced a significantly higher rate of nausea. There was no difference in disease recurrence at 1 mo, which was more, but not significantly greater than that in the low-volume group with ascorbate (25% *vs* 22.6%, respectively).

Moreover, in the context of ascorbate-based preparations, Maida *et al*[25] evaluated a preparation with 1 L of PEG in 185 patients with IBD, compared with 226 non-IBD controls. The study concluded a higher clearance rate (assessed by the BBSP) than in non-IBD controls (92.9% *vs* 85.4%), and a similar safety profile between IBD and non-IBD. No correlation was found between disease activity and incidence of adverse events. The rate of non-severe adverse events was 22.2% in IBD patients compared with 21.2% in controls, and there were no severe adverse events in the study.

Patients with phenylketonuria or glucose-6-phosphate dehydrogenase deficiency should not undergo this type of preparation due to the presence of ascorbate[26]. Some case reports of serious adverse events have also been described with ascorbic acid. For example, an > 70-year-old hypertensive diabetic woman experienced ischaemic colitis with 200 g of 3350 PEG in 1 L and 21 g of ascorbic acid solution [27]. An 82-year-old woman with atrial fibrillation and mild chronic renal failure received a 1 L PEG preparation with ascorbate and experienced non-occlusive mesenteric ischaemic colitis[28]. Both were elderly, non-IBD patients, with cardiovascular risk factors. Therefore, similar to bisacodyl, such preparations should be weighed carefully in elderly patients with IBD and cardiovascular risk factors. In addition, attention should be paid to patients with advanced heart failure, unstable angina, and creatinine clearance < 30 mL/min. In these patients, adequate hydration should be considered when such a formulation is used[18].

Finally, an attempt with very low-volume PEG-based preparations (1 L PEG) was made by Neri *et al* [29]. In a cohort of 103 IBD patients, with good distribution between CD and UC, Neri *et al*[29] showed an adequate preparation rate of 85.4% (assessed by BBSP), with an impact of disease activity on preparation rate. This evidence, coupled with a good safety profile, makes this preparation a good choice for patients with a very low tolerance for high-volume preparations.

Moreover, a final study by Mohsen *et al*[30] evaluated a comparative single-blinded randomised trial for both preparation type and population (IBD *vs* non-IBD patients). The authors compared a preparation based on sodium picosulphate/magnesium citrate in combination with PEG and a low-volume preparation of PEG with ascorbic acid. The two preparations did not differ in terms of efficacy (assessed by the Ottawa scale) or safety. Although, in the group of IBD patients on the low-volume preparation of PEG with ascorbic acid, the incidence of abdominal pain increased. Overall, only 10.5% of the patients had inadequate preparation.

What are the alternatives to polyethylene glycol-based preparations in focused studies in patients with IBD?

Alternatives to PEG-based preparations include those based on magnesium citrate plus picosulphate and oral sulphate solutions, a compound of magnesium sulphate, sodium sulphate, and potassium sulphate. However, few studies have evaluated these preparations for IBD treatment.

A 2019 French multicentre study examined several low-volume solutions based on sodium picosulphate, sodium phosphate, and trisulphate (sodium, magnesium, and potassium sulphate)[31]. All three of these non-PEG regimens had been administered in more than 50% of the sample in a split regimen, with a previous low fibre diet lasting between one and more than 3 d, depending on the regimen. The efficacy rate in the preparation with sodium picosulphate reached 78.4%, comparable with 76.7% of the 2 L PEG examined in the same study. Both formulations were significantly more effective than the control 4 L PEG group. In addition, patient tolerance was better in the picosulphate group than in the 2 L and 4 L PEG groups. The safety profile of sodium picosulphate was not extremely harmful because there was one case of fever and another of vomiting in CD patients (however, the sample receiving this formulation consisted of only approximately 80 patients). Oral sulphate tablets were evaluated in the study by Kim *et al*[32], however, only in 110 patients with inactive IBD in non-inferiority comparison with split regimens with a 2 L PEG preparation with ascorbic acid. The study showed a greater tolerance for the oral sulphate-based preparation, so much so that more than 90% of the patients taking it stated that they would reuse it for subsequent colonoscopy.

Regarding safety, although there were no severe events, a small percentage of patients (only two) on oral sulphate showed disease flare-ups after colonoscopy. Furthermore, caecal intubation was achieved more quickly in the PEG-based preparation (100%) than in the sulphate preparation (92.8%). Finally, the preparation with sulphate achieved a lower and, therefore, better score for bubble presence. There is still little evidence to justify the use of such alternative preparations to PEG-based preparations in patients

with IBD, so much so that the recommendations of endoscopic reference societies tend to recommend PEG-based solutions in patients with IBD[18].

In fact, previous evidence has shown that in settings other than IBD, solutions based on sodium phosphate or sodium picosulphate for intestinal preparation had a 10-fold increased risk of developing intestinal mucositis compared with preparations with PEG[33].

Cases of post-preparation shock with picosulphate-based solutions have also been described[34] as well as of acute renal failure[35]. Unlike PEG-based solutions, these solutions are hyperosmolar and challenging to handle and contraindicated in patients with heart failure, rhabdomyolysis, hypermagnesemia, gastrointestinal ulcerative lesions, and renal failure[18].

Role of simethicone as an additional component in bowel preparation

Simethicone is a compound of dimethicone and 4%-7% silicon dioxide. This surfactant can reduce the surface tension of bubbles in the intestinal lumen by removing them. This improves clarity of endoscopic examination and reduces abdominal tension (Figure 1)[36].

Few studies have investigated the role of simethicone in intestinal preparations, specifically for patients with IBD. Metanalytic evidence has suggested its potential to improve mucosal cleanliness and visibility, providing evidence to increase the detection rate of adenomas and polyps[37,38]. Therefore, Lazzaroni *et al*[15] began experimenting in a randomised controlled trial with high-volume 4 L PEG-ELS in IBD, comparing with a double-arm design by adding 120 mg of simethicone.

In the study, the mean age of the participants was under 40 years for both arms. The cohort mainly consisted of UC patients. Regarding efficacy rates, bowel preparation was at least acceptable in 96% of cases in both arms. Although efficacy was not found to be a significant distinguishing element between the arms with or without simethicone, it was interesting to note a significant ameliorative effect on the presence of bubbles. Bubbles were either not detected or minimally impacted the examination in 98% of the sample with simethicone *vs* 85% of patients taking 4 L PEG alone. The tolerability of patient preparation increased in favour of the simethicone-based preparation. Generally, in this study, the addition or non-addition of simethicone did not dramatically affect the differences in safety. These were mainly comparable in terms of nausea, cramping pain, and abdominal bloating, except for sleep disturbances and general malaise, which were drastically lower in patients in the simethicone group (19% *vs* 44%). Bezzio *et al*[39] also showed good efficacy and tolerability of a 2 L PEG-ELS solution with added simethicone in 126 patients with IBD.

Further evidence on simethicone in patients with IBD, was provided by studies in a different setting, namely, studies of patients undergoing small-bowel capsule endoscopy[40-42]. One study observed that adding 80 mg of simethicone to a 2 L PEG preparation improved visualisation of the intestinal mucosa more in the proximal rather than in the distal tract, but only in non-CD patients. This effect was likely due to altered motility in CD patients[42]. In addition, in the paediatric population, adding simethicone to the PEG preparation appears to give good results in small-bowel capsule endoscopy; however, good visualisation of the terminal ileum remains challenging[41].

In any case, it is noteworthy that the most recent European guidelines recommend adding simethicone to intestinal preparations, cautiously leaning towards improved cleanliness and tolerability, despite a strong need for evidence to reaffirm this recommendation[18].

A study which was not solely conducted in the IBD population, analysed the optimal timing of simethicone administration in bowel preparation. The study suggested that optimal simethicone administration in the PEG-based preparation was in the evening of the day before colonoscopy. Moreover, the ameliorative effect is primarily at the expense of caecal intubation and bubble improvement[43]. This evaluation was further conducted in another study, combining a PEG preparation with ascorbic acid. Again, patients who took simethicone in the evening of the day before colonoscopy, showed fewer bubbles and improved detection of diminutive adenomas less than or equal to 5 mm[44].

Although not directly analysed in patients with IBD, improvement in the ease of caecal intubation[43] should be considered. Patients with ileal CD, both at the first diagnosis and at follow-up, should be carefully studied in the small intestinal tract. One of the most widely used scores is the Simple Endoscopic Score for Crohn's Disease[45] uses a thorough assessment of the ileum to identify the presence of ulcerative lesions and/or stenosis. This need is also reaffirmed by another endoscopic score, the Crohn's Disease Index of Severity, most commonly used in patients with CD[46].

The use of intraprocedural simethicone requires several technical considerations. A spectroscopic study of residual fluid samples detected with borescopes in the colonoscope channel found residual simethicone[47]. This study indicated that as simethicone is an inert and hydrophobic compound, it can reduce the effectiveness of endoscope reprocessing. In addition, simethicone is often included in solutions containing sugars which can potentially increase intra-endoscopic microbial growth[48]. Moreover, several dimethicone crystals have been detected in the waterjet channel of a damaged endoscope[49]. Therefore, European guidelines have warned about using simethicone at the lowest effective dose[50], exclusively in the biopsy channel and not in the auxiliary water channel[18].

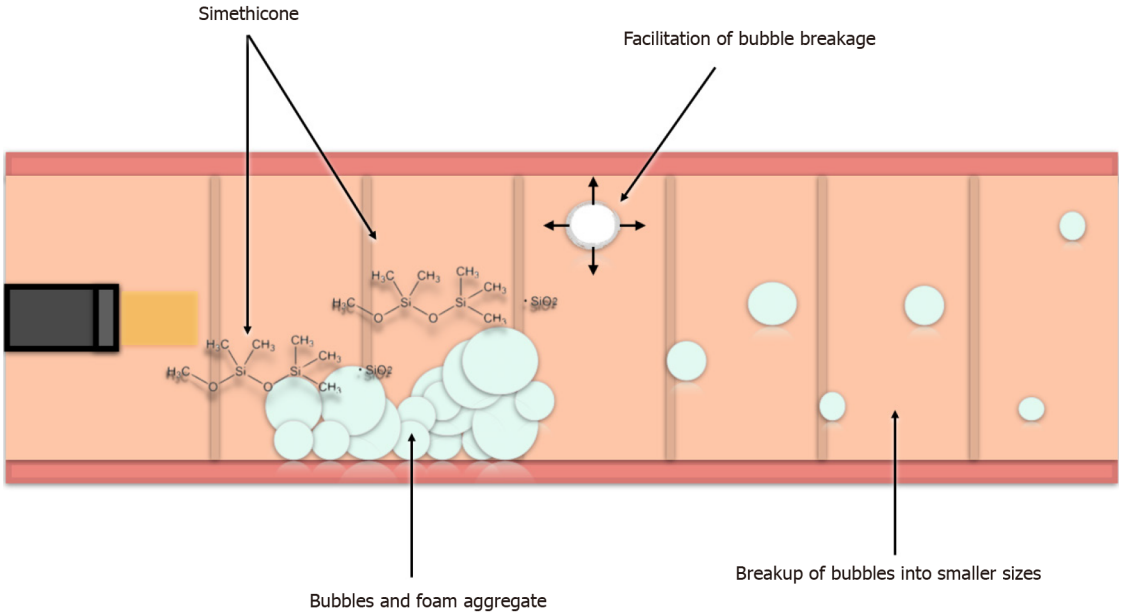

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Figure 1 Functioning of simethicone at the level of the intestinal mucosa. Simethicone is a surfactant causing a reduction in the surface tension of intestinal bubbles. This reduction results in the aggregate of bubbles adhering to the colic mucosa being weaker with the facilitation of bubble reduction. As a result, larger bubbles are divided into smaller bubbles that have a greater ease of intestinal transit. The silicon dioxide component of dimethicone has an additional role, with an extensive molecular surface area that can promote bubble rupture. The breakdown of foam and bubbles and formed gas can be either absorbed by the intestinal wall or eliminated by intestinal transit. This likely explains the ameliorative effect on patients' symptoms.

Role of high-volume colonic lavage as a bowel preparation strategy: A retrograde strategy

In addition to conventional oral bowel preparations, a promising method of retrograde bowel preparation (already evaluated in non-IBD patients), high-volume water irrigation with colonic lavage, has recently been explored for IBD. This is undoubtedly a preparation modality that overcomes the obstacles and predictors of poor bowel preparation observed for oral bowel preparation. Moreover, it is likely to be more "palatable" to patients who experience problems with oral bowel preparation. However, it can be practiced only in a hospital setting, and after prescription by experienced practitioners. In a recent study, Gajera *et al*[51] examined this modality (Figure 2) in a retrospective study of more than 300 patients with IBD. The efficacy of bowel preparation was above 90% (except in patients with severe hemorrhoidal disease, in whom it was just under 90%).

Interestingly, a high efficacy rate of 94% was recorded, even for patients with previous gastrointestinal surgery. No severe reactions were observed; the most frequent mild reaction was abdominal pain in approximately 15% of patients. This study was not restricted to a specific IBD and had a good distribution of UC and CD. In this study, IBD patients were required to take bisacodyl (10 mg) the day before colonic lavage. In other non-IBD cases, this was magnesium hydroxide, 1-5 d before.

Comparisons between preparations: What evidence in IBD?

There is still a need for numerous studies on the preparations already available in singles for patients with IBD, especially in the different IBD subgroups with increased severity, such as patients with perianal disease and CD with stenosing phenotype. However, there are even fewer available data of head-to-head comparisons among different regimens.

A meta-analysis by Restellini *et al*[52] was designed specifically for patients with IBD with adequate bowel preparation as the primary outcome. The study included four previously described studies by Gould *et al*[13], Lazzaroni *et al*, Manes *et al*[53], and Kim *et al*[22].

The study by Gould *et al*[13] was excluded owing to a lack of clinical applicability of castor oil or senna. Furthermore, the study by Lazzaroni *et al*[15] was excluded owing to a lack of robust data on the efficacy of preparation with the addition of simethicone. The remaining two studies compared high- and low-volume PEG-based solutions. Examining these two analytical methods, the authors concluded that there were no relevant differences in preparation quality. Shifting the perspective onto the patient's tolerability and willingness on the choice of regimen for subsequent colonoscopy, the winning regimens were the addition of simethicone to the 4 L PEG preparation, and the 2 L PEG preparation with bisacodyl or ascorbate compared with high volumes. Meta-analyses comparing PEG-based and non-PEG preparations are still needed. Even fewer comparative data exist between oral and retrograde rectal anterograde IBD preparations. An additional study, particularly relevant to colorectal cancer prevention in IBD, advised IBD patients undergoing chromoendoscopy to follow a clear fluid diet the day before

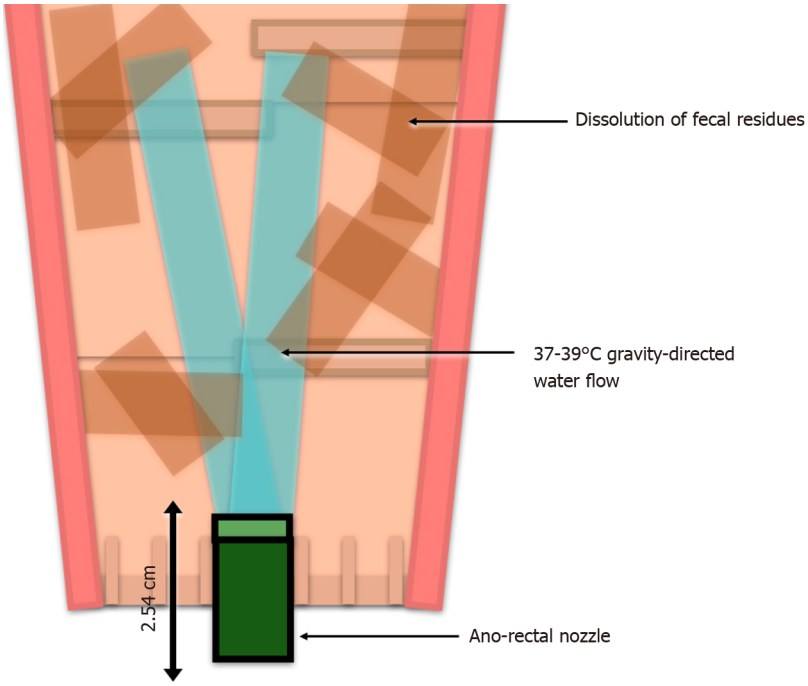

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Figure 2 Colonic lavage process. A nozzle is inserted approximately 2.54 cm into the rectum of the patient on a disinfected stand. According to the gravity gradient, a direct flow of water is dispensed from the nozzle at the rigidly controlled temperature of 37-39 °C, with immediate termination of the procedure if this temperature is exceeded. The water flow makes the stool soft, facilitating its dissolution and elimination. The procedure is generally complete within an hour, and the patient can subsequently undergo an endoscopic examination.

colonoscopy[54].

Predictors of IBD patients' poor bowel preparation?

The extreme phenotypic variability of patients with IBD and the different regimens available for bowel preparation pose a problem for stratifying bowel preparation, identifying which patients are most at risk of poor bowel preparation, and with which preparations.

Several predictors of poor bowel preparation have been identified in PEG-based and UC-based studies, including male sex, non-split regimen, poor patient compliance (less than 100% intake), and moderate to severe discomfort during preparation[53]. The split regimen was a predictor of good bowel cleansing success in the study by Maida *et al*[25] with a 1 L PEG regimen with ascorbate. In another study that included both PEG-based and non-PEG regimens, PEG 2 L or 4 L regimens were associated with greater efficacy. Having a CD or colonoscopy in private *vs* public centres has also contributed to this[31]. Other evidence indicates that patients with active CD, experience more abdominal pain during bowel preparation, and patients with worse anxiety experience more symptoms during bowel preparation[55].

In contrast, a recent study by Kumar *et al*[56] highlighted an interesting finding relating bowel preparation to disease activity and biological therapy. Moderate-to-severe disease activity and biological therapy were predictors of suboptimal bowel preparation. Additional predictors of poor preparation identified in the study were, a non-split regimen, and patient age of over 65 years.

One Digestive Disease Week 2022 abstract presented a retrospective study of factors of inadequate bowel preparation for colonoscopy related to underlying IBD in 309 patients. The authors described how the presence of diabetes mellitus and antidepressant use were independent general risk factors in this setting. Indeed, it is well known that diabetes mellitus is a non-negligible comorbidity in IBD patients, increasing the risk of hospitalisations and infections, while not increasing the general risk of IBD complications or mortality[57]. In patients with UC, a history of inadequate bowel preparation was an independent risk factor[58].

One study aimed to investigate the experiences of IBD patients who resorted to repeat colonoscopy through telephone interviews. Despite the small sample size of approximately 33 patients, it emerged that patients felt that repeated colonoscopy was a guarantee of their health, and an ongoing reminder of the chronic and incurable nature of IBD[59]. This underscores how beyond looking for predictors and patient compliance, healthcare providers should strive to assist patients who require continuity of care. This is also in view of the fact that, as demonstrated by the COVID-19 pandemic, patients with IBD are exposed to a higher rate of anxiety and depression than the general population[60], even in disease remission[61]. Moreover, IBD patients are exposed to a non-negligible rate of treatment nonadherence

[62,63].

Patients with active IBD: What factors to consider?

Bowel preparations can result in mucosal damage, with some studies having associated cases of toxic megacolon[64-67]. Therefore, caution becomes of utmost importance in patients with active IBD. PEG-based or sulphate-based solutions can induce colic mucosal damage by inducing metabolic or chemical damage[22]. Such histological damage results are also seen with sodium picosulphate[68]. As stated earlier, the risk of mucosal inflammation with PEG solutions is around ten times lower than that with those based on picosulphate or sulphate. Furthermore, picosulphate solutions can cause ulcerative lesions at the esophagogastric level[69,70]. In light of these facts, it is inevitable that for patients with active IBD, the only advisable solutions based on the available evidence, are PEG-based solutions[18,71]. Clearly, within active UC, a distinction must be made between moderate to severe and severe acute UC. Severe acute UC generally includes several diagnostic criteria (the presence of more than six bloody evacuations per day and at least one of the following: Body temperature greater than 37.8 °C, heart rate greater than 90 bpm, haemoglobin less than 105 g/L, and C-reactive protein greater than 30 mg/L. Under these conditions, the risk of impending megacolon, toxic megacolon, and colectomy is very high. Therefore, in addition to the initiation of treatment, it is appropriate to screen for confounding factors of disease activity. First, a faecal culture screening for *Clostridium difficile* should be performed. However, an evaluation of rectal biopsy for cytomegalovirus should also be performed. For cytomegalovirus evaluation, a complete colonoscopy is not recommended due to the high risk of bowel perforation and a simple sigmoidoscopy is appropriate[72]. Therefore, the problem of choosing the appropriate bowel preparation arises. In such cases, a simple phosphate enema generally suffices, as regular oral bowel preparation may increase the risk of colic dilatation[71].

Prospects: Role of artificial intelligence

More recently, artificial intelligence (AI) applications are emerging for use in digestive endoscopy, with indications from diagnosis to treatment[73-75]. In addition, promising AI results have also emerged for adenoma and polyp detection rates[76]. However, to date, the assessment of bowel preparation has been performed by the general application of scales by an endoscopist. Thus, assessment of bowel preparation is strongly dependent on the endoscopist[1].

However, even in bowel preparation, AI systems have been used in various experiments. For example, the ENDOANGEL system, which is based on deep convolutional neural network (CNN) technology, showed a higher BBPS calculation accuracy than operators with less than one year of experience, and operators with more than three years of experience. Furthermore, ENDOANGEL has an overall accuracy in classifying colonoscopy images of 91.89% and was associated with a 30-second reminder system for the endoscopist on bowel preparation assessment. Such a reminder system has the potential to overcome the limitations of BBPS. The reminder system is based on the selection of representative segments of different colic localisations. In contrast, this system is based on continuous video images, which are more representative of the bowel preparation of the whole colon[77]. The experience of Lee *et al*[78] also supports the use of AI systems, using two CNN algorithms and set on a BBPS. This study also provided encouraging results with an accuracy for inadequate bowel preparation of 85.3%, and an area under the curve of more than 0.8 (0.918).

Furthermore, the κ index of agreement between raters without and with AI was similar. Su *et al*[79] developed an automated quality control system for lower endoscopy, based on CNN. However, the system was not explicitly designed for exclusive evaluation of bowel preparation. Instead, it evaluated the withdrawal phase and stability, as well as the detection rate of colorectal polyps. In addition, the CNN system showed significant superiority in evaluating bowel preparation.

Ultimately, despite the paucity of available studies, the applications of AI and CNN in the real-time assessment of bowel preparation have non-negligible potential. Such an application may have a positive impact, improving several parameters including accuracy in the assessment of bowel preparation, prediction of the difficulty of caecal intubation, and estimation of the sensitivity of the examination in cancer screening.

CONCLUSION

Bowel preparation remains one of the main difficulties encountered by IBD patients undergoing colonoscopy. In general, PEG-based preparations appear to have the best safety profile and are recommended by endoscopic reference scientific societies for patients with IBD. Indeed, the timing of bowel preparation plays a relevant role, with split regimens being preferred. Caution must be exercised in patients with active intestinal inflammation due to the risk of mucosal damage associated with bowel preparation. New forms of preparation are emerging in both modalities, such as retrograde technology, with the integration of AI into quality assessment. However, new evidence is needed to enable tailoring of preparations to individual IBD patients. This will improve patient compliance and procedure efficacy.

FOOTNOTES

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Case Control Study

Orientation in upper gastrointestinal endoscopy—the only way is up

Arun Sivananthan, Georgina Kerry, Ara Darzi, Kinesh Patel, Nisha Patel

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Abstract

BACKGROUND

Oesophagogastroduodenoscopy is the gold standard investigation for the upper gastrointestinal (UGI) tract. Orientation during endoscopy is challenging and United Kingdom training focusses on technical competence and procedural safety. The reported location of UGI pathologies is crucial to post-endoscopic planning.

AIM

To evaluate endoscopists' ability to spatially orientate themselves within the UGI tract.

METHODS

A cross sectional descriptive study elicited, using an anonymised survey, the ability of endoscopists to orientate themselves within the UGI tract. The primary outcome was percentage of correct answers from all surveyed; secondary outcomes were percentage of correct answers from experienced *vs* novice endoscopists. Pearson's χ^2 test was applied to compare groups.

RESULTS

Of 188 respondents, 86 were experienced endoscopists having completed over 1000 endoscopies. 44.4% of respondents correctly identified the anterior stomach and 47.3% correctly identified the posterior of the second part of the duodenum (D2). Experienced endoscopists were significantly more likely than novice to identify the anterior stomach correctly [61.6% *vs* 31.3%, $X^2(1, n = 188) = 11.10$, $P = 0.001$]. There was no significant difference between the two groups in identifying the posterior of D2.

CONCLUSION
The majority of endoscopists surveyed were unable to identify key landmarks within the UGI tract. Endoscopic orientation appears to improve with experience yet there are some areas still not well recognised. This has potential considerable impact on post-endoscopic management of patients with posterior duodenal ulcers being more likely to perforate and associated with a higher rebleeding risk. We suggest the development of a consensus statement on endoscopic description.

Key Words: Endoscopy; Orientation; Upper gastrointestinal; Gastric cancer; Duodenal ulcer

Core Tip: The majority of endoscopists surveyed were unable to identify key landmarks within the UGI tract. Endoscopic orientation appears to improve with experience yet there are some areas still not well recognised. This has potential considerable impact on post-endoscopic management of patients with posterior duodenal ulcers being more likely to perforate and associated with a higher rebleeding risk. We suggest the development of a consensus statement on endoscopic description.

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INTRODUCTION

Oesophagogastroduodenoscopy (OGD) is the gold standard investigation for the upper gastrointestinal (UGI) tract allowing direct visualisation, tissue sampling and a widening remit of therapeutic curative procedures for early cancers.

Endoscopy's role in diagnosing UGI cancer continues to advance, with a better understanding of precursor changes such as Barrett's and atrophic gastropathy and evolving technologies like image enhanced endoscopy and computer aided detection systems. Despite this 11.3% of UGI cancers are missed by OGD[1]. The role of endoscopy in the management of benign UGI conditions has also improved. There are increasing therapeutic options to intervene endoscopically on complex bleeds, or UGI perforations, with patients who historically would have required surgery now often being managed endoscopically.

There are growing numbers of guidelines and statements to help support approaches to surveillance and management of UGI pathology including a standardised approach to photo-documentation of the UGI tract[2-4]. There are numerous widely accepted protocols on UGI surveillance such as the Seattle protocol for assessing Barrett's and the Sydney protocol for assessing chronic gastritis[5]. These guidelines require accurate identification of the endoscopic anatomy for appropriate sampling and photo- documentation. However, there is no clear consensus nor accepted statement in understanding orientation or reporting locations within the UGI tract.

Orientation within the UGI tract during endoscopy is challenging due to the complex interaction between the flexibility of the scope, the multiple degrees of freedom of the endoscope tip, use of torque and the predominant focus on the (inverted) displayed image.

Training in the United Kingdom focusses predominantly on technical competence and the safety of the procedure. Lesion detection and identification, reporting and management happen experientially during real-time endoscopy and competency is determined by the individual trainer, with no formal evaluation of these skills in place.

The reported location of UGI pathologies such as ulcers directly impacts post-endoscopy investigation and management. Gastric ulcers located on the greater curve are more commonly malignant, whereas benign gastric ulcers occur predominantly on the lesser curve[6]. Ulceration in the first part of the duodenum (D1) is more likely to lead to perforation if the ulcer is located on the anterior wall and although the overall perforation rate in peptic ulcer disease is relatively low most ulcers that do perforate are anterior D1[7].

The gastroduodenal artery is located directly behind the posterior aspect of the duodenum. Ulcers on the posterior duodenal wall are at risk of eroding into this artery which can result in massive bleeding and as such carry a worse prognosis[8]. Posterior duodenal ulcers are also associated with a higher rebleeding risk[9,10], and the accurate identification of a posterior duodenal ulcer is important to understand the proximity of the gastroduodenal artery and thus the understanding of endoscopic limits and appropriate targets for interventional radiology or surgery if required.

The RCA, PubMed, Cochrane Library and Embase databases were searched until January 10th 2023 to identify relevant research articles. This revealed limited available data on orientation within the UGI tract. One paper was identified from 1992 showing only a 28% accuracy in endoscopists identifying the posterior duodenal bulb[11].

The authors hypothesise that the combination of the focus of training, the complexities of orientation and the lack of a clear consensus guidance have compromised description of orientation and location in the UGI tract.

The aim of this study is to evaluate endoscopists' ability to spatially orientate themselves within the UGI tract during endoscopy as manifest in their reporting of locations.

MATERIALS AND METHODS

Study design

A cross sectional descriptive survey study design was used. The study was approved by the Imperial College London institutional review board. A questionnaire was developed by the authors using anonymised endoscopy pictures taken by the author (Sivananthan A) (with consent for publication given by the patients).

Anonymised endoscopic pictures of the gastro-oesophageal junction, gastric body and the first two parts of the duodenum were used. Images were annotated in each of the four quadrants of the image (Figure 1) to give four options. The patient position (left lateral decubitus) was specified. Orientation of the quadrants in the images and corresponding correct responses were determined in a two-stage process, initially proposed by Sivananthan A/Kerry G and agreed by Patel N/Patel K in the context of the available literature[3-5,12-15]. The questionnaire was developed in Qualtrics™ (Provo, UT, United States). Demographics including specialty and endoscopic experience were also collected.

The primary outcome was the percentage of correct answers amongst all surveyed. Secondary outcomes were the percentage of correct answers from experienced *vs* novice endoscopists.

Data collection

The survey was distributed through existing national endoscopic research networks including the "digital gastroenterology training network" and opportunistically to endoscopists at the British Society of Gastroenterology Annual Meeting. Inclusion criteria was any experience performing OGDs in adult patients. There were no exclusion criteria. Clinical role of the endoscopists were asked including consultant (equivalent to attendee), registrar (gastroenterology specialist trainee), senior house office (early-stage medical training) and nurse endoscopists (specialist nurses trained to independently perform endoscopy).

Statistical analysis

Results were collected anonymously using the Qualtrics software and exported to Microsoft Excel for basic statistical analysis. Experienced endoscopists were classified as those who had performed more than 1000 OGDs. Novice endoscopist were classified as those who has completed 1000 or less OGDs. Percentages were used to analyse the discrete data for all subjects. Pearson's χ^2 test was applied to compare the two groups using a p value below 5% to denote significance.

RESULTS

Demographics

There were 188 respondents to the survey (Table 1). Of these: 74 respondents were consultants, 91 were registrars and 23 were nurse endoscopists. Most were physicians (184) and four were surgeons. There were 163 independent accredited endoscopists and 25 training endoscopists. There were 86 experienced endoscopists having completed more than 1000 endoscopies with 102 novice endoscopists completing 1000 or fewer endoscopies.

All respondents

44.4% of all respondents identified the anterior oesophagus correctly (Table 2). 48.4% of all respondents were able to identify the anterior stomach correctly. 43.1% of all respondents were able to identify the anterior of the first part of the duodenum correctly. 47.3% correctly identified the posterior of the second part of the duodenum.

Experienced vs novice

Experienced endoscopists were significantly more likely than novice endoscopists to identify the anterior oesophagus (44.2% *vs* 22.5%, $\chi^2_{(1,\ n\ =\ 188)} = 9.97$, $P = 0.002$), the anterior stomach than novice

Table 1 Demographics of survey respondents

	Percentage (number)
Grade	
Consultant	39.4% (74)
Registrar	48.4% (91)
Nurse endoscopist	12.2% (23)
Speciality	
Medicine	97.9% (184)
Surgery	21.% (4)
Accreditation	
Independent	86.7% (163)
Not Independent	13.3% (25)
Experience	
Experienced (> 1000)	45.7% (86)
Novice (≤ 1000)	54.3% (102)

Table 2 Correct responses by total respondents, percentage—percentage and absolute number

	All (188)
Anterior oesophagus	32.4% (61)
Anterior stomach	48.4% (91)
Anterior D1	43.1% (81)
Posterior D2	47.3% (89)

D1: The first part of the duodenum; D2: The second part of the duodenum.

endoscopists (61.6% *vs* 31.3%, $\chi^2_{(1, n = 188)} = 11.10$, $P = 0.001$) and the first part of the duodenum than novice endoscopists (51.2% *vs* 36.3%, $\chi^2_{(1, n = 188)} = 4.22$, $P = 0.040$) (Table 3).

There was no significant difference between experienced endoscopists and novice endoscopists in identifying the posterior of the second part of the duodenum (41.9% *vs* 52.0%, $\chi^2_{(1, n = 188)} = 1.91$, $P = 0.167$).

DISCUSSION

This study demonstrates that the majority of endoscopists surveyed were unable to accurately identify key landmarks within the UGI tract. This is in keeping with previous work showing the majority of endoscopists being unable to identify the posterior duodenal bulb in 1992.

Although there is no clear evidence that accuracy of orientation and landmark identification during endoscopy has a direct impact on patient outcomes there are logical reasons to think that this would be the case.

Consensus statements on photo-documentation, including those from the British Society of Gastroenterology, European Society of Gastrointestinal Endoscopy, American Gastroenterological Association, American Society of Gastrointestinal Endoscopy and the World Congress of Gastroenterology are reliant on endoscopists correctly identifying key UGI landmarks[2,15]. Based on our findings there is doubt that many respondents are accurately recognising the position of anatomical landmarks and pathology which may have an impact on accurate photo-documenting and thus by inference inspecting all of the anatomical areas suggested.

Accurate anatomical identification of duodenal ulcer location may allow appropriate planning for further management and risk stratification but only a minority of respondents were able to differentiate the anterior and posterior duodenum. Gastrostomy feeding tubes placed endoscopically are accessed *via* the anterior stomach but the majority of endoscopists were also unable to accurately identify this.

Table 3 Correct responses: expert endoscopists *vs* novice endoscopists-percentage and absolute number

	Experienced (86)	Novice (102)	*P* value
Anterior oesophagus	44.2% (38)	22.5% (23)	0.002
Anterior stomach	61.6% (53)	31.3% (38)	0.001
Anterior D1	51.2% (44)	36.3% (37)	0.040
Posterior D2	41.9% (36)	52% (53)	0.167

D1: The first part of the duodenum; D2: The second part of the duodenum.

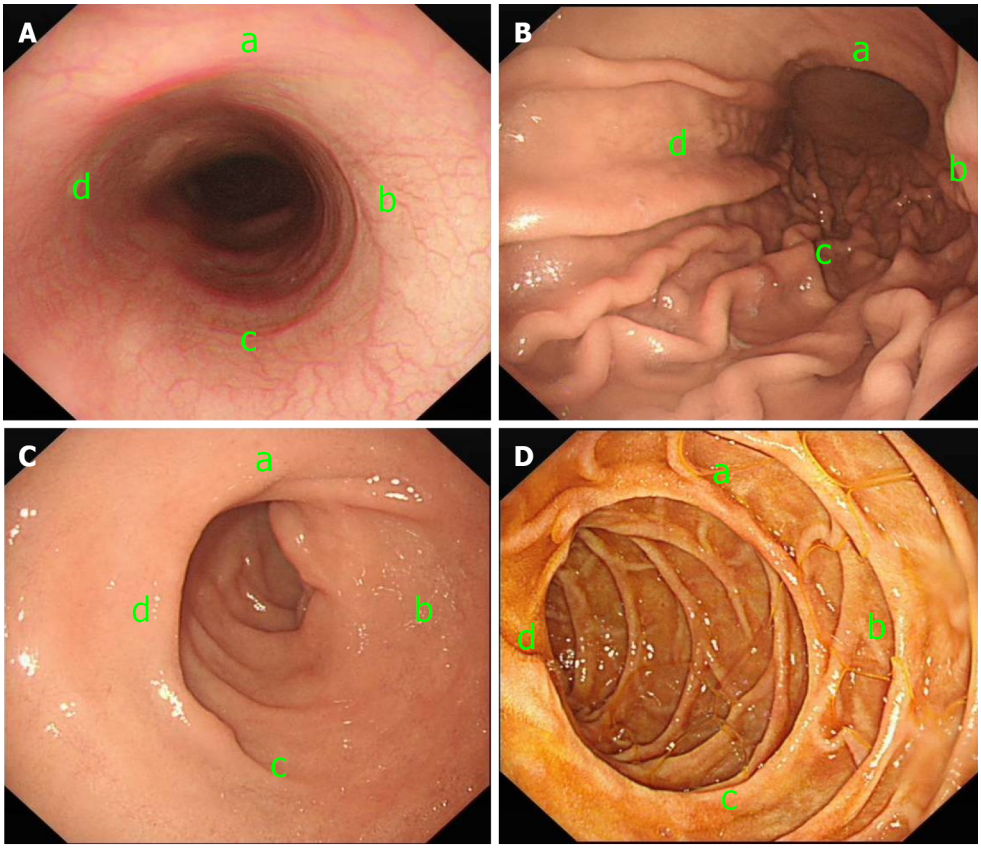

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Figure 1 Survey images. A: Image of mid oesophagus with anterior oesophagus corresponding to "d"; B: Image of mid gastric body with anterior stomach corresponding to "d"; C: Image of the first part of the duodenum with the anterior duodenum corresponding to "d"; D: Image of the second part of the duodenum with the posterior duodenum corresponding to "c".

With the increasing role of the multi-disciplinary team, reports are commonly interpreted by non-endoscopists and accurate reporting of lesion location would presumably advantage other specialists when considering management or correlating with radiological findings.

Although there is now wider availability of access to photo-documentation from previous endoscopies, the accurate reporting of the location of lesions may also offer medicolegal support in providing clear evidence that a lesion is new. This is especially relevant in the context of the high reported rate of UGI cancers missed at endoscopy[1].

Experienced endoscopists were significantly more likely to respond correctly in all but the question related to the second part of the duodenum. This suggests that experienced endoscopists more reliably orientate themselves correctly within the UGI tract and posits that understanding of orientation is gained experientially. Although, the correct recognition of posterior D2 by experienced *vs* novice endoscopists was not statistically significant, which suggests that experience is not the only factor impacting accurate endoscopic orientation.

The focus on the inverted on-screen image may lead to discrepancies in reported locations, often reports are written with lesions documented with respect to their position on a clock face. However, this does not always correlate with the anatomical orientation. For example, left of the screen, when looking

at the gastro-oesophageal junction, does not necessarily correlate to the anatomical left of the patient as the orientation of the screen is dependent on both patient position and steering of the endoscope. Orientation based on landmarks provides an objective assessment of location. The inaccuracy of the responses may be due to selecting the responses corresponding to the location on the image itself (*i.e.*, left of the image) rather than based on the anatomical landmarks.

There were limitations to this study including the use of still images which is not akin to real time endoscopic views which may improve orientation. The sample was of British endoscopists and is therefore not generalisable to other countries with different approaches to training and certification.

CONCLUSION

This study has signalled that orientation within the upper GI tract by endoscopists is generally inaccurate. This study has signalled that orientation within the upper GI tract by endoscopists is generally inaccurate. This may be due to a lack of a consensus statement and confusion between describing orientation on a screen *vs* anatomical orientation. Endoscopic orientation does appear to improve with experience. Accurate orientation may have beneficial impact on patient outcomes with respect to interventional procedures including rescoping after an UGI bleed and informed arterial embolisation. We suggest the development of a consensus statement on description endoscopically within the GI tract. This would require further controlled research in live endoscopy to allow generalisability to real time endoscopic orientation., but this would require further study with assessment during live endoscopy.

ARTICLE HIGHLIGHTS

Research background

Orientation within the upper gastrointestinal (UGI) tract is challenging due to the flexible nature of the endoscope. There is limited data assessing endoscopist's ability to orient themselves to UGI landmarks.

Research motivation

The ability to accurately identify landmarks is important to allow accurate reporting of UGI lesions and location. Accurate reporting can be important in further therapy and prognostication in UGI bleeds.

Research objectives

To evaluate endoscopists' ability to spatially orientate themselves within the UGI tract.

Research methods

A cross sectional descriptive study elicited, using an anonymised survey, the ability of endoscopists to orientate themselves within the UGI tract.

Research results

The majority of endoscopists surveyed were unable to identify key landmarks within the UGI tract. Experienced endoscopists were significantly more likely to identify landmarks in the oesophagus, stomach and duodenal bulb than novice endoscopists.

Research conclusions

Endoscopic orientation appears to improve with experience yet there are some areas still not well recognised. This has potential considerable impact on post-endoscopic management of patients with posterior duodenal ulcers being more likely to perforate and associated with a higher rebleeding risk.

Research perspectives

We suggest the development of a consensus statement on endoscopic description.

FOOTNOTES

Author contributions: Sivananthan A, Kerry G drafted and designed the work; Darzi A, Patel N, and Patel K conceptualised, revised and approved the work; Sivananthan A and Kerry G jointly contributed equally to the manuscript; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Aluminum phosphate gel reduces early rebleeding in cirrhotic patients with gastric variceal bleeding treated with histoacryl injection therapy

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Abstract

BACKGROUND

Esophageal-gastro varices bleeding (EGVB) is the most widely known cause of mortality in individuals with cirrhosis, with an occurrence rate of 5% to 15%. Among them, gastric varices bleeding (GVB) is less frequent than esophageal varices bleeding (EVB), but the former is a more critical illness and has a higher mortality rate. At present, endoscopic variceal histoacryl injection therapy (EVHT) is safe and effective, and it has been recommended by relevant guidelines as the primary method for the treatment of GVB. However, gastric varices after endoscopic treatment still have a high rate of early rebleeding, which is mainly related to complications of its treatment, such as bleeding from drained ulcers, rebleeding of varices *etc.* Therefore, preventing early postoperative rebleeding is very important to improve the quality of patient survival and outcomes.

AIM

To assess the efficacy of aluminium phosphate gel (APG) combined with proton pump inhibitor (PPI) in preventing early rebleeding after EVHT in individuals with GVB.

METHODS

Medical history of 196 individuals with GVB was obtained who were diagnosed using endoscopy and treated with EVHT in Shenzhen People's Hospital from January 2016 to December 2021. Based on the selection criteria, 101 patients were sorted into the PPI alone treatment group, and 95 patients were sorted into the

PPI combined with the APG treatment group. The incidences of early rebleeding and corresponding complications within 6 wk after treatment were compared between both groups. Statistical methods were performed by two-sample *t*-test, Wilcoxon rank sum test and χ^2 test.

RESULTS

No major variations were noted between the individuals of the two groups in terms of age, gender, Model for End-Stage Liver Disease score, coagulation function, serum albumin, hemoglobin, type of gastric varices, the dose of tissue glue injection and EV that needed to be treated simultaneously. The early rebleeding rate in PPI + APG group was 3.16% (3/95), which was much lower than that in the PPI group (12.87%, 13/101) (P = 0.013). Causes of early rebleeding: the incidence of gastric ulcer bleeding in the PPI + APG group was 2.11% (2/95), which was reduced in comparison to that in the PPI group (11.88%, 12/101) (P = 0.008); the incidence of venous bleeding in PPI + APG group and PPI group was 1. 05% (1/95) and 0.99% (1/101), respectively, and there was no significant difference between them (0.999). The early mortality rate was 0 in both groups within 6 wk after the operation, and the low mortality rate was related to the timely hospitalization and active treatment of all patients with rebleeding. The overall incidence of complications in the PPI + APG group was 12.63% (12/95), which was not significantly different from 13.86% (14/101) in the PPI group (P = 0.800). of abdominal pain in the PPI + APG group was 3.16% (3/95), which was lower than that in the PPI group (11.88%, 12/101) (P = 0.022). However, due to aluminum phosphate gel usage, the incidence of constipation in the PPI + APG group was 9.47% (9/95), which was higher than that in the PPI group (1.98%, 2/101) (P = 0.023), but the health of the patients could be improved by increasing drinking water or oral lactulose. No patients in either group developed spontaneous peritonitis after taking PPI, and none developed hepatic encephalopathy and ectopic embolism within 6 wk of EVHT treatment.

CONCLUSION

PPI combined with APG can significantly reduce the incidence of early rebleeding and postoperative abdominal pain in cirrhotic patients with GVB after taking EVHT.

Key Words: Gastric varices bleeding; Endoscopic variceal histoacryl injection therapy; Proton pump inhibitor; Aluminium phosphate gel; Early rebleeding

Core Tip: Gastric varices bleeding (GVB) is a serious life-threatening disease, and endoscopic variceal histoacryl injection therapy (EVHT) can effectively maintain hemostasis during the disease. Nevertheless, complications after EVHT, such as bleeding during drainage and ulceration at the injection site, can lead to early rebleeding. Currently, there are few clinical studies on preventing early rebleeding after EVHT in patients with GVB. We have found that using aluminium phosphate gel combined with proton pump inhibitor after EVHT could significantly reduce early rebleeding after endoscopic treatment in individuals with GVB.

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INTRODUCTION

Cirrhosis is caused by various etiologies (alcoholic fatty liver, hepatitis virus infection, non-alcoholic fatty liver, drugs, genetic metabolic diseases, autoimmune diseases, *etc.*), characterized by chronic liver inflammation, pseudo-lobular formation, and regenerative nodules[1]. It can be clinically divided into the compensatory and decompensation stages. Patients in the compensatory stage may not have any clinical signs or symptoms, while patients in the decompensation stage are characterized by liver dysfunction and portal hypertension[2-4]. EGVB is the most prevalent cause of death in individuals with cirrhosis, with an annual occurrence rate of about 5% to 15%, a 6-week case fatality rate of 20% and an incidence of rebleeding within 1 year of 60%.

The incidence of GVB is lower than EVB, accounting for about 20% of venous bleeding[5]. However, GVB is more dangerous, and it is difficult to stop bleeding in this condition because GV)are in the submucosa of the stomach and the gastric mucosa is thicker than the esophageal mucosa making it relatively difficult to rupture and bleed under the same or greater blood flow pressure[6]. The bleeding after rupture can be fatal, and hemostasis is difficult.

There are numerous ways to clinically prevent and treat GVB, such as drugs, endoscopic therapy, interventional radiology and traditional surgery. EVHT is safe and effective and has been recommended as the main treatment strategy for GVB, following the relevant guidelines. The success rate of hemostasis can reach 97.1% to 100%[7,8]. Related studies have reported that patients after EVHT still have a rebleeding rate of about 15% to 23.7%[7,9]. Early rebleeding refers to active bleeding events (including melena, hematemesis, or hematochezia; decrease in systolic blood pressure > 20 mmHg or increase in heart rate > 20 beats/min; decrease in hemoglobin > 30 G/L without blood transfusion) in patients with varicose veins within 72 h to 6 wk after initial bleeding control[10]. The occurrence of rebleeding is related to complications such as bleeding of glue discharge ulcer and rebleeding of varicose veins. Current clinical guidelines on the prevention of complications after EVHT are recommended[10-12]. Treatment with a proton pump inhibitor (PPI) may be given. As a mucosal protective agent, aluminium phosphate gel (APG) can increase the pH of the stomach, promote the formation of blood clots at the bleeding site, and promote the healing of gastric mucosa[13].

This study aims to investigate whether PPI combined with APG can lower the occurrence of early rebleeding after endoscopic treatment in patients with GVB and to provide a reference for clinical treatment.

MATERIALS AND METHODS

Collection of data

This study was a retrospective analysis of 257 individuals diagnosed with GVB by endoscopy and treated with EVHT in Shenzhen People's Hospital from January 2016 to December 2021. All patients were randomized to receive APG after EVHT. There were 13 patients with non-first bleeding, 31 patients with advanced liver cancer, portal vein thrombosis and other serious diseases and 17 patients discharged from the hospital were excluded. Finally, 196 cases were selected according to the standard. Based on the different postoperative treatment regimens for EVHT, 101 patients were divided into the PPI treatment group and 95 patients into the PPI combined with the APG treatment group, and the medical records of the two groups were collected respectively (the screening flow was shown in Figure 1). The approval for this research was given by the Ethics Committee of Shenzhen People's Hospital, and all patients consented to it.

Inclusion criteria

(1) Individuals aged 18-80 years old, regardless of gender; (2) Individuals with GVB diagnosed by gastroscopy; and (3) Individuals who underwent EVHT were used in all patients.

Exclusion criteria

(1) Individuals with incomplete clinical data; and (2) Individuals with other serious diseases (such as coronary heart disease, chronic renal insufficiency, advanced liver cancer, *etc*.) at the time of admission significantly affected the patients' prognosis.

EVHT treatment

All individuals included in this study underwent relevant examinations before the operation to comprehensively assess the patient conditions who signed an informed consent form for treatment. They were treated with EVHT using the "sandwich" method. Initially, 2.0 mL of 50% glucose solution was prestored in the injection needle, and then 2.0 mL of 50% glucose solution was injected into the bleeding target vein under endoscopy. According to the degree of varicosity, 0.5-2.0 mL of tissue glue was injected into each site, 2.0 mL 50% glucose was injected afterward, and finally, the injection needle was pulled out.

Post-endoscopic treatment and following up

PPI treatment group: After endoscopic treatment, the patients in this group were given a conventional dose of PPI (rabeprazole 20 mg daily before breakfast) for 4 wk[14]. PPI combined with APG treatment group: Rabeprazole 20 mg daily before breakfast was administered orally for 4 consecutive weeks, and APG 20 g (Boryung Pharmaceutical Co., Ltd. 20 g) was added twice (about 30 min before breakfast and dinner) a day on the postoperative day for 4 consecutive weeks. All individuals were assessed, and those without contraindications were administered with non-elective postoperatively β receptor blockers (propranolol) to prevent rebleeding treatment. All patients were followed up and observed closely, and the patients with suspected rebleeding were re-hospitalized and underwent endoscopy

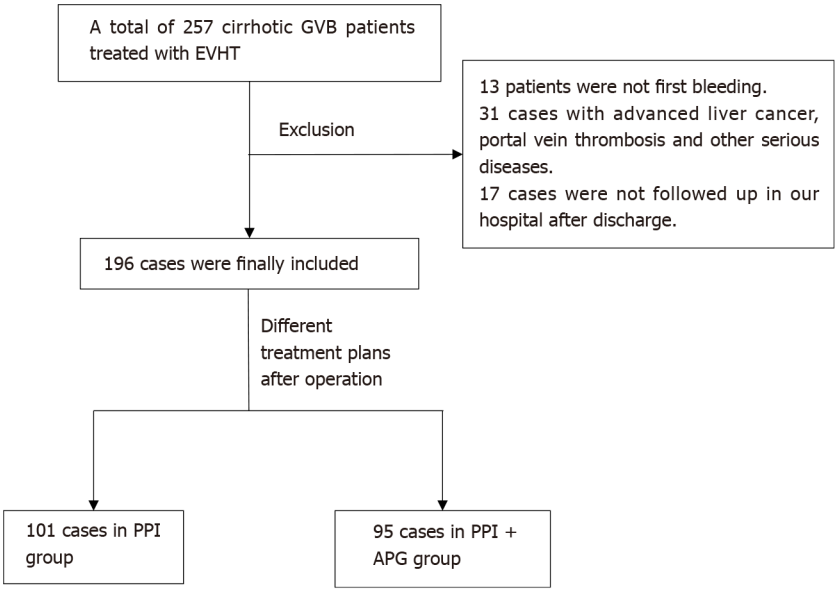

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Figure 1 The patient inclusion process in this study. GVB: Gastric varices bleeding; EVHT: Endoscopic variceal histoacryl injection therapy; PPI: Proton pump inhibitor; APG: Aluminium phosphate gel.

along with immediate treatment.

Observation of outcome measures

Signs of early postoperative rebleeding in patients with GVB: Active bleeding events (melena, hematemesis, or hematochezia; decrease in systolic blood pressure > 20 mmHg or increase in heart rate > 20 beats/min; decrease in hemoglobin > 30 g/L without blood transfusion) within 72 h to 6 wk after the initial bleeding control. Early rebleeding was the primary outcome measure in this study. Other complications such as death, abdominal pain, ectopic embolization, and related adverse events were considered secondary outcome measures.

Statistical analyses

Statistical analyses were carried out using SPSS 25.0. The measurement data with normal distribution were presented as mean ± SD, and a two-sample *t*-test was utilized to compare the two groups, median (lower quartile, upper quartile) presented the measurement data with skewed distribution and to compare the results of two groups Wilcoxon rank sum test was performed. The number of cases and percentage presented the enumeration data, and the χ^2 test was used for comparison between the two groups. A P value of < 0.05 was deemed statistically significant for all the calculated differences.

RESULTS

Basic information individuals in both groups

Table 1 demonstrates the basic conditions of individuals in both groups at the time of discharge after stable bleeding was counted. A comparison of different features of individuals in both groups was carried out; these include age (P = 0.245), gender (P = 0.289), Model for End-Stage Liver Disease score (P = 0.329), prothrombin activity (PTA, P = 0.157), fibrinogen (FIB, P = 0.064) and platelet count (PLT, P < 0.05). Serum albumin (ALB) (P = 0.622) and hemoglobin (Hb) (P = 0.524) were not statistically different. There was no significant difference in the number of patients taking beta blockers after discharge between the two groups (P = 0.586). Table 2 demonstrates categorizing the patients' GV status according to Sarin Criteria[5]. Statistically significant variations were not observed between the PPI group and the PPI + APG group in terms of the GV type (GOV1 10 patients *vs* 12 patients, P = 0.545), (GOV2 50 patients *vs* 41 patients, P = 0.373), (GOV3 34 patients *vs* 38 patients, P = 0.358) and (IGV1 7 patients *vs* 4 patients, P = 0.408); in addition, 68 (67.33%) subjects in the PPI group and 69 (72.63%) subjects in the PPI + APG group with severe EV requiring concomitant endoscopic therapy did not differ significantly between both groups (P = 0.418). The mean value of histogel dosage in the PPI group was 2.22 ± 0.80 mL, which was not statistically different from 2.21 ± 0.76 mL in the PPI + APG group (P = 0.875).

Table 1 Baseline data of both groups

Characteristic	PPI group (*n* = 101)	PPI + APG group (*n* = 95)	*P* value
Age (yr)	51.55 ± 12.23	53.57 ± 11.90	0.245
Female/Male	26/75	31/64	0.289
MELD score	10.07 ± 3.32	9.61 ± 3.24	0.329
Prothrombin activity (%)	68.53 ± 15.48	65.63 ± 12.90	0.157
Fibrinogen (g/dL)	2.30 ± 0.76	2.09 ± 0.80	0.064
Platelet (109/L)	102.21 ± 83.68	111.16 ± 100.57	0.498
Albumin (g/dL)	3.52 ± 0.47	3.48 ± 0.58	0.622
Hemoglobin (g/dL)	9.73 ± 2.15	9.55 ± 1.88	0.524
Patients treated with beta blockers	89	86	0.586

PPI: Proton pump inhibitor; APG: Aluminium phosphate gel; MELD: Model for End-Stage Liver Disease.

Table 2 Comparison of varicose veins and dose of histoacryl between two groups, *n* (%)

Characteristic	PPI group (*n* = 101)	PPI + APG group (*n* = 95)	*P* value
GOV1	10 (9.90)	12 (12.63)	0.545
GOV2	50 (49.50)	41 (43.16)	0.373
GOV3	34 (33.66)	38 (40.00)	0.358
IGV1	7 (6.93)	4 (4.21)	0.408
Combine with EV need treatment	68 (67.33)	69 (72.63)	0.418
Amount of histoacryl (mL)	2.22 ± 0.80	2.21 ± 0.76	0.875

EV: Esophageal varices; PPI: Proton pump inhibitor; APG: Aluminium phosphate gel; GOV: Gastro varices; GV: Gastric varices.

Incidence of early rebleeding

The patients were followed up closely after the operation and returned to the hospital immediately if they had early rebleeding, and all of them underwent emergency gastroscopy and treatment. The cases of early esophageal rebleeding after EV treatment were excluded, and the cases of early gastric rebleeding after GV treatment were compared (Table 3). The incidence rate of early rebleeding in the PPI + APG group was 3.16% (3/95), which was considerably lower than that in the PPI group (12.87%, 13/101), and the difference was statistically significant ($P = 0.013$). The incidence of ulcer bleeding in the PPI + APG group was 2.11% (2/95), which was reduced compared to that in the PPI group (11.88%, 12/101) ($P = 0.008$); The incidence of venous bleeding was 1.05% (1/95) in the PPI + APG group and 0.99% (1/101) in the PPI group, ($P > 0.999$). There was no significant difference between the two groups. One patient (1.05%) in PPI + APG group needed a blood transfusion, which was lower than that in the PPI group ((9 patients, 8.91%), $P = 0.030$). Patients with venous bleeding in both groups needed a blood transfusion, and no considerable difference was observed between the two groups ($P > 0.999$). The re-hospitalization rate of the PPI + APG group was 2.11% (2/95), which was reduced compared to that in the PPI group (9.90%, 10/101), $P = 0.023$). The early mortality rate was 0 in both groups within 6 wk, and the reason for the low mortality rate was the timely hospitalization and treatment of all patients with early rebleeding.

Other related complications and adverse reactions

As shown in Table 4, the overall complication rate was 13.86% (14/101) in the PPI group and 12.63% (12/95) in PPI + APG group, with no significant difference ($P = 0.800$). The incidence of abdominal pain in PPI + APG group was 3.16% (3/95); lower than that in PPI group (11.88%, 12/101, $P = 0.022$). The incidence of constipation in the PPI + APG group was 9.47% (9/95), higher than that in the PPI group (1.98%, 2/101) ($P = 0.023$). Constipation in PPI + APG group was improved by drinking more water or taking lactulose. There were no cases of spontaneous bacterial peritonitis after taking PPI in both groups and no cases of hepatic encephalopathy and ectopic embolism in both groups within 6 wk after the first EVHT treatment.

Table 3 Main outcomes of both groups, *n* (%)

Characteristic	PPI group (*n* = 101)	PPI + APG group (*n* = 95)	*P* value
Early rebleeding	13 (12.87)	3 (3.16)	0.013
Source of rebleeding			
Glue extrusion ulcer	12 (11.88)	2 (2.11)	0.008
Gastric varice	1 (0.99)	1 (1.05)	> 0.999
Transfusion after rebleeding			
Glue extrusion ulcer	9 (8.91)	1 (1.05)	0.030
Gastric varices	1 (0.99)	1 (1.05)	> 0.999
Re-hospitalization	10 (9.90)	2 (2.11)	0.023
6-wk mortality	0	0	> 0.999

PPI: Proton pump inhibitor; APG: Aluminium phosphate gel.

Table 4 Other adverse events in the two groups, *n* (%)

Characteristic	PPI group (*n* = 101)	PPI + APG group (*n* = 95)	*P* value
Total complications	14 (13.86)	12 (12.63)	0.800
Abdominal pain	12 (11.88)	3 (3.16)	0.022
Constipation	2 (1.98)	9 (9.47)	0.023
Spontaneous peritonitis	0	0	> 0.999
Ectopic embolism	0	0	> 0.999
Hepatic encephalopathy	0	0	> 0.999

PPI: Proton pump inhibitor; APG: Aluminium phosphate gel.

DISCUSSION

The incidence of GV is lower than that of EV because of the difference in the location of varicose veins in GV and EV. The varices of EV are mainly located in the lamina propria and submucosa, while GV is located in the submucosa, and the gastric mucosa is thicker than the esophageal mucosa[15]. Therefore, under the same blood pressure, GV is less likely to form varices on the mucosal surface, but they are usually larger than those formed by EV. This unique pathophysiological structure also determines the treatment difference of GVB from that of EVB. Endoscopic variceal ligation (EVL) is the preferred method for EVB as the first-line treatment and the prevention of rebleeding[16,17]. It is unsuitable for GVB because of the limited effect of ligation on submucosal deep branch veins and larger veins (diameter 2 cm), and gastric peristalsis can cause the ligature to fall off, increasing the risk of bleeding [18]. At present, relevant guidelines recommend EVHT as the preferred treatment for GVB, and the therapeutic effect is better than EVL, which has been confirmed by relevant studies[19,20].

EVHT is primarily hemostatic as it functions by injecting tissue glue into the bleeding vein. Tissue glue is a rapid water-like solidification, which can quickly solidify in the blood in the presence of trace anions, forming a permanent intravascular embolism in a few seconds and blocking the bleeding veins [21]. However, the effect of tissue glue on vascular fibrosis is weak, failing to inhibit the formation of new blood vessels, often resulting in postoperative rebleeding. Currently, the causes of rebleeding are related to glue discharge ulcers and venous bleeding (Figure 2).

Tissue glue, as a foreign body, is rejected by the human body after being injected into blood vessels which are eventually eliminated through the gastric cavity in a process called glue expulsion[22]. Wang *et al*[23] found that after EVHT, patients began to discharge glue about 1 wk later, and about 4 wk later was the peak period of postoperative glue discharge. At this time, endoscopy could find various colors and forms of glue discharge ulcers, which was also the peak period of glue discharge ulcer bleeding [23]. Draining ulcer bleeding is multifactorial: (1) Bleeding from incomplete fibrosis of the occluding vessel due to inflammatory exudation at the injection site; (2) The histogel mixture did not completely enter the blood vessels and transferred into the extravascular gastric mucosa, causing inflammation and caseous necrosis of the mucosa and the formation of large ulcers; (3) Insufficient amount of tissue glue,

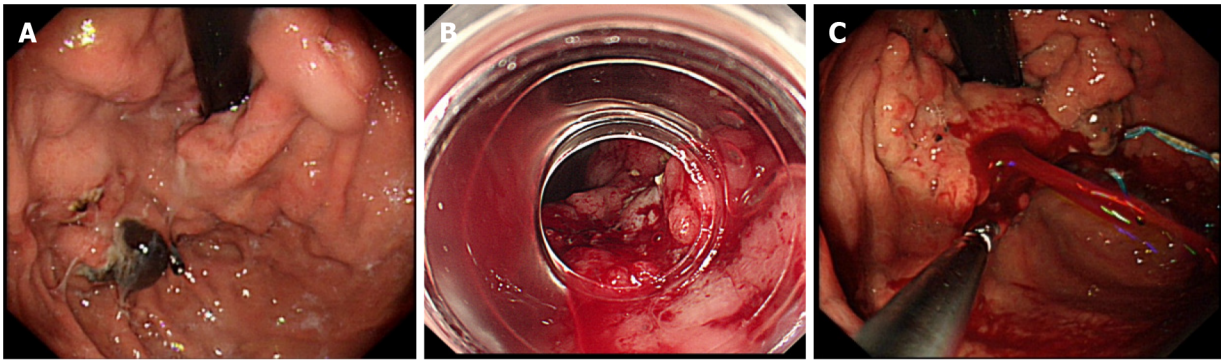

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Figure 2 The causes of rebleeding are related to glue discharge ulcers and venous bleeding. A: After 2 wk of endoscopic treatment, the gastric fundus shows a draining ulcer; B: Fundic vein bleeding after 3 wk of endoscopic treatment, there was gastric fundic drainage, formation of an ulcer, and bleeding; C: Varices that did not disappear completely were spurting bleeding after 14 d of endoscopic therapy.

which failed to effectively occlude the vessel; and (4) A small number of multisite injections are made, forming multi-site glue lined ulcers. In addition, varices that are not completely obliterated are also an important cause of early rebleeding[24]. In our study, there were 12 cases of bleeding ulcers in the PPI group and 1 in the PPI + APG group, accounting for 87.50% (14/16) of early rebleeding cases.

PPI is a kind of H+-K+-ATP enzyme inhibitor, the most important drug to clinically inhibit gastric acid secretion and treat digestive tract ulcers. It can also promote the healing of glue discharge ulcers [25]. It is also a routine method to prevent postoperative complications. However, some studies have reported that long-term use of PPI may increase the incidence of spontaneous peritonitis and hepatic encephalopathy in patients with cirrhosis[26]. APG is a mucosal protective agent that can neutralize gastric acid and protect the mucosa. Its active ingredient aluminum phosphate, can mix with gastric acid to form a relatively strong buffer system: Phosphate and aluminum ions. The former can combine with H + to rapidly increase the PH value in the stomach, which benefits blood clots' formation and stability in gastrointestinal bleeding patients. Its auxiliary ingredients, pectin and agar, are similar to the structure of natural mucus, which can form a layer of colloidal protective film on the surface of a postoperative ulcer to protect the gastric mucosa from damage after oral administration[27]. The combination of PPI and APG can theoretically promote the stabilization of blood clots at the bleeding site and the rapid healing of glue discharge ulcers in patients with GVB, ultimately reducing the incidence of early rebleeding.

In this retrospective study, the author found that the incidence of early rebleeding after EVHT in GVB patients treated with PPI + APG was 3.16% (3/95), significantly lower than that in the PPI group (12.87%, 13/101). As APG had been shown to promote ulcer healing, the incidence of bleeding from a drained ulcer after EVHT was 2.11% (2/95) in GVB patients treated with PPI + APG, which was significantly lower than the 11.88% (12/101) in PPI group. However, in terms of gastric vein bleeding, no statistical difference was observed between the two groups. The use of APG reduces the incidence of postoperative abdominal pain following EVHT in patients with GVB. Although the use of APG increased constipation in the patients, they improved both by extensive drinking of water and taking lactulose. None of the patients in either group developed spontaneous peritonitis after taking PPI. There were no cases of hepatic encephalopathy, ectopic embolism, or death within 6 wk after EVHT in either group, which was supported by timely endoscopic treatment for all patients with early rebleeding and rapid clearance of the hematochezia intestinalis.

However, this study has some limitations: (1) This study is retrospective; (2) The sample size of this experiments is small, and it is a single-center study. The incidence of early rebleeding in patients is related to the experience of endoscopists, diet along with other factors. There are a lot of confounding factors, and the applicability of the experimental results is limited; and (3) This study has conducted a follow-up period of only 6 wk. It has only investigated the occurrence of early rebleeding and related secondary outcome measures after EVHT in patients. Further studies are lacking regarding some clinical data and long-term indicators (such as survival, number of hospitalizations, long-term treatment costs, *etc.*) after the end of 6 wk of the follow-up. It is also possible that other mucosal protective agents may reduce the incidence of early rebleeding by promoting ulcer healing after EVHT treatment, but further studies are needed to prove this. Therefore, follow-up clinical randomized controlled experiments with prospective, multi-center large sample with medium and long-term follow-up is also needed.

CONCLUSION

The combination of APG and PPI therapy after endoscopic EVHT for cirrhotic patients with GVB can

promote the healing of gastric glue ulcers and relieve abdominal pain in patients. Moreover, it can significantly reduce the incidence of early rebleeding after EVHT. It is also possible that other mucosal protective agents may reduce the incidence of early rebleeding by promoting ulcer healing after EVHT treatment, but further studies are needed to prove this.

ARTICLE HIGHLIGHTS

Research background

The incidence of early rebleeding after endoscopic variceal histoacryl injection therapy (EVHT) of varicose veins in the fundus of the stomach is high, which may lead to serious consequences. It is very important to reduce the incidence of early rebleeding.

Research motivation

Reducing the incidence of early rebleeding after EVHT treatment reduces the risk of patients and may extend their life expectancy. Proton pump inhibitor (PPI) treatment has been found to reduce the incidence of early rebleeding. Aluminium phosphate gel (APG) can promote the healing of gastric ulcers. Can the combination of APG and PPI further reduce the incidence of early rebleeding?

Research objectives

This study aimed to verify whether the combination of APG and PPI can reduce the incidence of early rebleeding after EVHT.

Research methods

We randomly divided patients after EVHT into two groups. One group was treated on PPI after EVHT, and the other group took PPI in combination with APG. We statistically analyzed the data of both groups and observed the early rebleeding rates in both groups.

Research results

The early rebleeding rate in PPI + APG group was 3.16% (3/95), which was much lower than that in the PPI group (12.87%, 13/101). Causes of early rebleeding: The incidence of gastric ulcer bleeding in the PPI + APG group was 2.11% (2/95), which was reduced in comparison to that in the PPI group (11.88%, 12/101); the incidence of venous bleeding in PPI + APG group and PPI group was 1.05% (1/95) and 0.99% (1/101), respectively, and there was no significant difference between them. The incidence of abdominal pain in the PPI + APG group was 3.16% (3/95), which was lower than that in the PPI group (11.88%, 12/101).

Research conclusions

PPI combined with APG can significantly reduce the incidence of early rebleeding and postoperative abdominal pain in cirrhotic patients with GVB after taking EVHT.

Research perspectives

The combination of APG with PPI can reduce the bleeding incidence of gastric ulcers after EVHT.

FOOTNOTES

Author contributions: Xu ZL conceived the idea for the manuscript; Zeng HT and Zhang ZL contributed equally to this study, are considered as co-first authors, and wrote the first draft of the manuscript; Lin XM and Peng MS searched part of the information; Wang LS reviewed and revised the manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There is no any conflict-of-interest.

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ORIGINAL ARTICLE

Prospective Study

Medium-term surgical outcomes and health-related quality of life after laparoscopic *vs* open colorectal cancer resection: SF-36 health survey questionnaire

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Abstract

BACKGROUND

Previous studies that compared the postoperative health-related quality of life (HRQoL) outcomes after receiving laparoscopic resection (LR) or open resection (OR) in patients with colorectal cancer (CRC) have different conclusions.

AIM

To explore the medium-term effect of postoperative HRQoL in such patients.

METHODS

This study randomized 567 patients undergoing non-metastatic CRC surgery managed by one surgeon to the LR or OR groups. HRQoL was assessed during the preoperative period and 3, 6, and 12 mo postoperative using a modified version of the 36-Item Short Form (SF-36) Health Survey questionnaire, emphasizing eight specific items.

RESULTS

This cohort randomly assigned 541 patients to receive LR (n = 296) or OR (n = 245) surgical procedures. More episodes of postoperative urinary tract infection (P < 0.001), wound infection (P < 0.001), and pneumonia (P = 0.048) were encountered in the OR group. The results demonstrated that the LR group subjectively gained mildly better general health (P = 0.045), moderately better physical activity (P = 0.006), and significantly better social function recovery (P = 0.0001) 3 mo postoperatively. Only the aspect of social function recovery was claimed at 6 mo, with a significant advantage in the LR group (P = 0.001). No clinical difference was found in HRQoL during the 12 mo.

CONCLUSION

Our results demonstrated that LR resulted in better outcomes, including intra-operative blood loss, surgery-related complications, course of recovery, and especially some health domains of HRQoL at least within 6 mo postoperatively. Patients should undergo LR if there is no contraindication.

Key Words: Health-related quality of life; Medium-term result; Laparoscopic; Open surgery; Non-metastatic colorectal cancer

Core Tip: Previous randomized controlled trials that compare laparoscopic (LR) and open resection (OR) in colorectal cancer (CRC) management have led to different conclusions regarding the health-related quality of life (HRQoL). Our study analyzed the objective surgical outcomes and subjective HRQoL in 541 patients with non-metastatic CRC randomized to the LR (n = 296) or OR (n = 245) group operated by one surgeon. Better HRQoL was noticed in the LR group in general health, physical activity, and social function recovery with various degrees. These patients should consider LR to gain better HRQoL if not contraindicated because these two operative methods resulted in similar cancer-oriented outcomes and survival.

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INTRODUCTION

Colonic resection under laparoscopy was first performed in 1991, and several randomized clinical trials that compare laparoscopic resection (LR) with open resection (OR) in patients with colorectal cancer (CRC) have been performed since then[1-3]. Initial studies revealed that LR patients gained similar clinical results, along with short-term advantages, such as lesser blood loss, reduced analgesic use, and a shorter hospital stay[4].

Health-related quality of life (HRQoL) is often overlooked, emphasizing more focus on survival and oncologic outcomes[5]. However, patients' self-assessed outcomes must reveal the effects of their health status on their physical and psychological functioning[4]. Some studies revealed LR's superiority regarding HRQoL in managing patients with colon cancer[2], but others demonstrated the opposite results. However, most studies focused on the longer-term effects (more than one year)[3,6]. Moreover, Li *et al*[7] revealed improved HRQoL 1 week after laparoscopic rectal cancer surgery but not after 1 year.

Our prospective study aims to assess the HRQoL effects within 1 year after non-metastatic CRC surgery by a single surgeon since previous studies that compare postoperative HRQoL outcomes of CRC after LR and OR have come to different conclusions and lack medium-term results (from 3 mo to 1 year)[2,6,8-12].

MATERIALS AND METHODS

Study design and patients

Dr. Chiu performed surgeries for 575 patients with CRC in two regional hospitals from January 2014 to October 2021 (Chi Mei Medical Center, Liouying, Tainan, and E-Da Cancer Hospital, Kaohsiung, Taiwan) (Figure 1). The guidelines of the National Comprehensive Cancer Network (NCCN) were followed. Our study included patients with non-metastatic colon or rectal cancer with no adjacent organ invasion. However, we excluded patients with colon polyposis conditions, repeated episodes of adhesion-related ileus, synchronous tumors, operative method conversion, emergent surgeries, denial of participation, loss of follow-up, refusal of subsequent postoperative management, or expiration not related to cancer within 1 year postoperatively. All patients must sign the informed consent form. This study was reviewed and accepted by the Institutional Review Board of both surgical hospitals.

Patients were divided into several groups based on different tumor locations. Patients were randomly assigned to perform LR or OR, as blindly selected by the surgeon using sealed envelopes preoperatively.

Preoperative staging evaluation

The clinical stage of oncologic status was described according to the tumor node metastasis (TNM) system, as advocated by the American Joint Committee on Cancer. Physical examination, colonoscopy with biopsy, carcinoembryonic antigen serum level, and abdominal computed tomography were performed for each patient.

Surgical techniques

We followed the standard procedures of right or left-side hemicolectomy, sigmoid colectomy, or rectal resection by performing a standard medial-to-lateral way. High ligation of related vessels was routinely

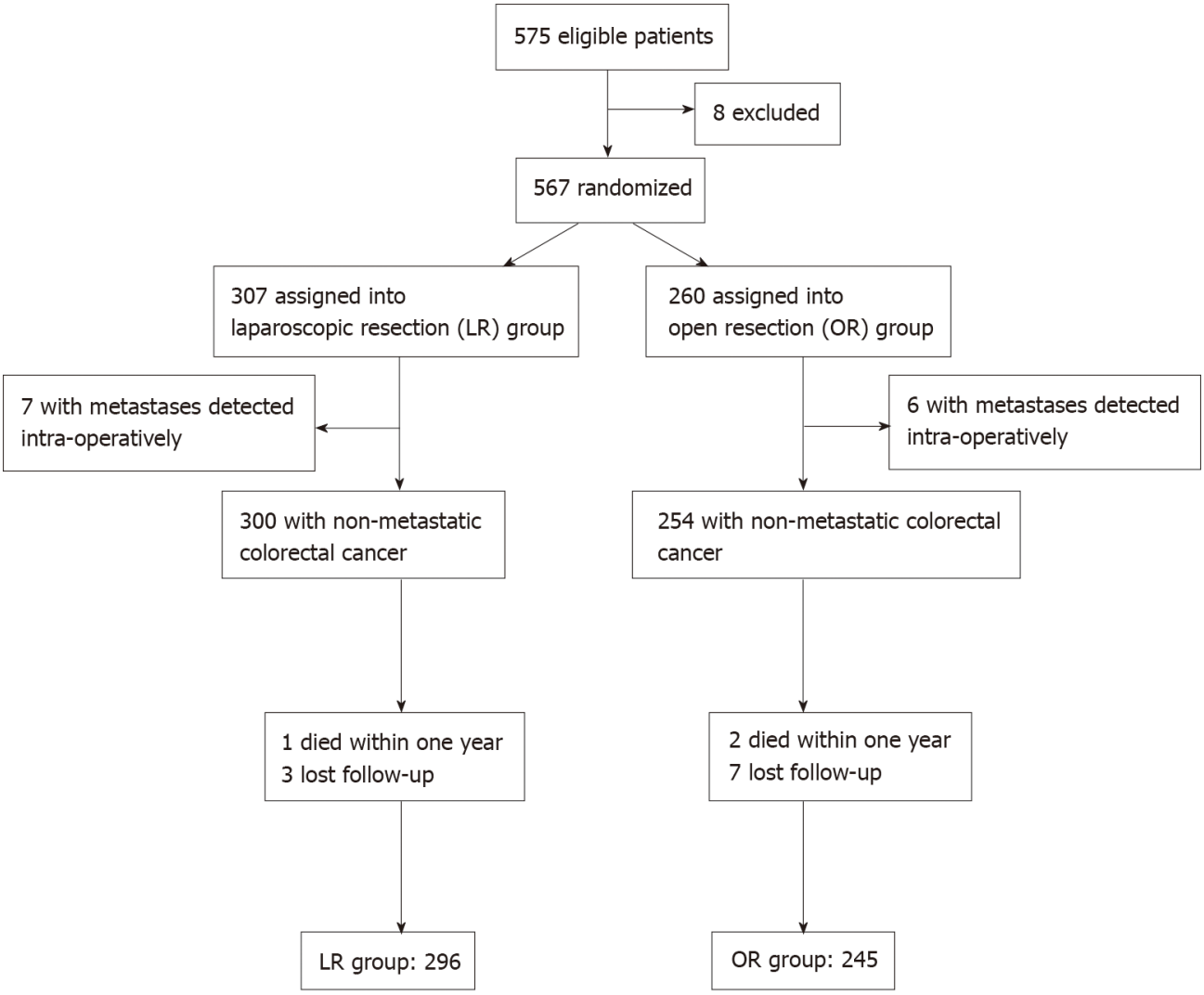

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Figure 1 The flowchart of the study design.

performed for all patients based on the non-touch technique concept. The rule of keeping the surgical safety margin at 5 cm for all patients with colon cancer was followed. Additionally, intestinal anastomosis was done extra-corporeally for proximal lesions. An immediate intra-corporeal intestinal anastomosis with circular stapling was performed *via* a trans-anal approach following left-side colon or rectum lesion resections. However, a protective diversional stoma would be considered if the anastomosis dehiscence is possible, mainly for high-risk patients with ultra-low rectal cancer. Further, a preoperative endoscopic tattoo would be requested for patients with a smaller or probably non-palpable intestinal lesion to mark the location for subsequent surgical resection 1 day later. An intra-operative endoscopy examination would be requested if we could not localize the lesion by vision or palpation under laparoscopy.

Postoperative follow-up and treatment

Follow-up examinations would be arranged according to the NCCN guidelines[13]. All patients were expected to visit the outpatient department every 3 mo for follow-up within the first postoperative year. All patients with stage III CRC would be arranged to receive intravenous or oral adjuvant chemotherapy.

HRQoL assessment

HRQoL was assessed by professionally trained members in the outpatient department preoperatively and 3, 6, and 12 mo postoperatively using a modified version of the 36-Item Short Form (SF-36) Health Survey questionnaire.

SF-36 included a multi-item scale and estimated eight health domains, including: (1) Physical activity limits related to health issues; (2) Social activity limits associated with physical or emotional issues; (3) Vitality (energy and fatigue); (4) General mental health (well-being and psychological distress); (5)

Usual role activity limits caused by physical health issues; (6) Usual role activity hindered by emotional issues; (7) Physical pain, and (8) General health awareness[14]. The scores ranged from 0 to 100 in each domain, with higher scores revealing better HRQoL[3]. This study concentrated on HRQoL assessment *via* these self-reported domains.

Statistical analysis

Tables 1 and 2 show the baseline patient information. The difference between medians of continuous variables was investigated with the unpaired Student's *t*-test. Categorical variables were compared by χ^2 test with Yates' correction. All *P* values were two-tailed, and those < 0.05 implied a significant statistical difference. The calculations were performed using the Statistical Package for the Social Sciences version 20.0 statistical package (IBM Co., Armonk, NY, United States).

RESULTS

Baseline patient characteristics

Figure 1 demonstrates our patient profile. At first, we sorted 575 patients with CRC managed by Dr. Chiu. Eight patients were excluded based on our study design (three received laparotomies several times with severe intestine adhesion noted at the beginning of the operation, three received emergent surgeries, one refused to participate study and one received conversion). We assessed 567 patients receiving curative resection, distributed as 307 LR, and 260 OR. Incidental peritoneal carcinomatosis was noticed in seven LR and six OR patients during the operation, and they were excluded. Additionally, nine patients in the OR group were excluded because two expired unrelated to cancer within 1 year postoperatively, and five patients with stage I and two with stage II did not show up at the outpatient department. Similarly, four patients in the LR group were excluded because one expired unrelated to cancer, and three with stage I lost contact. Finally, 296, and 245 patients in the LR and OR groups, respectively, were eligible, and compliant with subsequent follow-ups at the outpatient department. The median follow-up period was 69.4 mo.

Demographic and clinicopathologic variables of patients were well matched in both groups, with no statistical difference (Table 1). A slight disparity was found between the preoperative (clinical/radiologic) and postoperative (pathological) TNM stages in both groups. Moreover, nearly all patients with rectal cancer in both groups received preoperative concurrent chemoradiotherapy (CCRT) according to the guideline. Two and one patients in the LR and OR groups, respectively, received radical proctectomy directly due to partially obstructive symptoms.

Objective surgical outcomes

Table 2 shows no significant statistical difference in the number of removed lymph nodes (15.2 ± 4.5 in LR and 16.3 ± 5.5 in OR, $P = 0.067$). None of the surgical specimen margins was involved with the tumor. However, we noted that patients could benefit from LR with a shorter hospitalization period ($P < 0.001$) and less blood loss ($P < 0.001$). On the contrary, the operation time was longer in the LR group than the OR group (182.1 ± 35.2 min *vs* 130.5 ± 21.3 min, $P < 0.001$).

More episodes of urinary tract infection (UTI) ($P < 0.001$), surgical wound infection ($P < 0.001$), and pneumonia ($P = 0.048$) were found in the OR group during the recovery course. No statistical difference was found regarding postoperative ileus ($P = 0.273$). Additionally, anastomosis leakage was complicated in 6 and 10 patients in the LR and OR groups, respectively, whose tumors were all located at lower rectum status postproctectomy without a protective diversional stoma. However, two and five patients in the LR and OR groups, respectively, needed re-operation for abscess drainage and stoma establishment for stool diversion. Others could recover after conservative treatment, and this complication did not reach a statistical difference (Table 2).

Moreover, any significant difference was not noticed in the complication rate of abdominal incisional hernia or ileus after a median follow-up period of 69.4 mo. Additionally, no patient in both group encountered these complications within the postoperative year (Table 2).

Regarding the oncologic outcome of tumor recurrence during the follow-up of 1 year postoperatively, only two patients with stage III in the OR group encountered tumor recurrence with peritoneal metastasis, which did not reach a statistical difference ($p = 0.054$) (Table 2).

Postoperative change of HRQoL

All follow-up patients were compliant in answering the questionnaires within 1 year. Table 3 demonstrates that the LR group subjectively gained mildly better general health ($P = 0.045$), moderately better physical activity ($P = 0.006$), and significantly better social function recovery ($P = 0.0001$) 3 mo postoperatively. We noted that the LR group only mentioned a significant advantage in social function recovery at 6 mo follow-up ($p = 0.001$). No clinical difference was found in HRQoL between both groups at 12 mo follow-up.

Table 1 Comparison of baseline characteristics between patients receiving laparoscopic resection *vs* those undergoing open resection

Variables	LR (*n* = 296)	OR (*n* = 245)	*P* value
Gender			0.412
Male	162	135	
Female	134	110	
Age (mean ± SD)	67.2 ± 11.3	70.1 ± 8.9	0.19
ASA class			0.673
I	162	129	
II	111	99	
III	23	17	
Pre-operative TNM stage			0.342
0	9	5	
I	93	71	
II	99	80	
III	95	89	
Tumor location			0.452
Cecum	42	31	
Ascending colon	57	45	
Transverse colon	33	25	
Descending colon	51	42	
Sigmoid colon	71	62	
Rectum	42	40	
Pre-surgery serum CEA level			1.021
< 5 ng/mL	51	34	
≥ 5 ng/mL	245	211	
Pre-operative CCRT	40	39	0.391
Intervention			0.729
Right hemicolectomy	93	76	
Left hemicolectomy	64	45	
Transverse colectomy	28	22	
Sigmoid colectomy	69	60	
Proctectomy	39	38	
Abdominal perineal resection	3	4	
Protective diversional stoma	13	15	
Post-operative TNM stage			0.359
0	9	5	
I	92	70	
II	96	79	
III	99	91	
Histopathology			0.637
Well differentiated	112	105	
Moderate differentiated	122	93	
Poorly differentiated	62	47	

ASA: American Society of Anesthesiologists; TNM: Tumor, Node and Metastasis; CEA: CarcinoEmbryonic Antigen; CCRT: Concurrent chemoradiotherapy; LR: Laparoscopic resection; OR: Open resection.

Table 2 Comparison of surgical outcomes between patients receiving laparoscopic resection *vs* those undergoing open resection

Variables	LR (*n* = 296)	OR (*n* = 245)	*P* value
Lymph nodes removed	15.2 ± 4.5	16.3 ± 5.5	0.067
Hospitalization (days)	11.3 ± 2.5	17.6 ± 5.3	< 0.001[c]
Operation blood loss (mL)	60.5 ± 21.2	156.2 ± 30.4	< 0.001[c]
Operation time (min)	182.1 ± 35.2	130.5 ± 21.3	< 0.001[c]
Peri-operative complications			
Total	26	62	
Ileus (Grade II)	8	11	0.273
Urinary tract infection (Grade II)	3	14	< 0.001[c]
Wound infection (Grade I)	4	15	< 0.001[c]
Pneumonia (Grade II)	5	12	0.048[a]
Anastomosis leakage (Grade IIIb)	6	10	0.14
Abscess drainage, stoma diversion	2	5	0.231
Recurrence within 1 year	0	2	0.054
Long-term (> 1 year) complications			
Incisional hernia (Grade I)	4	7	0.261
Ileus (Grade II)	10	14	0.343

[a]$P \leq 0.05$;
[c]$P \leq 0.001$.
Grading of complications is according to the criteria of "Clavien-Dindo classification". LR: Laparoscopic resection; OR: Open resection.

Moreover, our results revealed that the LR group subjectively gained a better presentation of the Physical Component Summary ($P = 0.021$) and Mental Component Summary ($P = 0.015$) 3 mo postoperatively. Similarly, we noticed this phenomenon regarding the short form 6 dimensions (SF-6D) ($P = 0.045$).

DISCUSSION

Over 1.8 million people were diagnosed with CRC worldwide, and >880000 related patients expired in 2018, accounting for approximately one-tenth of total cancer occurrence and mortality. CRC ranks third in cancer incidence but second in mortality[15]. Many elderly are found with CRC indicated for surgical intervention as the population ages. The laparoscopic approach for CRC resection has become the mainstay of surgery in the recent two decades. Clinicians gradually alerted this evidence-based fact through more and more results of extensive and well-conducted studies and reinforced by numerous meta-analysis data[16-17].

LR is related to better short-term outcomes, including decreased postoperative pain, morbidity, minor immune impairment, faster recovery, shorter hospital stay, and better cosmetics than OR[11]. Additionally, a secure oncologic dissection could be acquired under laparoscopy, and current trials proved that LR did not adversely influence the prognosis of cancer treatment[1]. All this evidence is expected to result in a highly improved postoperative HRQoL. Moreover, HRQoL assessments further contribute to improved treatment.

Traditionally, surgical care outcomes were merely assessed by mortality, morbidity, cancer-free, and overall survival rates. Recently, additional judgment criteria have emerged and been illuminated with significant concern. The success of each therapeutic strategy is carefully explored in the management or its effects on patients' daily lives and well-being. For example, the uncontrolled case series suggested that patients undergoing LR experience a more rapid bowel function return[2].

Table 3 Comparison of Quality of life between patients receiving laparoscopic resection *vs* those undergoing open resection

Health domains	LR group	OR group	*P* value
Physical functioning			0.121
Preoperative	91.3 (20.5)	92.7 (23.6)	0.541
3 months after surgery	82.3 (18.0)	65.6 (23.4)	0.006[b]
6 months after surgery	86.3 (20.4)	84.2 (22.5)	0.399
12 months after surgery	88.3 (14.3)	85.0 (23.0)	0.081
Social functioning			0.113
Preoperative	88.9 (21.8)	86.5 (18.3)	0.213
3 months after surgery	86.5 (20.3)	52.1 (22.0)	0.0001[d]
6 months after surgery	87.0 (21.0)	60.3 (19.0)	0.001[c]
12 months after surgery	86.5 (18.3)	83.3 (19.2)	0.321
Vitality			0.749
Preoperative	74.0 (18.5)	74.2 (19.9)	0.983
3 months after surgery	70.9 (14.3)	70.6 (23.2)	0.97
6 months after surgery	72.2 (14.1)	70.3 (15.5)	0.503
12 months after surgery	73.1 (13.8)	72.8 (16.8)	0.675
Mental health			0.553
Preoperative	75.6 (15.1)	78.0 (22.1)	0.631
3 months after surgery	84.5 (12.8)	81.2 (18.7)	0.724
6 months after surgery	84.2 (11.5)	82.6 (14.3)	0.621
12 months after surgery	81.6 (13.5)	82.2 (17.1)	0.827
Role physical			0.112
Preoperative	70.2 (32.1)	68.3 (32.4)	0.734
3 months after surgery	49.7 (33.2)	45.1 (39.2)	0.346
6 months after surgery	70.5 (28.6)	65.6 (32.1)	0.933
12 months after surgery	80.2 (32.4)	77.3 (29.4)	0.192
Role emotional			0.922
Preoperative	81.0 (32.5)	79.1 (29.1)	0.633
3 months after surgery	84.7 (32.4)	81.3 (28.1)	0.21
6 months after surgery	89.2 (24.3)	86.8 (29.1)	0.191
12 months after surgery	90.2 (22.1)	87.6 (28.4)	0.422
Bodily pain			0.315
Preoperative	52.1 (21.3)	55.2 (29.1)	0.937
3 months after surgery	59.3 (22.1)	65.4 (29.6)	0.432
6 months after surgery	63.2 (23.9)	65.1 (22.6)	0.341
12 months after surgery	66.2 (29.2)	62.0 (21.5)	0.653
General health			0.253
Preoperative	66.4 (22.7)	62.8 (19.3)	0.571
3 months after surgery	59.2 (23.1)	49.7 (22.9)	0.045[a]
6 months after surgery	70.2 (16.3)	67.6 (23.2)	0.31
12 months after surgery	68.7 (23.2)	69.2 (28.1)	0.449
PCS			0.812

Preoperative	71.0 (8.5)	69.1 (10.1)	0.423
3 months after surgery	54.7 (11.4)	43.3 (13.1)	0.021[a]
6 months after surgery	69.2 (7.3)	67.8 (9.7)	0.592
12 months after surgery	72.2 (12.1)	70.6 (12.4)	0.482
MCS			0.451
Preoperative	69.2 (11.2)	68.4 (8.2)	0.621
3 months after surgery	55.9 (12.8)	49.4 (10.6)	0.015[a]
6 months after surgery	65.2 (8.4)	61.3 (12.6)	0.414
12 months after surgery	71.2 (14.2)	69.0 (10.3)	0.543
SF-6D			0.513
Preoperative	0.851 (0.142)	0.812 (0.213)	0.571
3 months after surgery	0.732 (0.121)	0.617 (0.149)	0.045[a]
6 months after surgery	0.781 (0.213)	0.722 (0.192)	0.320
12 months after surgery	0.807 (0.192)	0.781 (0.122)	0.495

[a]$P \leq 0.05$;
[b]$P \leq 0.01$;
[c]$P \leq 0.001$;
[d]$P \leq 0.0001$.
PCS: Physical component summary; MCS: Mental component summary; SF-6D: Short-form 6 dimension; LR: Laparoscopic resection; OR: Open resection.

Generally, applying some objective parameters to assess the postoperative outcome is crucial in defining a patient's degree of health. However, subjective patient perceptions and expectations should be factored into objective assessment to determine their real HRQoL. Thus, assessing self-reported HRQoL in surgical patients is of paramount importance. Accordingly, HRQoL measures have helped forecast the mortality and cost of health care[3].

The modified SF-36 Health Survey questionnaire is a comprehensive health status assessment tool, including an evaluation of physical functioning, social functioning, vitality, mental health, role physical, role emotional, bodily pain, and general health recovery over a specific period. Most interviewed patients could easily understand and complete the questionnaire within 10 min. In 2003, one study revealed that the concepts embodied in the SF-36 measurement model could be feasibly applied in the translated version in Taiwan[18]. Most items related to the psychometric properties were satisfactory based on the criteria of the International Quality of Life Assessment project. The rate of missing data was approximately 0%-2.7% at the item level, which was favorably compared with the original Medical Outcomes Study results in the United States[19] and other Western countries[20]. Additionally, this multitrait scaling study supported the hypothesized scale structure of the SF-36 Taiwan version and indicated the use of standard scoring algorithms score the eight SF-36 scales. All patients visiting the outpatient department in our study were compliant in answering the questionnaire within a 1-year postoperative follow-up, except two patients who expired within this period.

The surgery-related inconvenience of daily life and complications were actual events that significantly impacted the patients' medium-term (from 3 to 12 mo after the operation) HRQoL, showing lower SF-36 scores in some domains. Table 3 shows that patients undergoing OR encountered peri-operative complications that mainly reflect burden in the social ($P = 0.0001$) and physical ($P = 0.006$) functioning items in their daily lives instead of facing significant general health deterioration ($P = 0.045$) 3 mo postoperatively. The reported higher HRQoL scores after LR at this period could be attributed to the essential benefit of minimally invasive surgery. Minimally invasive surgical approaches cause more minor wounds, lesser peri-operative blood loss, lesser inflammatory response, lesser postoperative pain, fewer respiratory complications, faster postoperative recovery, and enhanced postoperative mobilization[1-2]. LR could cause less surgical injury to the abdominal wall. Thus, the disparity in HRQoL is expected to be more evident within the first week postoperatively. However, these consequences may benefit patients' well-being and report higher HRQoL scores in the medium-term period. The fascia is the most critical layer during abdomen wound healing because this tissue provides the most remarkable wound tensile strength. Patients might still feel discomfort during this period because the recovery of tensile strength could last over 70 days; even maximum strength exceeds 80%-90% of the intact fascia. However, only 15%-20% maximum strength is necessary for normal daily activities[21].

However, the decreasing negative effect of social functioning on patients undergoing OR had a mildly significant influence on the patients' HRQoL as the inconvenience of daily life and complications improved 6 mo postoperatively (P = 0.001) (Table 3).

HRQoL outcomes of 12 mo after LR for CRC were not superior to OR (Table 3). The absence of statistical difference between the two groups in the modified SF-36 scores associated with postoperative 12-month complications might be interfered with by our small-size patient cohort. Hence, a prospective study of more significant patient numbers is undoubtedly necessary to address this issue in the future.

Most complications encountered by our patients belonged to grade I and II levels according to the Clavien-Dindo classification. The concepts regarding UTI, ileus, and incisional hernia must be clarified because postoperative HRQoL is closely related to surgical complications.

A discrepancy exists in UTI incidence among various methods of interventions in surgical patients, with a significantly higher occurrence rate after colorectal surgery than others[22]. Kang *et al*[23] examined a nationwide inpatient sample database for patients with CRC undergoing surgery and revealed the elderly, female gender, open approach method, and some morbidities as risk factors. They concluded that pelvic dissection surgeries were prone to a significant risk of UTI, as we noticed all UTI cases in the groups receiving radical proctectomy and abdominal perineal resection in our study. We admitted that rectal-associated surgical intervention is an independent risk factor. Pelvic dissection leads to various degrees of regional inflammation and nerve injury, which might increase the risk of urinary retention after catheter removal, thereby limiting the trial of early catheter removal[24]. We try to remove the urinary catheters as soon as possible when patients can mobilize postoperatively although published studies do not indicate the exact timing of catheter removal. Our study revealed that LR was significantly beneficial to preventing the episodes of postoperative UTI, which might be related to minor tissue injury and pain because of its minimally invasive characteristics, thereby bringing patients the benefits of earlier mobilization and catheter removal.

Ileus is defined as the presence of a dilated loop of the small intestine on abdominal imaging with the clinical presentation of abdominal pain, distension, or vomiting. The most common complication of abdominal and pelvic surgery is postoperative adhesion caused by aberrant fibrous bands connecting the tissues or organs that should be separated, usually within the abdominal cavity. Approximately 65%-75% of episodes of acute ileus are the consequences of adhesions, mainly involving the small intestine. A study of over four years revealed that colorectal surgeries lead to approximately 30% risk of adhesion-associated complications in various surgical fields. Additionally, OR for colorectal surgery has been the most common cause of adhesion-relevant readmissions[25].

The onset of adhesive ileus after CRC incredibly differs after index surgery. Some specialists have revealed that the median time of its first episode was approximately 1.3 years[26], and others stated it should be 3 years[27]. The earliest time was > 1 year in our patients who encountered postoperative adhesive ileus, with a median time of approximately 2.7 years. However, LR should lead to a much lower possibility of postoperative adhesion formation. Adhesion formation is regarded as a consequence of a stepwise failure during the repair process of peritoneal tissue. Technically, we used microsurgical instruments for LR, which brings patients the benefits of less direct surgical trauma, meticulous hemostasis, and minimal blood loss. Moreover, constant irrigation, manipulation within a smaller operative field, avoidance of bowel exposure to the environment, and clean dissection might lower the adhesion formation rate, despite no statistical difference between our patients undergoing LR and OR.

The incidence of incisional hernia ranges from 10% to 20% of patients receiving abdominal operations [28], which could influence patients' HRQoL and body image. Factors predicting incisional hernia development after CRC surgery include dehiscence of the fascial layer, obesity, intestinal anastomosis leak, and surgical wound infection. A Denmark nationwide research studied 8489 patients with colon cancer receiving elective surgery with primary intestinal anastomosis from 2001 to 2008. It concluded that patients undergoing LR faced a relatively lower risk of this complication than those receiving OR approach[29]. However, our study revealed no significant statistical difference between the two groups.

One retrospective study, including 2983 patients undergoing OR, revealed that approximately 31.5% of incisional hernias occurred in the first 6 mo postoperatively, 54.4% in 12 mo, 74.8% in 2 years, and 88.9% in 5 years[30]. Winslow and Ng noticed that incisional hernia mainly developed in patients undergoing LR at the specimen extraction site[31-32]. Additionally, Ng *et al*[32] emphasized a similar incidence rate of incisional hernia at the midline extraction site in both the LR and OR groups. Moreover, no relationship was found between the incision wound length and hernia occurrence incidence. However, the burden of an incisional hernia caused by a large midline OR incision may be more severe than a small hernia at a limited specimen extraction site. The degree of challenge in hernia repair is positively related to the hernia size and is usually not amenable to minimally invasive repair techniques[31]. In our practice, we always tried to remove the specimen *via* the extraction wound as small as possible under a wound retractor's protection.

The anastomotic leakage rate is not rare but challenging to surgeons (Clavien-Dindo classification Grade III). The decision of re-operative strategies is arduous and highly complex[33], which depends on the anastomosis location and the characteristics of the anastomotic dehiscence, *e.g*., the degree of tissue trauma during operation. Laparoscopy could provide a clear view of the pelvis, which is usually inaccessible to the naked eye during the process of OR, based on our experience. Additionally, precise

dissection in a narrow male pelvis is comparatively easier to follow for the anatomic planes and completely secure hemostasis under the well-illuminated and magnified laparoscopic view. More importantly, we could reduce tissue trauma with less inadvertent handling by gently displacing the rectum and mesorectum from side to side during the LR procedure, which could lower the leakage rate. Fortunately, we successfully treated all patients after abscess drainage and stoma establishment for stool diversion. Additionally, no statistical difference was found in the complication between our LR and OR groups.

Some researchers studied the HRQoL after LR and OR but have miscellaneous conclusions. Several studies revealed no significant disparity in postoperative HRQoL[8-10], but others reported improved results in HRQoL after LR[2,6,11-12]. We have the following assumptions about this phenomenon. First, surgical techniques influenced the HRQoL, which might differ among the studies, especially with inconsistent surgeon volumes of multiple surgeons in the same survey. However, all patients in our study were treated by a single surgeon in two institutions, which could lower this bias. Second, HRQoL was not regarded as a chief outcome parameter in many studies, which probably resulted in an incompetent HRQoL analysis. Third, HRQoL might be interfered with various postoperative factors, although the baseline patient characteristics were identical at the initial preoperative evaluation. Fourth, different patients might experience other subsequent clinical courses even if they had the same pathologic TNM staging, which might affect the HRQoL. Finally, the clinical heterogeneity among various studies might be one important cause, mainly when we chose different HRQoL assessment instruments. Therefore, future ideal studies should be designed based on the standard guidelines with evidence-based consensus.

Our study on postoperative HRQoL evaluation has limitations. First, pelvic surgeries, especially rectal tumor excisions, lead to long-term and perilous consequences to male sexual function because of possible surgical trauma to the pelvic autonomic nerves[34]. However, this aspect is not included in the modified SF-36 Health Survey questionnaire. Thus, our study could not evaluate the effect on male sexual function after OR or LR. Second, two patients with stage III cancer were excluded because they expired within 6 mo after another radical surgery for cancer recurrence. Third, our study's case number is small, and the latter two limitations may cause a bias. Therefore, more significant patient numbers in further research are necessary to certify our conclusion.

CONCLUSION

Few studies focused on the HRQoL of patients between 3 and 12 mo postoperatively, and our study discussed the LR approach with significantly better HRQoL than OR 3 mo postoperatively. Meanwhile, fewer detrimental factors (complication rates and blood loss) and similar oncologic results were found in the LR group than in the OR group. Thus, we suggest patients with non-metastatic CRC to undergo the LR approach if not contraindicated.

ARTICLE HIGHLIGHTS

Research background

There are seldom studies about the medium-term effect on postoperative health-related quality of life (HRQoL) in patients undergoing colorectal cancer (CRC) surgery.

Research motivation

This study aimed to evaluate the medium-term effect of postoperative HRQoL in patients undergoing surgical CRC.

Research objectives

This study analyzed the objective outcomes and subjective HRQoL in 541 patients with non-metastatic CRC operated by one surgeon.

Research methods

This study randomized 541 patients undergoing surgery for non-metastatic CRC by one surgeon to the laparoscopic resection (LR) (n = 296) or open resection (OR) (n = 245) groups. We used a modified version of the 36-Item Short Form (SF-36) Health Survey questionnaire to assess the HRQoL preoperatively and 3, 6, and 12 mo postoperatively.

Research results

The LR group reported better HRQoL in general health, physical activity, and social function recovery with various degrees and had lower complications of postoperative urinary tract infection, wound

infection, and pneumonia than the OR group.

Research conclusions

Patients with CRC should consider LR to gain better HRQoL if not contraindicated.

Research perspectives

Seldom studies were conducted about the medium-term effect on postoperative HRQoL in patients undergoing surgery for CRC, and this study could provide vital information for reference.

FOOTNOTES

Author contributions: Hung CM and Hung KC contributed equally to this work; Hung CM, Hung KC, Lee HM, and Chiu CC designed the research study; Shi HY, Hsieh MC, Tseng CH, and Chiu CC performed the research; Tsai JF contributed analytic tools; Su SB analyzed the data and performed data validation; Chen CC, Tseng CM, Tsai YN, and Chen CZ provided critical opinion and feedback; Lin SE, proceeded language editing; Chiu CC, performed the operation, cared the patients, and obtained an IRB approval and supervision.

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META-ANALYSIS

Endoscopic biliary treatment of unresectable cholangiocarcinoma: A meta-analysis of survival outcomes and systematic review

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Abstract

BACKGROUND

Endoscopic radiofrequency ablation (ERFA), percutaneous radiofrequency ablation (PRFA), and photodynamic therapy (PDT), when used in conjunction with conventional biliary stenting, have demonstrated a survival benefit in patients with unresectable cholangiocarcinoma.

AIM

To compare pooled survival outcomes, adverse event rates, and mean stent patency for those undergoing these procedures.

METHODS

A comprehensive literature review of published studies and abstracts from January 2011 to December 2020 was performed comparing survival outcomes in patients undergoing ERFA with stenting, biliary stenting alone, PRFA with stenting, and PDT with stenting for unresectable cholangiocarcinoma (CCA).

RESULTS

Data from four studies demonstrated a pooled mean survival favoring ERFA as compared to biliary stenting alone (12.0 ± 0.9 mo *vs* 6.8 ± 0.3 mo, $P < 0.001$) as well as statistically improved median survival time (13 mo *vs* 8 mo, $P < 0.001$). Both ERFA with stenting and PRFA with stenting groups demonstrated statistical superiority to biliary stenting alone ($P < 0.001$ and $P = 0.004$, respectively).

However, when comparing ERFA to PRFA, pooled data demonstrated overall higher mean survival in the ERFA with stenting cohort as compared to PRFA with stent cohort (12.0 + 0.9 mo *vs* 8.1 + 2.1 mo, $P < 0.0001$). Data from two studies demonstrated a pooled median survival favoring ERFA with stenting as compared to PDT with stenting (11.3 mo *vs* 8.5 mo, $P = 0.02$).

CONCLUSION

While further prospective, randomized studies are needed to assess efficacy of ERFA, our meta-analysis demonstrated that this technique offers endoscopists a reasonable palliative method by which to treat patients with unresectable CCA that results in longer survival as compared to biliary stenting alone, percutaneous radiofrequency ablation with biliary stenting, and PDT with biliary stenting as well as an acceptable adverse event profile based on available published data.

Key Words: Endoscopic radiofrequency ablation; Percutaneous radiofrequency ablation; Photodynamic therapy; Cholangiocarcinoma; Meta-analysis; Systematic review

Core Tip: Endoscopic radiofrequency ablation offers endoscopists a reasonable palliative method by which to treat patients with unresectable cholangiocarcinoma that results in longer survival as compared to biliary stenting alone, percutaneous radiofrequency ablation, with biliary stenting, and photodynamic therapy with biliary stenting.

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INTRODUCTION

Cholangiocarcinoma (CCA) is a primary cancer of the bile ducts accounting for 15% of primary hepatic malignancies and nearly 3% of malignant gastrointestinal tumors. 90% of CCA are extrahepatic (perihilar or main bile duct), while the remaining 10% are intrahepatic[1-3]. Due to location and delayed onset of symptoms, CCA has a poor prognosis with 5-year survival rates of 2%-25% and median survival of 3-6 mo for unresectable cancers[1,4]. 20%-30% of cholangiocarcinoma cases are surgically resectable, leaving the majority of CCA patients with only palliative options, namely, systemic chemotherapy and relief of biliary obstruction through surgical, percutaneous, and endoscopic approaches. The complex molecular landscape of cholangiocarcinoma, however, has limited the effectiveness of systemic chemotherapy in the treatment of unresectable cancer[5,6]. As a result of poor chemotherapeutic options, the mainstay of care for these patients with unresectable CCA revolves around endoscopic retrograde cholangiopancreatography (ERCP), interventional radiologic, or endoscopic ultrasound (EUS)-guided approaches for biliary decompression with biliary stenting and/or percutaneous drainage. While in the majority of cases these approaches are technically feasible and particularly effective at relieving biliary obstruction, the life-prolonging effects of these interventions remain poor, and adverse events, such as stent occlusion and cholangitis, limit their overall effectiveness [7,8].

Photodynamic therapy (PDT) is a well-studied, ablative technique resulting in cellular apoptosis or necrosis in cells that absorb a photosensitizer, an agent activated by a specific wavelength of light[9,10]. PDT protocols for CCA involve a two-stage treatment consisting of systemic administration of the photosensitizing agent (that is preferentially absorbed by pre-malignant and malignant tissue) followed 48 to 96 h later with transpapillary intra-biliary placement of a laser-emitting diode placed into the bile duct *via* cholangioscopy or ERCP. This diode, when activated, emits a wavelength of 630 nanometers (nm), and when directed towards cells that have absorbed the photosensitizer, results in cell death and necrosis of the target tissue. In a recent meta-analysis of ten studies assessing outcomes of PDT combined with biliary stenting compared to conventional biliary stenting alone, survival in the PDT group was 413 d, which was statistically superior to the 183 d for patients who underwent biliary stenting alone[10].

The limitations of this technology involve the two-stage approach and the resulting phototoxicity of the skin from the photosensitizer (lasting 4-6 wk in decreasing intensity), occurring in 0%-25% of patients undergoing PDT with meta-analytic data demonstrating a photosensitivity rate of 10.5%[9-15].

To minimize the risk of this adverse event, most protocols requires the patient to take significant measures to prevent any exposure to light following administration of the photosensitizer. Other reported adverse events reported include cholangitis and hepatic abscess.

Radiofrequency ablation (RFA) is a technology that delivers thermal energy *via* a catheter or probe to malignant tissue, resulting in locoregional coagulative necrosis and cellular death. RFA has been previously used successfully *via* percutaneous (PRFA) or intraoperative routes for the treatment of other solid organ tumors[16]. However, there is limited data available evaluating the role of endoscopic biliary RFA (ERFA) and PRFA as palliative measures in patients with unresectable cholangiocarcinoma. Our meta-analysis aims to evaluate survival outcomes of ERFA with biliary stenting compared with both the conventional stent-only approach and PRFA with stenting in the setting of unresectable CCA.

MATERIALS AND METHODS

A comprehensive literature search was conducted querying the PubMed, EMBASE, and Cochrane databases from January 2011 to December 2020. Keywords in our search included: "endoscopic radiofrequency ablation" and "cholangiocarcinoma". In compiling studies assessing percutaneous radiofrequency ablation, the keywords in our search included: "percutaneous radiofrequency ablation" and "cholangiocarcinoma". In compiling studies assessing photodynamic therapy, the keywords in our search included: "cholangiocarcinoma" and "photodynamic therapy." The connector word "AND" was used to capture articles that were pertinent to our study. Reference articles were analyzed multiple authors for use in our initial inclusion. Our study was limited to articles published after the 2011 pilot study documenting the initial use of endoscopic radiofrequency ablation in human subjects[17]. Articles eligible for inclusion were limited to published retrospective (case-control studies) or prospective studies (randomized controlled trials) in the English language, conducted on human subjects. Additionally, studies included must have assessed both populations of interest with the intervention provided under similar medical conditions. Exclusion criteria included: Systematic reviews and/or meta-analyses; opinion papers; editorials; studies in which a contingency of data could not be extrapolated to generate the targeted outcome of survival duration; studies in which the patients underwent previous surgical intervention; studies in which other malignancies resulting in biliary obstruction (namely, pancreatic adenocarcinoma or ampullary carcinoma) were included, particularly if a contingency of data could not be extrapolated to generate the targeted conclusions or outcomes in cholangiocarcinoma subgroups. PRISMA flow charts (Figures 1A and B) were compiled to illustrate the results of our literature search with an additional detailed search strategy included as Supplementary Table 1 and 2.

Three authors (Rebhun J, Shin CM, and Villa E) independently reviewed each article yielded from the above search strategy. Full text of the articles was then assessed to determine if inclusion criteria were met. Any missing or unclear data resulted in an attempt to contact the original author with relevant questions. Data pulled from each article included the following: Author and year of the article; Origin of the study; Type of study conducted; Subgroup total population; Patient age and gender distribution; Mean survival in months; Median survival in months; Mean stent patency in months; Adverse Events; Chemotherapy status.

Outcome assessed

Data was extracted from articles meeting inclusion criteria and combined to perform a meta-analysis. The primary objective was to compare mortality outcomes in patients undergoing endoscopic RFA with biliary stenting (henceforth to be referred to as the "ERFA" subgroup) to those undergoing endoscopic stenting alone as well as to those undergoing percutaneous RFA with biliary stenting (henceforth to be referred to as the "PRFA" subgroup). Secondary outcomes included duration of stent patency and rates of adverse events between the treatment groups.

Quality assessment of included studies

To better assess the quality of individual studies, we used the Newcastle-Ottawa scale (NOS) for retrospective case-control studies and the Cochrane tool for risk of bias for randomized controlled trials The NOS uses 3 domains: Selection, comparability, and ascertainment of outcome to award a maximum of 9 total points. A score > 7 indicates a study of good quality. The NOS has been shown to be a marker of individual study quality when using non-randomized studies in meta-analyses[18,19]. NOS scores are reported in the supplementary portion of the article. In order to best evaluate the quality of evidence for each outcome amenable to meta-analysis, we used the Grading of Recommendations, Assessment, Development, and Evaluation system to interpret the clinical implications of our findings.

Statistical analysis

Continuous variables were reported as mean ± standard deviation. Categorical variables were calculated as frequencies or percentages. Pooled survival data was used to generate Kaplan-Meier survival curves with log-rank test performed to assess for statistically significant differences in survival.

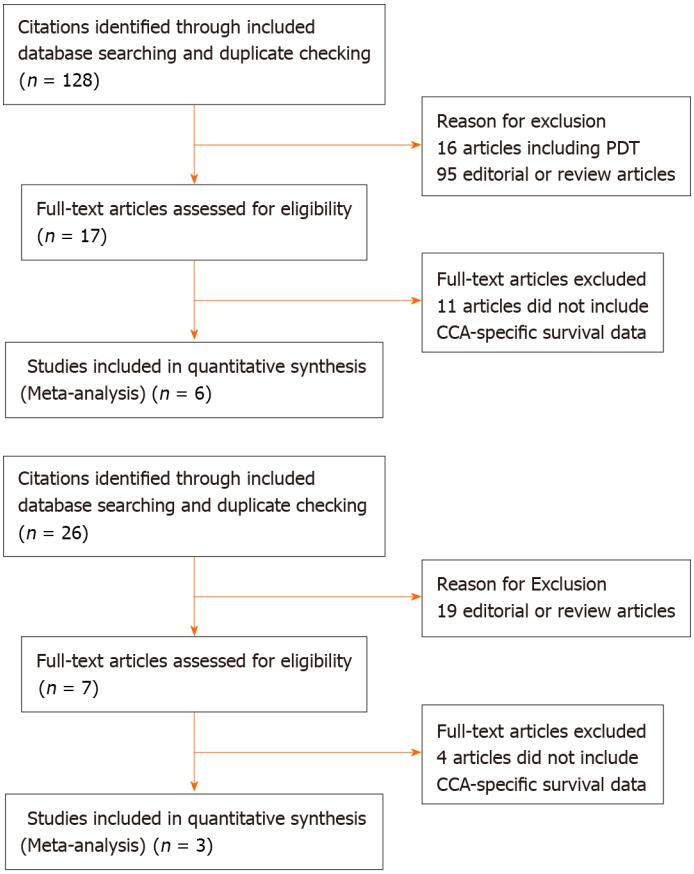

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Figure 1 PRISMA flow charts. A: Flowsheet diagram demonstrating inclusion of studies for meta-analysis of endoscopic radiofrequency ablation (ERFA) with stenting versus biliary stenting alone; B: Flowsheet diagram demonstrating inclusion of studies for meta-analysis of ERFA with stenting versus photodynamic therapy with stenting. CCA: Cholangiocarcinoma; PDT: Photodynamic therapy.

Median days of survival was either reported in each study or extrapolated with use of study-specific survival tables and/or curves. Between-study heterogeneity was reported with the I^2 statistic with values greater than 50 suggestive of substantial heterogeneity[20]. Categorical data underwent chi-square analysis to ascertain statistically significant differences. Mann-Whitney U-Test was performed to compare mean stent patency. If survival or stent patency was reported in number of days, conversion to number of months was made by dividing number of days by 30.42. Time in months was then rounded to the nearest tenth decimal place. *P* values were 2-sided and statistical significance was achieved with a *P* value of < 0.05. Data was analyzed using IBM SPSS Statistics for Macintosh, Version 27.0 (IBM Corp. Armonk, NY, United States). The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

RESULTS

ERFA compared to biliary stenting alone

Our initial search returned 128 studies. After exclusion of studies that did not satisfy inclusion criteria and/or met no exclusion criteria, four studies[21-24] were included for quantitative and qualitative analyses. Summary of study characteristics (Table 1) as well as procedural and survival outcomes of each study (Table 2) are demonstrated in the corresponding tables.

Patients in the ERFA cohort had a pooled mean survival time of 12.0 ± 0.9 mo (I^2 = 37.0) while patients undergoing stenting alone had a mean survival time of 6.8 ± 0.3 mo (I^2 = 78.4). Difference in survival was calculated to be 4.9 ± 0.1 mo and the analysis was associated with minimal heterogeneity (P < 0.001, I^2 = 0) (Figure 2). Median survival of the ERFA cohort was calculated to be 13 mo while median survival of the stent only cohort totaled 8 mo with log-rank test performed to suggest a significant difference (P < 0.001, Figure 3).

Two of four studies reported data on stent patency[21,22] (Table 3). Stent patency was not found to be significantly different in the study by Hu *et al*[21] (P = 0.7); however, stent patency was significantly higher in the ERFA cohort in Yang *et al*[22] (P = 0.02)[19,20]. Both studies contributed similarly to the

Table 1 Summary of included studies

Ref.	Country	Study type	Total patients	Mean age	Female gender (%)	Chemotherapy
Sampath *et al*[23], 2016	United States	Case-Control	25	69.7	10 (40.0)	19 (76)
Hu *et al*[21], 2016	China	RCT	63	71.4	32 (50.8)	-
Wu *et al*[26], 2017	China	Case-Control	71	57.9	28 (39.2)	59 (83)
Cui *et al*[25], 2017	China	Case-Control	39	64.7	17 (43.5)	2 (5)
Yang *et al*[22], 2018	China	RCT	65	63.2	32 (49.2)	-
Bokemeyer *et al*[24], 2019	Germany	Case-Control	44	67	-	13 (30)

RCT: Randomized controlled trial.

Table 2 Procedural and survival outcomes of individual studies

Ref.	Total patients		Technical success		Major adverse events		Mean survival (mean ± SD)		*P* value[a]
	Stent only	RFA-stent	Stent only	RFA-stent	Stent only	RFA-stent	Stent only	RFA-stent	
Endoscopic									
Sampath *et al*[23], 2016	15	10	-	100	8	9	4.7 ± 5.5	12 ± 5.9	0.001
Hu *et al*[21], 2016	31	32	-	-	22	26	5.7 ± 0.5	10.4 ± 1.2	0.001
Yang *et al*[22], 2018	33	32	100	100	3	2	8.3 ± 0.5	13.2 ± 0.6	< 0.001
Bokemeyer *et al*[24], 2019	22	20	100	100	10	4	7.4 ± 0.9	11.4 ± 1.9	0.046
Percutaneous									
Wu *et al*[26], 2017	36	35	-	100	5	0	6.5 ± 2.6	8.4 ± 2.3	0.80
Cui *et al*[25], 2017	14	25	-	-	-	-	4.5 ± 2.1	6.7 ± 5.3	0.30

[a]*P* value as it relates to mean survival in each respective study. SD: Standard deviation; RFA: Radiofrequency ablation.

Table 3 Pooled stent patency analysis among included endoscopic radiofrequency ablation studies

Ref.	Stent only patients (%)	Mean stent patency	ERFA-stent patients (%)	Mean stent patency	*P* value
Hu *et al*[21], 2016	31 (48.5)	3.9	32 (50)	5	0.7
Yang *et al*[22], 2018	33 (51.5)	3.4	32 (50)	6.8	0.02
Cumulative	64	3.6	64	5.9	< 0.001

ERFA: Endoscopic radiofrequency ablation.

pooled analysis with only slightly more patients in the stent only treatment group being represented by Yang *et al*[22]. Pooled results of the two studies were calculated and demonstrated a mean stent patency in the ERFA with stent group to be 5.9 mo compared to 3.6 mo in the stent only group ($P < 0.001$). All four studies reported adverse event data and were used in our analysis (Table 4). Biliary stent occlusion was the most frequent adverse event that arose in both treatment groups, however there was no significant difference between ERFA (81%) and stent alone (67.3%, $P = 0.148$). Cholecystitis data was only reported in the Hu *et al*[21] and Bokemeyer *et al*[24] studies; however pooled analysis showed a 12.5% risk for cholecystitis in the ERFA cohort compared with 0% risk in the stent only cohort ($P = 0.01$). The frequency of hemobilia/bleeding was similar among the two groups (1.5% for both, $P = 1.0$).

ERFA compared to percutaneous biliary RFA

Of the 128 articles in our initial literature search, six studies were included for meta-analytic comparisons of survival between ERFA and PRFA groups[21-26]. From these studies, there were 106 patients that underwent ERFA with concomitant stenting, and 60 patients who underwent PRFA with stenting for unresectable CCA. Comparison control groups included 101 patients who underwent

Table 4 Pooled adverse event data among included endoscopic radiofrequency ablation studies

Adverse event	ERFA-stent *n* (%)	Stent alone*n* (%)	*P* value
Biliary stent occlusion	34 (81.0)	31 (67.3)	0.148
Cholangitis	27 (25.5)	15 (19.0)	0.298
Cholecystitis	8 (12.5)	0 (0)	0.010
Pancreatitis	4 (4.2)	3 (4.7)	0.875
Hemobilia/Bleeding	1 (1.5)	1 (1.5)	1.000

ERFA: Endoscopic radiofrequency ablation.

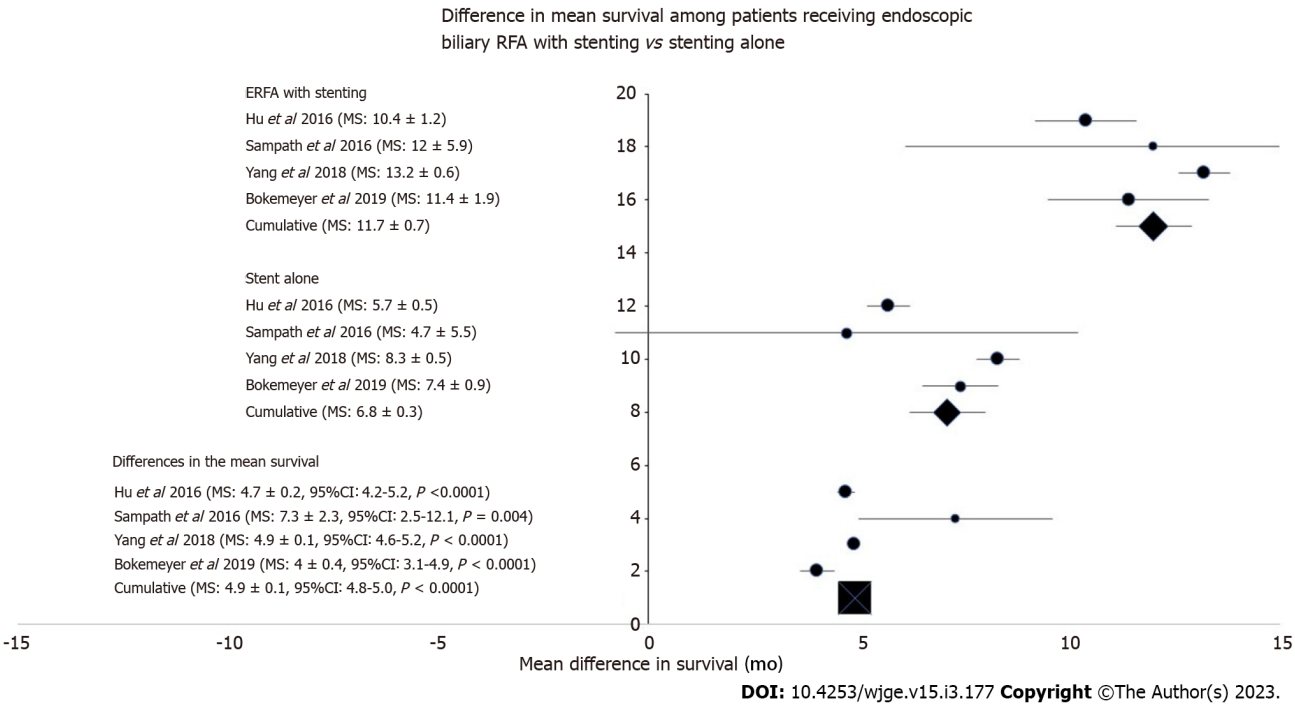

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Figure 2 Forest plot of mean stent survival among treatment groups along with difference in survival. RFA: Radiofrequency ablation.

biliary stenting in the ERFA studies and 50 patients who underwent biliary stenting in the PRFA studies.

The ERFA with stent cohort had a mean survival of 12.0 + 0.9 mo (Q = 4.8, I = 37%, Figure 4). The PRFA with stent cohort had a mean survival of 8.1 + 2.1 mo (Q = 0.09, I = 0%, Figure 4). In both ERFA and PRFA studies, mean survival was significantly increased compared to biliary stent alone control groups ($P < 0.001$ and $P = 0.004$, respectively). The difference in mean survival among both biliary RFA groups favored ERFA with stenting by 3.9 + 0.2 mo (95%CI: 3.4-4.4, *t*-test =16.6, $P < 0.0001$; Figure 4).

The ERFA group had a median survival (Figure 5) of 13 mo compared to the PRFA group median survival of 5.2 mo (log-rank test $Z = 5.3$, $P < 0.0001$). Only patients undergoing ERFA with stenting had a significant difference in median survival as compared to the biliary stent alone control group ($P < 0.001$).

Adverse event data went unreported in the Cu *et al*[25] study, thus comparison of PRFA adverse event was limited to those of procedures reported by Wu *et al*[26]. In comparing this study to those of the ERFA cohort, the risk of cholangitis was increased in the ERFA with stent cohort ($\chi^2 = 11.0$, $P = 0.001$).

ERFA compared to PDT

Of the 26 studies identified in our initial literature search, two studies provided data contingent for direct comparison of PDT and ERFA survival in patients with unresectable CCA (Table 5)[13,14]. From these studies, 49 patients underwent ERFA, and 56 underwent PDT (Table 5). All patients underwent concomitant biliary stenting whether *via* ERCP or *via* percutaneous transhepatic biliary drainage. Pooled median survival of the ERFA group was 11.3 mo, and median survival of the PDT group was 8.5 mo, a

Table 5 Demographics, procedural, and survival outcomes of endoscopic radiofrequency ablation *vs* photodynamic therapy

	Demographic data								
	Strand *et al*[13], 2014				Schmidt *et al*[15], 2016				Gao *et al*[14], 2018
Number of patients	RFA	16		P = 0.1	RFA	14		NA	RFA
	PDT	32			PDT	20			PDT
Gender (male)	RFA	10		P = 1.0	RFA	8		P = 0.1	RFA
	PDT	19			PDT	6			PDT
Age (mean, yr)	RFA	64.3 ± 11.9		P = 0.1	RFA	73 ± 9		P = 0.2	RFA
	PDT	69.5 ± 13.6			PDT	70 ± 12			PDT
Number of treatments	RFA	28 (mean: 1.2)		P = 0.02	RFA	31		NA	RFA
	PDT	60 (mean: 2.1)			PDT	36			PDT
Median survival (month)	RFA	9.6		P = 0.8	RFA	NA		NA	RFA
	PDT	7.5			PDT	NA			PDT
Lead time to initial treatment (days)	RFA	NS		P = 0.6	RFA	300 ± 270		NA	RFA
	PDT	NS			PDT	120 ± 90			PDT
Total bilirubin concentration (μmol/dL)	RFA	NA		NA	RFA	3.3 ± 3.9		P = 0.7	RFA
	PDT	NA			PDT	4.1 ± 6.9			PDT
Tumor location	RFA	Intrahepatic	1	P = 0.1	RFA	Intrahepatic	1	P = 0.5	RFA
		Hilar	13			Hilar	11		
		Distal/Extrahepatic	2			Distal/Extrahepatic	1		
	PDT	Intrahepatic	0		PDT	Intrahepatic	3		PDT
		Hilar	32			Hilar	15		
		Distal/Extrahepatic	0			Distal/Extrahepatic	1		
N1 staging	RFA	7		P = 0.8	RFA	3		P = 0.4	RFA
	PDT	12			PDT	2			PDT
M1 staging	RFA	6		P = 0.2	RFA	2		P = 0.8	RFA
	PDT	6			PDT	6			PDT
Stents placed	Total	RFA	115	NA	Total	RFA	29	NA	Total
		PDT	307			PDT	44		
	Plastic	RFA	69	NA	Plastic	RFA	26	NA	Plastic
		PDT	264			PDT	38		
	Total metallic	RFA	46	NA	Total metallic	RFA	3	NA	Total metallic
		PDT	43			PDT	6		
	Fully covered	RFA	17	NA	Fully covered	RFA	NA	NA	Fully covered
		PDT	14			PDT	NA		
	Uncovered	RFA	29	NA	Uncovered	RFA	NA	NA	Uncovered
		PDT	29			PDT	NA		
Number of ERCPs	RFA	91		NA	RFA	NA		NA	RFA
	PDT	170			PDT	NA			PDT
Percutaneous transhepatic biliary drainage (PTBD)	RFA	2		P = 0.2	RFA	2		P = 0.3	RFA
	PDT	10			PDT	6			PDT

RFA: Radiofrequency ablation; PDT: Photodynamic therapy; NA: Not available; NS: Not significant; *P*: *P* vaule as it relates to each comparator category.

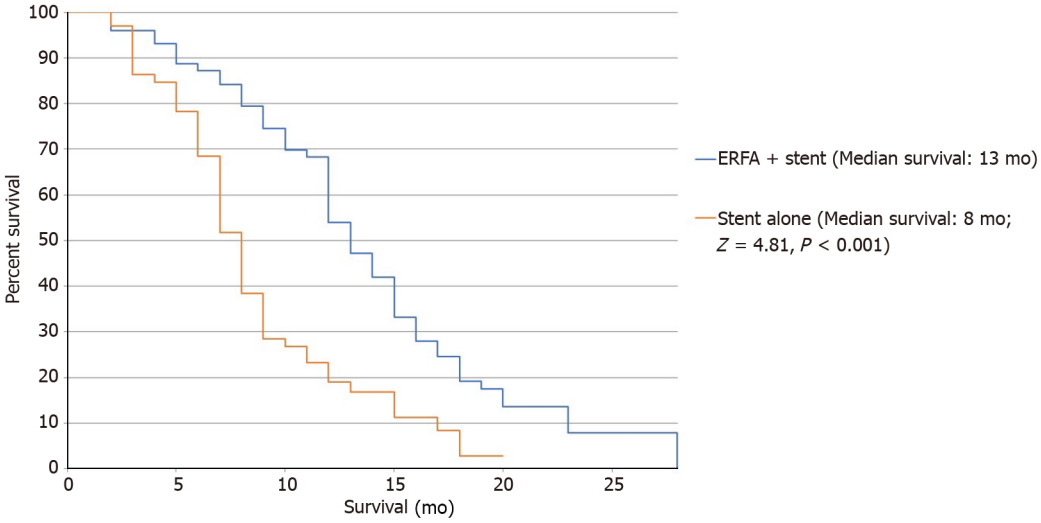

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Figure 3 Kaplan-Meier survival curve of endoscopic radiofrequency ablation with stenting *vs* stenting alone. ERFA: Endoscopic radiofrequency ablation.

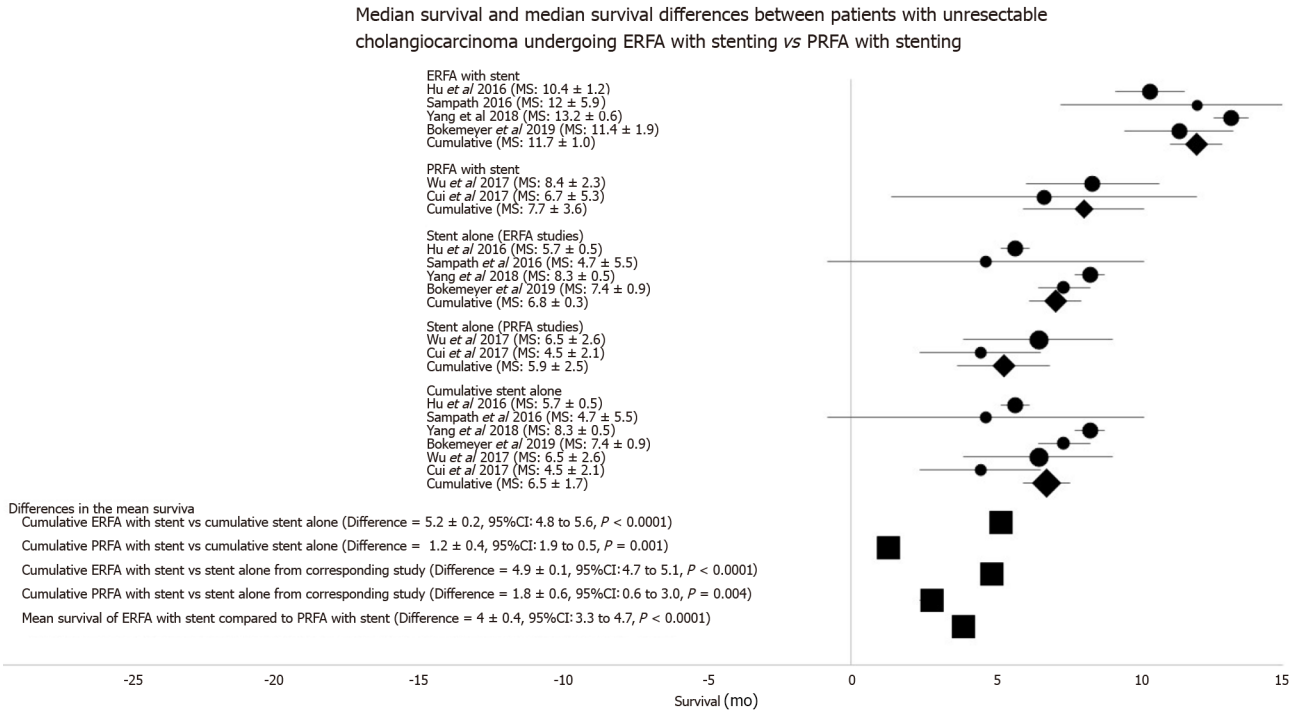

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Figure 4 Forest plot of mean survival of endoscopic radiofrequency ablation with stenting; percutaneous radiofrequency ablation with stenting; comparisons to corresponding biliary stenting alone subgroups; and overall comparisons in mean survival. ERFA: Endoscopic radiofrequency ablation; PRFA: Percutaneous radiofrequency ablation.

difference that was statistically significant (Figure 6; $P = 0.02$).

Of the 26 studies identified, three studies provided data contingent for direct comparison of PDT and ERFA adverse events (Table 5)[13-15]. With regard to pooled adverse events among 62 patients who underwent ERFA and 75 patients who underwent PDT, there were statistically higher rates of stent occlusions (22.6% *vs* 6.7%, $P = 0.008$) and cholangitis (74% *vs* 41.3%, $P = 0.001$) in the ERFA group (Table 6); however, there were increased rates of stent migration (16% *vs* 4.8%, $P = 0.04$), moderate or

Table 6 Adverse events of endoscopic radiofrequency ablation *vs* photodynamic therapy

Adverse events			
	RFA	PDT	*P* value
Stent related complications	17	17	0.7
Stent occlusion	14	5	0.008
Stent migration	3	12	0.04
Cholangitis	46	31	0.001
Hepatic abscess	4	3	0.5
Bleeding	1	1	0.9
Moderate/Severe abdominal pain	3	17	0.003
Post-ERCP pancreatitis	3	2	0.5
Phototoxicity	0	2	NA

ERCP: Endoscopic retrograde cholangiopancreatography; NA: Not applicable; RFA: Radiofrequency ablation; PDT: Photodynamic therapy; *P*: *P* vaule as it relates to comparisons of each adverse event.

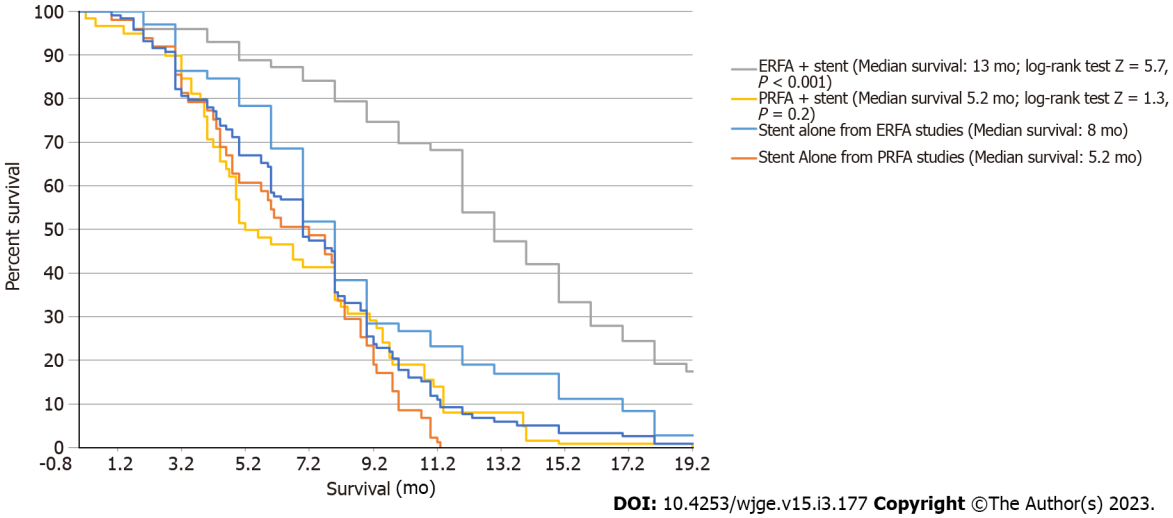

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Figure 5 Kaplan-Meier survival curve of endoscopic radiofrequency ablation and percutaneous radiofrequency ablation with stenting compared to biliary stenting alone. ERFA: Endoscopic radiofrequency ablation; PRFA: Percutaneous radiofrequency ablation.

severe post-procedure pain (22.7% *vs* 4.8%, *P* = 0.003), and phototoxicity (2.7% *vs* 0%) in the pooled PDT cohort as compared to the pooled ERFA cohort (Table 6).

Quality assessment and risk for bias

The study by Strand *et al*[13] received a score of "9" out of 9 as confounders such as tumor stage, performance status, and number of procedures did not differ among cohorts. While described as a case series, the study from Schmidt and colleagues was largely retrospective and partly prospective. Designation of intervention in the prospective portion was determined by choice of the patient, thus losing a point in selection of the cohorts and receiving a score of "8" out of 9. The study performed by Wu *et al*[26] received a NOS score of "7" out of 9, as there were no cofounders corrected for. Additionally, the study by Cui *et al*[25] also received a score of "7" out of 9 because age significantly differed among study groups and was uncorrected for. The study by Bokemeyer *et al*[24] received a NOS score of "9" out of 9. In this case, confounders were adjusted for by age, extent of disease, the use of endoprostheses, and the application of systemic palliative chemotherapy. The study from Yang and colleagues was assessed using the Cochrane risk of bias tool. While subjects were randomized, patients and interventionalists could not be blinded. Additionally, there was some unclear risk for bias in this study as detailed in Supplementary Figure 1. Two studies that were published only as abstracts were not able to be assessed for bias. Detailed analysis of these scores can be seen in the appendix as Supplementary Table 3.

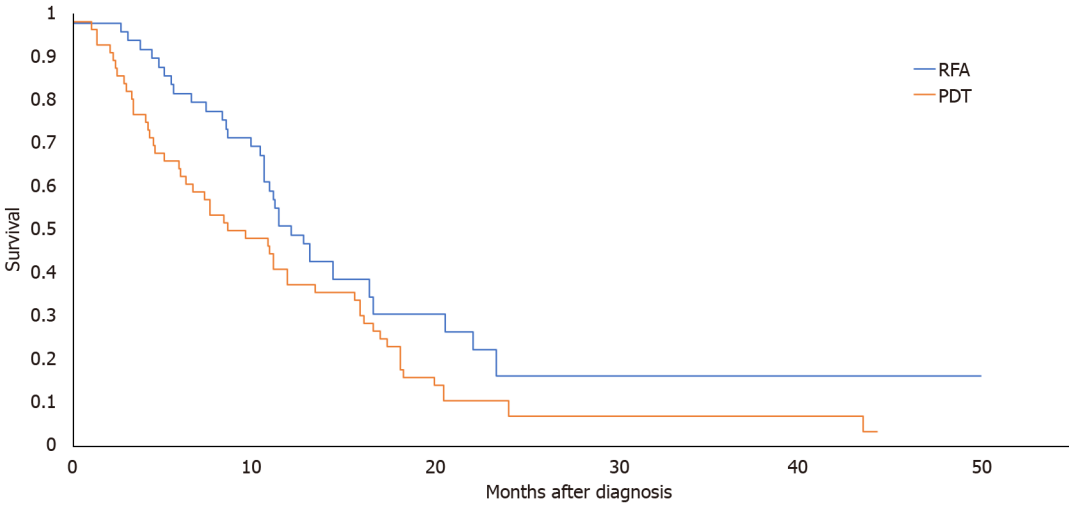

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Figure 6 Kaplan-Meier survival curve of endoscopic radiofrequency ablation with stenting compared to photodynamic therapy with stenting. RFA: Radiofrequency ablation; PDT: Photodynamic therapy.

DISCUSSION

Although it remains a relatively rare disease, the incidence of CCA continues to increase worldwide. Surgical resection remains the only curative treatment option; however, resection is only an available option in up to 30% of patients diagnosed, likely due to a variety of factors, including delayed diagnosis, which is, in large part, due to late onset of symptoms[27]. As such, for many patients, palliative approaches become the mainstay treatment options.

Our study compiles pooled data from previous investigations to better describe the roles ERFA and PRFA with stenting have in the palliation of unresectable cholangiocarcinoma and ascertain the survival benefits, thereof, while identifying adverse events that could portend poor quality of remaining life.

The meta-analytic outcomes in our study demonstrated a statistically significant improvement in both mean and median survivals when comparing ERFA to endoscopic biliary stenting alone in this cohort of patients with unresectable cholangiocarcinoma. While percutaneous RFA (PRFA) performed by capable Interventional Radiologists leads to improvement in mean survival, median survival is not impacted. While there are no studies assessing direct comparisons between ERFA and PRFA, available data does suggest superiority of ERFA with regard to median survival in these CCA patients, arguing for more widespread implementation of this palliative technique.

Safety concerns have been raised, however, given risk of stent occlusion or migration-with resulting cholangitis or delays in chemotherapy due to ensuing hyperbilirubinemia-as well as the risk of hemobilia and cholecystitis. However, the pooled data of included studies did not reveal an increase in stent occlusion rates, cholangitis, or hemobilia as compared to biliary stenting alone but did demonstrate increased risk of cholecystitis. Subgroup analyses were insufficient to conclude whether reported cholecystitis occurred in those with plastic or metallic biliary stenting. As compared to PRFA, there was an increased risk of reported cholangitis cases. However, given the lack of PRFA adverse event data reported (only one study allowed for analysis), definitive conclusions are difficult to make.

While technically feasible with reasonable safety outcomes, ERFA is an appealing option for palliation in these patients. However, the technique is limited in certain respects to degree of stricture, as severe strictures make passage of the RFA probe difficult and mild strictures may not result in adequate contact of the RFA to achieve adequate ablation. There is also a lack of consensus with regard to the timing of repeat ablation, particularly in those with successful first ablations. Further studies are needed to ascertain the optimal period between procedures as well as endoluminal and clinical parameters that would otherwise warrant repeating or avoiding the procedure.

Given the paucity of comparative studies, this meta-analysis was restricted to a small number of published studies, which could potentially overstate the benefit of the approach. Thirteen articles in our literature review were excluded in this meta-analysis due to a lack of contingency of data to separate CCA patients from those studies with other malignant biliary obstructions (ampullary and pancreatic carcinomas), and another 15 articles were excluded for inclusion of other palliative endotherapies (photodynamic therapy) or included patients in whom a previous surgical intervention was undertaken.

To this point, a recent meta-analysis by Zheng and colleagues suggested that patients undergoing ERFA for malignant biliary obstruction had a pooled survival of 9.6 mo but included all patients with malignant biliary obstruction[28]. Similarly, a separate meta-analysis compared ERFA with biliary stenting and to biliary stenting alone for malignant biliary obstructions found a mean survival of 9.4 mo

[29]. While the exact mechanism for prolonged survival is unknown, it has been postulated that the ablative process induces a systemic immune response which is then amplified by immune modulating agents resulting in improved clinical outcomes[30-32].

Our cohort of 94 cumulative patients with unresectable CCA receiving ERFA with stenting demonstrated a median survival of 13 mo. This difference may be explained by the exclusion of other etiologies for malignant biliary obstruction; technique advancement with the availability of improved cholangioscopic visualization of the malignant stricture; patient selection; or other confounders, such as stent selection.

PDT with biliary stenting is another endoscopic approach that has been well-studied as a palliative option for patients with unresectable CCA and has been shown to be superior to biliary stenting alone. While there is a paucity of studies, our meta-analysis demonstrated that in two comparative studies with available relevant contingency data, the median survival with ERFA is statistically superior than in PDT. This difference may be explained by lack of studies comparing the two modalities directly and the need for more study for adequate comparison of survival outcomes.

With lack of available studies, the direction of endoscopic palliative therapy is one that, at present, is largely center-dependent. PDT has the inconvenience of requiring two stages of intervention, one for administration of the photosensitizer and one for the delivery of therapy for tumor necrosis and cell death and also comes with the added inconvenience for the patient of avoiding direct exposure to light due to risk of skin photosensitivity. This is not the case with ERFA, which can be performed as a single procedure. It is worth noting, however, that increased rates of cholangitis and stent occlusion in ERFA cohorts would increase the need for subsequent interventions and increase costs related to repeat procedures, but this is an outcome that must also be studied further. In comparing ERFA with stenting compared to biliary stenting alone, however, there was no statistically significant difference in stent occlusion or cholangitis adverse events, so as a singular modality, safety outcomes are still comparable to biliary stenting alone while offering the benefit of longer survival as compared to biliary stenting. Interestingly, while PDT did have higher rate of stent migration, this may potentially reflect significant decrease in size of the obstructing tumor, which is a desirable outcome; this, however, was not quantified in the comparative studies and is an area for potential investigation.

CONCLUSION

In any event, endoscopic palliation of unresectable CCA with ERFA has shown significant promise in this patient population, but further studies are needed to assess our specific cohort of patients to further understand palliative, technical, and clinical outcomes, especially as they compare to other palliative therapies that extend beyond conventional biliary stenting alone.

ARTICLE HIGHLIGHTS

Research background

Further prospective studies comparing all therapeutic modalities are needed to best understand their role in the treatment of unresectable cholangiocarcinoma.

Research motivation

Endoscopic radiofrequency ablation with biliary stenting is a promising palliative therapeutic option in patients presenting with unresectable cholangiocarcinoma.

Research objectives

Endoscopic radiofrequency ablation when used in conjunction with biliary stenting showed improved survival benefit when compared to alternative palliative therapies.

Research methods

This is a comprehensive literature review of studies evaluating survival benefit and other clinical outcomes as it relates to the proposed therapeutic interventions.

Research results

To better understand, qualify, and quantify the survival outcomes of endoscopic radiofrequency ablation, percutaneous radiofrequency ablation, and photodynamic therapy in the treatment of unresectable cholangiocarcinoma as it compares to conventional therapy alone.

Research conclusions

Our motivation for this study was to better understand alternative approaches to palliative endoscopic

intervention for patients with unresectable cholangiocarcinoma.

Research perspectives

There is limited data evaluating the clinical outcomes of endoscopic radiofrequency ablation and photodynamic therapy as interventions for unresectable cholangiocarcinoma.

FOOTNOTES

Author contributions: Villa E contributed to conception and design; Rebhun J and Villa E contributed to analysis and interpretation of the data; Rebhun J, Shin CM, Villa E contributed to drafting of the article; Siddiqui UD and Villa E contributed to critical revision of the article for important intellectual content; Rebhun J, Shin CM, Siddiqui UD, Villa E contributed to final approval of the article.

Conflict-of-interest statement: Uzma Siddiqui has served as a speaker/consultant for Boston Scientific, Medtronic, and Olympus. Edward Villa has served as a consultant/speaker for ConMed as well as a speaker for Ovesco.

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CASE REPORT

Colonic ductal adenocarcinoma case report: New entity or rare ectopic degeneration?

Clara Benedetta Conti, Giacomo Mulinacci, Nicolò Tamini, Marta Jaconi, Nicola Zucchini

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Abstract

BACKGROUND

Ectopic pancreatic tissue is a congenital anomaly where a part of pancreatic tissue is located outside of the pancreas and lacks vascular or anatomical communication with it but shows the same histological features. Currently, the literature reports only two anecdotal cases of malignant transformation of colonic ectopic pancreas.

CASE SUMMARY

We present a case of an 81-year-old patient presenting with anemia, with right colonic neoplasia and carbohydrate antigen 19-9 above the normal values. She underwent laparoscopic right hemicolectomy. The final histology was consistent with a primitive adenocarcinoma with ductal morphology and solid-predominant growth pattern. Benign ectopic pancreatic tissue was absent in the surgical specimen.

CONCLUSION

The case describes a very rare complete degeneration of a colonic ectopic pancreatic tissue. However, the absence of benign ectopic pancreatic tissue in the surgical specimen is suggestive of the first description of a primitive ductal adenocarcinoma of the colon.

Key Words: Pancreatic cancer; Colorectal cancer; Colonic ductal adenocarcinoma; Ectopic pancreas; Case report

Core Tip: Ectopic pancreatic tissue is a congenital anomaly. Currently, only two anecdotal cases of malignant transformation of colonic ectopic pancreatic tissue have been described. We present a case of an 81-year-old patient with a primitive adenocarcinoma of the right colon, with ductal morphology and solid-predominant growth pattern. Carbohydrate antigen 19-9 value was above the normal values, and both pancreas and biliary tree were healthy. Benign ectopic pancreatic tissue was missing in the surgical specimen. This observation is suggestive of a complete degeneration of a rare colonic ectopic pancreatic tissue or, even more interesting, the first description of a primitive ductal adenocarcinoma of the colon.

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INTRODUCTION

Ectopic pancreatic tissue is a congenital anomaly where a part of pancreatic tissue is located outside of the pancreas and lacks vascular or anatomical communication with it while showing the same histological features: Pancreatic acinar formation, duct development and islets of Langerhans. Ectopic pancreatic tissue is found in 0.2% of laparotomies and 0.5%-14.0% of autopsies. The most common locations are the stomach (25%-40%), duodenum (9%-36%) and proximal jejunum (0.5%-35.0%). The ileum, including ectopic pancreas within Meckel diverticulum, accounts for 2.8% to 7.5% of cases, being the fourth most common site. The colon, appendix, mesentery, esophagus, liver, gallbladder, bile duct, spleen, umbilical cord, retroperitoneal cavity, lung and mediastinum are extremely rare sites[1]. Usually ectopic pancreas is an asymptomatic condition. However, the complications described in the literature are pancreatitis, bleeding, intussusception and malignant degeneration[2,3].

According to the Guillou description, carcinoma arising from ectopic pancreatic tissue is surely diagnosed when tumor cells are found within or close to the ectopic pancreas. A transitional area between pancreatic structures and carcinoma is clearly detected and the benign ectopic pancreatic tissue shows acini and ductal structures[4].

Currently, the literature reports only two anecdotal cases of malignant transformation of colonic ectopic pancreatic tissue: One occurred in the splenic flexure and one in the sigmoid colon[5].

CASE PRESENTATION

Chief complaints

A 81-year-old woman underwent colonoscopy for severe anemia (hemoglobin 6 g/dL) in the absence of overt gastrointestinal bleeding.

History of present illness

She had ongoing anticoagulant therapy due to atrial fibrillation. The liver enzyme test, cholestasis test and two previous abdominal sonography exams were normal. However, of note, blood tests showed carbohydrate antigen 19-9 (CA 19-9) value repeatedly above normal values (2 × upper limit of normal) since 2016.

History of past illness

The medical history of the patient reported a loss of 4 kg in the previous 6 mo, and an invasive lobular carcinoma of the breast occurred 10 years prior to admission.

Personal and family history

Family history was unremarkable. The patient did not smoke and did not drink alcohol. She was normal weight before the weight loss occurred due to the neoplasia.

Physical examination

The patient's vital signs were normal. She was pale due to the anemia and reported fatigue. No abnormal findings were present at the physical examination, apart from the atrial fibrillation.

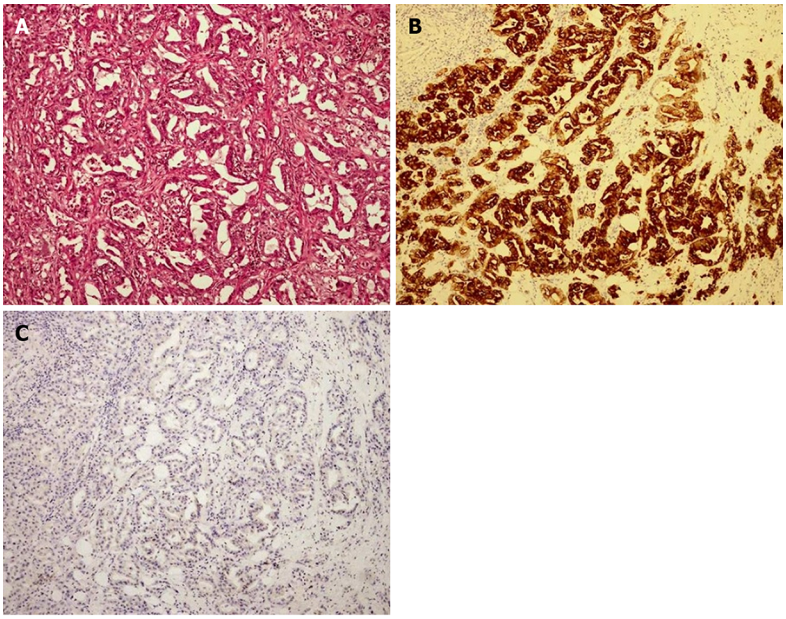

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Figure 1 Right colon adenocarcinoma with ductal morphology. A: Hematoxylin and eosin, × 10; B: With diffuse positive staining for cytokeratin 7 (× 10); C: Complete absence of CDX-2 immunoreactivity (× 10).

Laboratory examinations

Liver enzyme and cholestasis tests were normal.

Imaging examinations

Two previous abdominal sonography exams were normal. Computed tomography scan, performed after the diagnosis of the colonic neoplasia showed local peritoneal infiltration and local lymphadenopathies, in the absence of distant organ metastasis. Colonoscopy revealed a large lesion of 40 mm in size extending from the ileocecal valve fold to the ascending colon. The superficial pattern, the spontaneous bleeding and the ulcerated surface suggested the diagnosis of primitive colonic neoplasia. Biopsies were taken. The terminal ileum results were normal. Surprisingly, the histological diagnosis was consistent with a primitive ductal adenocarcinoma of the colon (Figure 1A). A total body computed tomography scan showed local peritoneal infiltration and local lymphadenopathies, in the absence of distant organ metastasis. Notably, both the pancreas and biliary tree did not report abnormalities. CEA was normal, whereas CA 19-9 value was 3 × upper limit of normal. Cholestasis and liver enzyme tests were again normal.

FINAL DIAGNOSIS

The final histology of the surgical specimen confirmed the diagnosis of adenocarcinoma with ductal morphology and solid-predominant growth pattern.

TREATMENT

After a multidisciplinary discussion, the patient underwent surgical treatment, with laparoscopic right hemicolectomy and ileocolic anastomosis. The final histology of the surgical specimen confirmed the diagnosis of adenocarcinoma with ductal morphology and solid-predominant growth pattern. The immunohistochemistry documented the diffuse positive staining for cytokeratin 7 and the absence of CDX2 immunoreactivity (Figure 1B and C). CK20, GATA3, PAX8, and ER were also negative. The final lymph node involvement occurred in three pericolic lymph nodes out of thirteen.

OUTCOME AND FOLLOW-UP

The outcome was very good, with no complications. The follow-up imaging performed six months after surgery was negative. The patient was very satisfied with the outcome and the curative surgery.

DISCUSSION

We described a rare case of primitive ductal adenocarcinoma of the right colon. The neoplasia was located in the right colon and included part of the ileocecal valve. Thus, it was mandatory to rule out an ileal origin[1]. The ileum was both macroscopically and microscopically intact. Interestingly, the pathologist did not recognize a benign ectopic pancreatic tissue in the surgical specimen. This observation suggests the complete degeneration of a rare colonic ectopic pancreas or, even more interesting, the first description of a primitive ductal adenocarcinoma of the colon.

CONCLUSION

In our opinion, it is useful to consider the existence of this entity, although very rare, in the diagnostic workup of patients with clinical suspicion of organic disease and elevated CA 19-9 value.

FOOTNOTES

Author contributions: Conti CB and Zucchini N designed and directed the project; Conti CB and Mulinacci G wrote the first draft of the manuscript with support of Tamini N and Jaconi M; Zucchini N and Jaconi M performed the histological analysis; Zucchini N. supervised the study and reviewed for important intellectual contents. All authors approved the final manuscript.

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