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EDITORIAL

Use of *Clostridium botulinum* toxin in gastrointestinal motility disorders in children

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Abstract

More than a century has elapsed since the identification of *Clostridia* neurotoxins as the cause of paralytic diseases. *Clostridium botulinum* is a heterogeneous group of Gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria that produce a potent neurotoxin. Eight different *Clostridium botulinum* neurotoxins have been described (A-H) and 5 of those cause disease in humans. These toxins cause paralysis by blocking the presynaptic release of acetylcholine at the neuromuscular junction. Advantage can be taken of this blockade to alleviate muscle spams due to excessive neural activity of central origin or to weaken a muscle for treatment purposes. In therapeutic applications, minute quantities of botulinum neurotoxin type A are injected directly into selected muscles. The Food and Drug Administration first approved botulinum toxin (BT) type A in 1989 for the treatment of strabismus and blepharospasm associated with dystonia in patients 12 years of age or older. Ever since, therapeutic applications of BT have expanded to other systems, including the gastrointestinal tract. Although only a single fatality has been reported to our knowledge with use of BT for gastroenterological conditions, there are significant complications ranging from minor pain, rash and allergic reactions to pneumothorax, bowel perforation and significant paralysis of tissues surrounding the injection (including vocal cord paralysis and dysphagia). This editorial describes the clinical experience and evidence for the use BT in gastrointestinal motility disorders in children.

Key words: Botulinum toxin; Gastrointestinal motility disorders; Children; Swallowing disorders; Gastroparesis; Defecation disorders

Core tip: *Clostridium botulinum* toxin has been used to alleviate symptoms associated to muscle spams due to excessive neural activity of central origin or to weaken a muscle for treatment purposes. In therapeutic applications, minute quantities of botulinum neurotoxin type A are injected directly into selected muscles. Ever since, therapeutic applications of botulinum toxin have expanded to other systems, including the gastrointestinal tract. This editorial presents the current evidence and evaluates the clinical experience for the use of botulinum

toxin in gastrointestinal motility disorders in children.

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SWALLOWING DISORDERS

Cricopharyngeal achalasia

Cricopharyngeal achalasia is characterized by abnormal relaxation of the upper esophageal sphincter associated to abnormal coordination with pharyngeal contraction resulting in oropharyngeal dysphagia and at times resulting in aspiration. The disorder has been treated with medications, dilatations, botulinum toxin (BT) and myectomy. BT has been reported as safe and effective in patients with cricopharyngeal achalasia[1-3], particularly in those who failed medical therapy and are poor surgical candidates, as a diagnostic tool in complex cases[3], to alleviate symptoms until surgery can be safely performed[4] and to provide relief for residual symptoms after myotomy[5] with minimal side effects reported. In our experience the potential complications with the use of BT in cricopharyngeal achalasia can be important so we recommend its use for experienced hands, particularly ENT surgeons.

Esophageal achalasia

Esophageal achalasia is a disease of unknown etiology characterized by loss of esophageal peristalsis and failure of the lower esophageal sphincter (LES) to relax with swallowing. Decrease in nitric oxide synthase containing nerve fibers and interstitial cells of Cajal in the distal esophagus have been proposed as potential causes[6]. It is an uncommon condition in pediatrics and has an estimated incidence that ranges from 0.11-0.18/100000 children per year[7,8]. Symptoms vary with age of presentation. Progressive dysphagia, vomiting and regurgitation are common complaints in older children[9]. Initial diagnostic studies include barium swallow and upper endoscopy, but esophageal manometry is considered to the gold standard test for diagnosis and will provide diagnostic certainty in approximately 90% of the cases[10,11]. The goal of treatment in children with achalasia is to improve bolus transport across the LES by reducing the pressure at that level. Current treatment options include pharmacotherapy, pneumatic dilation, surgery or injection of BT and recently the Peroral Endoscopic Myotomy[12]. BT is endoscopically injected at the LES with a sclerotherapy needle in 4 different quadrants. The short-term efficacy of BT in treating esophageal achalasia has been well established in adults. Multiple double blind placebo controlled studies have revealed BT to be safe and effective in reducing symptoms and improving esophageal clearance in adults with esophageal achalasia[13]. It has been described to be as effective as pneumatic dilation[14-17] and comparable to surgical myotomy[18] in the short term (< 6 mo). It has been reported to improve residual symptoms after myotomy and pneumatic dilations[19]. It has been recommended primarily in those who are poor surgical candidates resulting in important symptomatic response[20]. BT has also been used as a diagnostic tool in cases where diagnosis of achalasia is not clear and to indicate definitive therapy[21]. Most of the information of BT use in children is found as case reports and case series. Most authors reported a short-lived (2-6 mo) improvement on symptoms[9,22-24]. Walton *et al*[22] reported a single case with sustained clinical improvement of 8 mo after a single BT injection. Khoshoo *et al*[25] reported BT as a safe and less invasive alternative for symptomatic relief of symptoms in 3 children with achalasia. They also observed weight gain prior to surgery and noted that it could also be a choice in patients with incomplete response following balloon dilatation or myotomy[25]. Hurwitz *et al*[24] found that among children receiving BT as initial treatment for achalasia, 83% responded to therapy with a mean duration of effect of 4.2 mo and more than half of responders required additional procedure 7 mo after receiving BT. Another study demonstrated an inverse relationship between pre-BT LES resting pressure and duration of response[23]. All authors agree that BT should be reserved for children with achalasia who cannot undergo pneumatic dilatation or surgery or to alleviate residual symptoms after these interventions.

BT has been also reported as useful in the management of esophageal spastic disorders in adults[26], to our knowledge no reports are available for this indication in children. The only fatality related to the use of botulinum toxin for gastrointestinal motility disorders has been reported in an adult patient with esophageal spasms who developed a fatal mediastinitis[27].

GASTRIC DISORDERS

Gastroparesis

Gastroparesis is defined as the presence of upper gastrointestinal symptoms with evidence of delayed gastric emptying by a standardized gastric transit study in the absence of mechanical obstruction. Symptoms classically include nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and weight loss. The etiology of gastroparesis in the pediatric population is limited to a few studies. An observational descriptive analysis of a large pediatric population with gastroparesis reported that approximately 70% of the cases were idiopathic[28]. Another series found gastroparesis to be associated with post-viral gastroenteritis (18%), medications (18%), post-surgical (12.5%), mitochondrial disease (8%) and diabetes mellitus (2%-4%)[29]. Gastroparesis has been treated with medications and in some cases

with surgical interventions aiming to facilitate the transfer of bolus from stomach to small bowel. The endoscopic application of BT injections in gastroparesis has been well studied in adult patients. Multiple large uncontrolled studies have demonstrated symptom improvement with the use of BT[30-32]. However, two small randomized control studies showed no significant difference between BT and placebo on symptomatic as well as gastric emptying improvement[33,34], but some concerns have been raised about the power of such studies. In pediatrics, Rodriguez *et al*[35] assessed the long-term clinical outcomes after intra-pyloric BT injection in children with gastroparesis. After the first injection, 33% of patients reported no response and 67% described improvement in their symptoms. The mean duration of improvement was 3 mo and no significant side effects were reported[35]. From their analysis they also described that older age and vomiting were predictive of response to the initial injection, and male sex predicted response to repeated injections. There are currently no guidelines that indicate the timing of BT injections in pediatric patients with gastroparesis, but the consensus is that its use should be limited to patients that fail medical therapy with prokinetics and before more invasive interventions are considered (gastrojejunostomy, gastric electric stimulator). Although have not observed complications with its use in gastroparesis we have noticed short-lived vomiting in some patients followed by complete resolution of symptoms.

DEFECATION DISORDERS

Chronic constipation is one of the most common complaints at the pediatric offices. Although constipation may have several etiologies, in most children no underlying etiology can be found. Symptoms refractory to aggressive therapy with stool softeners and laxatives should prompt further work up to rule out etiologies like Hirschsprung's disease and internal anal sphincter (IAS) achalasia.

Hirschsprung's disease

Hirschsprung's disease (HD) is characterized by obstructive defecation due to distal colonic aganglionosis caused by a defect in cranio-caudal migration of neuroblasts leading to lack of relaxation resulting in functional obstruction. The diagnosis is confirmed by rectal biopsy demonstrating absence of ganglion cells in the submucosa and myenteric plexus. The treatment of HD consists in surgical removal of the aganglionic segment. Despite many improvements in diagnostic and surgical techniques, many patients continue to exhibit symptoms after surgical correction. The treatment of obstructive defecation initially consists of rectal dilatations to avoid stricturing of the surgical anastomosis. Some advocate performing a myectomy for those who fail medical therapy and dilatations, but results are variable with some reporting good outcomes[36] and others reporting only a moderate success[37] with complications like fecal incontinence. Due to the inconsistent efficacy and concerns of permanent incontinence, other non-invasive and self-limited alternatives have been contemplated, including use of topical nitric oxide[38] and BT. Langer *et al*[39] reported significant clinical improvement in 3/4 children as well as reduction of IAS resting pressure at 4-8 wk post-BT. Minkes *et al*[40] also reported clinical improvement in 14/18 children and described an association between clinical improvement and a post-BT decrease in IAS resting pressure. Another study showed an improvement in short and long-term obstructive symptoms, frequency of enterocolitis episodes and short-term decrease in hospitalization rates in 30 children with HD and prolonged use of BT[41]; 7 patients developed transient fecal incontinence; and, 1 patient reported anal pain after the BT injection. Elevated IAS resting pressure was associated with higher clinical success. A recent report by Han-Geurts *et al*[42] reported similar findings, with clinical improvement in 25/33 (76%) and decrease in hospitalizations due to enterocolitis. Importantly, they reported 2 children developing transient pelvic muscle paresis with walking impairment. General consensus is to use BT for those patients with obstructive defecation and elevated anal canal resting pressure. In our experience BT is more effective when IAS resting pressure is over 50 mmHg.

IAS achalasia

The hallmark of IAS achalasia is absent IAS relaxation with balloon rectal distention in the presence of ganglion cells on rectal biopsy. Some have called it ultra-short segment Hirschsprung's disease. The treatment of IAS achalasia has been aimed at relieving obstructive defecation with dilations or myectomy. IAS myectomy has been reported to be effective in relieving obstructive symptoms and helping achieve normal bowel control in children with IAS achalasia[43,44]. However, it is associated to fecal incontinence. BT has shown excellent results in relieving functional obstructive symptoms and has become the treatment of choice for IAS achalasia[41,45-47]. In several studies, transient fecal incontinence was the most common minor complication reported that resolved within 4 wk after BT injection[41,45,46]. Foroutan *et al*[48] demonstrated that BT has similar efficacy and less complications when compared to myectomy. Nevertheless, a recent meta-analysis found that regular bowel movements and short and long-term improvements were more frequent after surgery with no difference in the continued use of laxatives or rectal enemas, episodes of constipation and soiling and, overall complication rates between the two procedures[49]. BT should be considered the first option of treatment for IAS achalasia.

Chronic anal fissure

Chronic anal fissure is a common and benign anorectal condition associated to elevated anal canal

resting pressures, although other factors might also play a role. The classic symptom is pain on or after defecation that is often severe and may last from minutes to several hours. Most fissures occur in the posterior midline of the anal canal[50]. By definition, an acute anal fissure typically heals within 6 wk with conservative local management, while a chronic anal fissure fails medical management at times requiring more aggressive interventions[51]. Lateral internal sphincterotomy is a surgical technique commonly used to treat chronic anal fissure. It has been favored by most surgeons because it offers long-lasting relief in sphincter spasm by permanently weakening the IAS. However, it may lead to anal deformity and incontinence in 8%-30% of patients that can be permanent in a subset of patients[50]. BT injection to the IAS has been demonstrated to improve healing in chronic anal fissure in adult studies. In a randomized placebo controlled study BT demonstrated to be superior to placebo in healing of chronic anal fissure at two month follow up (73% *vs* 13%), only a small number of patients required a second injection and no relapses were reported after a 16-mo follow up[52]. Its use has also been shown to be effective when used in combination with topical nitroglycerin[53]. Pediatric studies have shown that BT injection to the external anal sphincter is an effective therapy in children with chronic anal fissures[54,55]. Nonetheless, there is discrepancy in the injection site when compared to adult studies. Prospective and long-term studies are needed to evaluate BT therapy in children with chronic anal fissures.

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REVIEW

Risk factors affecting the Barrett's metaplasia-dysplasia-neoplasia sequence

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Abstract

Esophageal adenocarcinoma has the fastest growing incidence rate of any cancer in the United States, and currently carries a very poor prognosis with 5 years relative survival rates of less than 15%. Current curative treatment options are limited to esophagectomy, a procedure that suffers from high complication rates and high mortality rates. Metaplasia of the esophageal epithelium, a condition known as Barrett's esophagus (BE), is widely accepted as the precursor lesion for adenocarcinoma of the esophagus. Recently, radio-frequency ablation has been shown to be an effective method to treat BE, although there is disagreement as to whether radio-frequency ablation should be used to treat all patients with BE or whether treatment should be reserved for those at high risk for progressing to esophageal adenocarcinoma while continuing to endoscopically survey those with low risk. Recent research has been targeted towards identifying those at greater risk for progression to esophageal adenocarcinoma so that radio-frequency ablation therapy can be used in a more targeted manner, decreasing the total health care cost as well as improving patient outcomes. This review discusses the current state of the literature regarding risk factors for progression from BE through dysplasia to esophageal adenocarcinoma, as well as the current need for an integrated scoring tool or risk stratification system capable of differentiating those patients at highest risk of progression in order to target these endoluminal therapies.

Key words: Barrett's esophagus; Esophageal adenocarcinoma; Endoscopy; Risk factors; Radiofrequency ablation; Antireflux surgery

Core tip: The transformation of Barrett's esophagus to dysplasia and finally to esophageal adenocarcinoma is a multifactorial process encompassing effects from multiple known and unknown risk factors. Previously, radiofrequency ablation was reserved for use in high risk patients with high-grade dysplasia, but recent evidence supports the expansion of this technique to be potentially used to treat additional patients at moderate risk of progression, such as those with long segments, long duration of symptoms, and those patients who are unable or unwilling to take proton-pump inhibitors's.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has been estimated to affect nearly 20% of the United States population at any given time[1]. Of this group suffering from GERD, roughly 15% are estimated to have Barrett's esophagus (BE), a condition characterized by columnar-lined epithelium in the esophagus[2]. It is well established that BE is the link between GERD and esophageal adenocarcinoma (EAC), a neoplastic lesion with an extremely poor prognosis with 5-year survival rates of less than 15% and which currently has the fastest rising incidence rate of any cancer with approximately a 10-fold increased incidence rate among men aged 15-74 in the last 40 years[3-6]. Unfortunately, little progress has been made in treating this extremely aggressive cancer, with median survival time increasing only 3.2 mo over the last 30 years[7]. BE has been shown to be a paradigmatic model for progression from metaplastic disease through dysplasia to neoplasia[8]. In this review, we summarize the current literature regarding the etiology and pathophysiology of BE and EAC.

RESEARCH

We performed a literature review in the PubMed/Medline database using MeSH term "Barrett's Esophagus" combined with subheadings "etiology", "physiopathology", "therapy", "diagnosis" and "epidemiology" as well as MeSH term "Esophageal Neoplasms" with selected subheadings "diagnosis", "etiology", "physiopathology", "epidemiology" and "therapy" combined by Boolean operator AND with MeSH term "Adenocarcinoma" with selected subheadings "diagnosis", "epidemiology", "etiology", "pathophysiology" and "therapy". We reviewed abstracts published between 1980 and April of 2013 in English and selected articles relevant to topics discussed herein.

EPIDEMIOLOGY

Columnar lined epithelium has been shown to be present in almost 25% of individuals with GERD symptoms, and columnar lined epithelium with intestinal metaplasia is reported as affecting almost 15% of those with GERD symptoms. The probability of progressing to EAC from BE has been estimated to be approximately 0.5%/year[9,10], with the most convincing evidence provided in a meta-analysis of 47 studies by Yousef *et al*[11] showing a pooled cancer incidence of 6.4/1000 person-years for the 13 studies conducted in the United States and 6.1/1000 person-years for all 47 studies pooled. EAC incidence has increased roughly 10-fold in select demographics over the last 40 years, with only a small fraction being attributed to increasing obesity rates[12]. Recent data suggests this increase is slowing but still substantial, with average annual percentage increase in incidence rising 6.1% in men and 5.9% in women[13]. Other causes for this rapid increase in incidence have yet to be elucidated, but this continues to be a highly active area of research.

ETIOLOGY AND PATHOPHYSIOLOGY

BE is caused by reflux of gastric contents into the esophagus, which causes damage to the stratified squamous epithelium. Not surprisingly, it has also been shown that GERD symptoms increase odds of EAC by 7.7 fold, odds which increase to 43.5 fold when comparing patients with long-standing and severe GERD symptoms[13]. It is currently contested as to whether gastric acid, bile reflux, or the combination is responsible. Several studies have shown increased intraluminal bilirubin content, a proxy for duodenal juice content, in patients with BE, suggesting that bile acid plays an important role in BE development[14]. Likewise, gallbladder function was shown to be impaired in patients with BE and EAC in a real-time ultrasonography experiment following a 10-h fast leading to increased duodenogastric reflux[15]. Cholecystectomy has also been shown to increase risk of EAC, albeit slightly[16,17]. The body's compensatory mechanism can but does not always include metaplasia in the form of simple columnar epithelium, which is thought to be more tolerant to the low pH[18,19]. BE is the most predictive risk factor for the development of EAC, with a relative risk for developing esophageal cancer of 11.3 when compared to the general population[20]. Much research recently has been focused on determining what the risk factors are for developing BE. Age has been shown to be correlated with increased risk of developing BE, with a low of 2 diagnoses per 100000 person-years for those aged 21-30 years and peaking at 31 diagnoses per 100000 person-years in those aged 61-70 years[21]. Males also experience BE incidence rates roughly twice that of females, although the reason for this difference remains to be elucidated[21].

Obesity and its related conditions have been shown to be a risk factor for many diseases, and BE is no exception. A meta-analysis by Cook *et al*[22] suggests that increasing obesity is correlated with an increased risk for BE development but only indirectly due to obesity's effect on GERD development. This view is contested by El-Serag *et al*[23], who suggest that increasing visceral adipose tissue to subcutaneous adipose tissue ratio is correlated with the presence of BE [adjusted OR = 1.47 (95%CI: 0.92 to 4.09)]

as well as Kendall *et al*[24], whose data shows a significant correlation between all measures of obesity tracked (waist circumference, waist-hip ratio, sagittal abdominal diameter, and waist-height ratio) and presence of BE in males even after adjusting for GERD symptoms. It has been proposed that the association between obesity and risk of BE is due to several factors including increased intra-abdominal pressure leading to worsening GERD, as well as increased circulating levels of leptin, adiponectin, and other chemicals secreted by adipose tissue, although this link remains to be confirmed. Recently, low birth weight and preterm birth have been implicated as a risk factor for BE, with several studies reporting those born very small for gestational age, < 3rd percentile in one study and < 2000 g in another, having between a three and eleven-fold increase in odds when compared to those born at a normal weight for gestational age[25,26]. Hiatal hernia has been shown to be another risk factor for BE, with size of hiatal hernia correlating with increasing risk of both BE as well EAC[27,28]. Metabolic syndrome, another obesity related factor, has been shown to increase risk for BE by two-fold relative to those without metabolic syndrome[29].

It is being currently debated as to whether *Helicobacter pylori* (*H. pylori*) infection leads to increased or decreased risk of developing BE, but two meta-analyses, of 49 studies conducted by Fischbach *et al*[30] and 19 studies conducted by Islami *et al*[31], both suggest that, although significant selection and information bias may be present in these studies, *H. pylori* infection appears to be associated with a decreased risk of BE. Aggressive eradication of *H. pylori* infection over the last 30 years may provide an explanation for a small portion of the drastic increase in incidence.

Along with being male and older age[32-34], those with low dietary antioxidant intake have also been shown to not only have an increased risk of developing BE, but also have an increased risk of developing EAC[35,36]. Similarly, length of GERD symptoms is a risk factor for both development of BE as well as EAC[36,37]. The reasons for males experiencing high incidence rates is not well understood, but it appears to be due to other reasons than differential exposure to known risk factors[38,39]. Hormonal factors, studied by comparing patients undergoing hormone therapy, do not appear to account for the discrepancy in EAC incidence rates between males and females[40]. Heme iron intake in the diet has been suggested as a risk factor corresponding to EAC development as well[41]. Dietary iron has been shown to be a growth factor for *H. pylori,* making this association one in need of further investigation.

Many studies recently have elucidated relationships between various risk factors and the development of EAC, a goal that has potential to directly affect patient outcomes and change clinical practice with respect to ablative therapy. Sikkema *et al*[42] conducted a prospective cohort study in which they found statistically significant associations between many risk factors and progression to high grade dysplasia (HGD) and/or EAC including esophagitis and length of BE segment, with a risk ratio of 1.11 per centimeter increase in length, and known duration of BE of greater than or equal to 10 years with a risk ratio of 3.2. Also, previous partial gastrectomy is linked to EAC development[43]. Patients who underwent esophagectomy for EAC were shown in a case-control study to have a 45% prevalence of colonic polyps when compared to control patients who also underwent screening colonoscopies, of whom only 14% were shown to have colon polyps[44]. Whether there is a predictive relationship between presence of colon polyps and risk of EAC is still a contested topic and deserves further attention. Also, early research shows no evidence of viral genomic sequences present in tumors[45]. The single most predictive clinical factor for progression to HGD and/or EAC found to date is the presence of low grade dysplasia (LGD) found during biopsy with a relative risk of 9.7 (95%CI: 4.4-21.5) according to Sikkema et al and 5.5 (95%CI: 1.1-28.6) according to Oberg *et al*[46] compared to those without LGD.

Biomarkers have the potential to drastically improve our ability to risk stratify. p53 as well as KI-67, both proteins involved in cell cycle progression, have been shown to be expressed at higher levels in BE samples that progress to EAC[47-51]. Likewise, it has also been shown that cell-free circulating DNA methylation patterns correlate extremely closely (r = 0.92) with aberrant DNA methylation patterns in matched tumor tissue in patients with EAC and also that 911 loci for DNA methylation could perfectly discriminate between EAC and controls, suggesting that cell-free DNA methylation patterns could be used as a non-invasive method to screen premalignant lesions[52]. Promoter hypermethylation of p16 and APC is also strongly correlated with progression to EAC, with one study reporting hypermethylation of p16 and APC, either separately or together, in over 50% of HGD/EAC samples with hypermethylation of the same promoters totally absent in samples from patients with normal esophagus[53]. In a similar way, Mcm2 expression in BE is directly correlated with degree of dysplasia, with 91% of patients diagnosed with dysplasia or EAC in one prospective cohort showing Mcm-2-positive cytological brushings, while brushings from controls without BE showed no signs of Mcm-2 expression on the luminal surface[54]. COX-2 expression is upregulated in BE patients and degree of overexpression is correlated with risk of malignant transformation, suggesting that COX-2 expression could be used as a potential marker as well[55]. This increase in COX-2 expression has been shown to be strongly induced by deoxycholic acid incubation *in vitro* using OE-19 cells as a Barrett's model, suggesting a potential mechanism for this phenomenon[56]. Several bile acids have also been shown to induce the expression of other proteins important in cancer progression such as CDX2 as well as induce

NF-κB signaling[57]. Other notable biomarkers include increased DNA damage detected by Comet Assay, decreased Beclin-1 expression, increased cyclin A, cyclin B1, and cyclin D1 expression, and abnormal DNA content[49,58-65]. Notably, abnormal DNA content, measured by the number of chromosomes arms with loss, has been shown to be directly correlated with the progression from metaplasia, through low and high grade dysplasia, and finally to neoplasia[66]. Likewise, telomerase reverse transcriptase has been shown to be overexpressed in increasing levels along the metaplasia-dyplasia-neoplasia sequence of BE[67]. Whether these two markers can be used to differentiate between BE patients who will progress and those who will not remains to be studied. The field would benefit from further research into how these biomarkers can be integrated and utilized in a clinical setting as well as which can be used cost effectively to better predict risk of progression to EAC.

Interestingly, high serum leptin levels were associated with increased risk of EA, whereas increased levels of high molecular weight adiponectin conferred a protective effect, with a hazard ratio (HR) of 0.34 (95%CI: 0.14-0.82)[68]. The mechanism for this association might be due to leptin's effect on proliferation of adenocarcinoma cells independent of apoptosis or necrosis, as has been shown in BIC-1 and SEG-1 cells *in vitro*[69]. Type 2 diabetes mellitus has been shown to be more prevalent in those diagnosed with EAC, although the effect was attenuated after controlling for differences in BMI[70].

The consumption of several substances have shown to confer protective effects, with use of a multivitamin pill showing a HR of 0.38 (95%CI: 0.15-0.99) when compared to those not taking a multivitamin[71]. Vitamin D intake, however, was found to increase the risk of EAC, showing an OR of 1.99 (95%CI: 1.03-3.86), although vitamin D intake was not associated with BE or reflux esophagitis[72]. Taking proton-pump inhibitors (PPIs) has been shown to confer a protective affect against progressing from BE to EAC, with a hazard ratio of 0.41 (95%CI: 0.18-0.93) and 0.21 (95%CI: 0.07-0.66) for those using proton pump inhibitors at inclusion of the study or during the follow-up period, respectively; a finding supported by several other studies[73,74]. In addition to the use of proton-pump inhibitors, several studies recently have shown decreased rates of progression to EAC from BE when taking aspirin and/or statins, although the mechanism for this protection remains to be elucidated fully[75]. Sadaria *et al*[76] found that simvastatin attenuated growth and increased apoptosis in human esophageal adenocarcinoma (FLO-1) cells in tissue culture, providing one potential mechanism by which statins reduce risk of progression to EAC. One meta-analysis investigating this protective effect found a number needed to treat of 389 patients with statins to prevent one case of EAC[77]. ACE inhibitors could potentially provide a protective effect, although studies regarding this question were underpowered[78]. Medications that have relaxing effects on the lower-esophageal sphincter, specifically anticholinergics and theophyllines, have been associated with a roughly 1.5-2.5 fold increased risk of EAC, a relationship not seen for other types of cancers of the upper digestive tract[79,80].

As is expected, tobacco smoking has been shown repeatedly to increase the probability of progression to EAC. Interestingly, one study from the NIH Barrett's Esophagus and Esophageal Adenocarcinoma Consortium found an increased risk of progression to EAC with smoking and even showed a dose-response effect when considering pack-years, but there was a weaker association when considering cigarettes/day[81]. This study corroborates several other studies showing deleterious effects of smoking on risk of progression to EAC, estimating the risk at roughly double for those who smoke relative to those who do not smoke[82-85]. There appears to be no association between alcohol intake and risk of EAC according to several recent studies including meta-analysis, although this has been contested according to a matched case-control study out of North China[81,83,86-88].

Currently, no definitive genetic cause of BE or EAC has been identified. Several case reports, however, have found a remarkable history of BE and EAC among members of the same family, providing evidence that a subset of the population may be genetically susceptible to BE and potential progression to EAC[89-92]. Additionally, a single nucleotide polymorphism in the gene coding for epidermal growth factor (EGF) has been shown to be associated with decreased levels of EGF expression and has also been shown to be more prevalent in patients with BE and EAC[93]. Further research in this area could help identify specific genotypes that would allow clinicians additional tools when risk stratifying patients and making decisions regarding the management of patients with BE.

Surgical management of GERD has been shown to decrease odds of progression to EAC compared to no therapy, however a 2007 systematic review found that, in controlled studies, there was no statistically significant difference in EAC incidence rates between patients treated surgically and those treated medically. If data from uncontrolled case-series are included, the difference becomes significant. Interestingly, surgical management increased the probability of regression of BE and/or dysplasia by almost 15%[94]. This study shows puzzling results given the data from previous studies showing that fundoplication can reduce or even eliminate the reflux of bile acids into the esophagus, compared to medical therapy which only treats the reflux of hydrochloric acid[95]. One possible answer to this question could come from recent case-control data showing that, among patients who've undergone antireflux surgery, those with recurrent reflux symptoms are three times more likely to develop EAC than those without, underscoring the importance of addressing continuing reflux symptoms after antireflux surgery[96].

Randomized trials to date have only compared antireflux surgery to medical therapy in patients who were complete responders to medical therapy. This, unfortunately, is not the comparison of interest given the current role for surgery in GERD management. Patients selected for antireflux surgery in practice almost exclusively have failed medical therapy as their indication for surgical management. This suggests that there is some fundamental difference between patients who are responders and those who are not, and limits the usefulness of the comparison in these studies. The question of antireflux surgery *vs* continued medical management remains unanswered conclusively, but continues to be an active area of research and could benefit heavily from a randomized controlled trial comparing antireflux surgery to continued medical management in a population of patients who have continued reflux symptoms despite full dose medical therapy. Current data suggests that there is a role for antireflux surgery in the management of patients with BE, but the question of exactly which patients should be receiving these procedures remains to be answered.

CONCLUSION

As can be seen from the wealth of information outlined above, the risks associated with progression from BE to esophageal adenocarcinoma are multifactorial, with many different risk factors each contributing a relatively small portion to the overall risk of progression. This suggests that a single intervention aimed at reducing exposure to individual risk factors other than refluxed gastric contents is unlikely to have a drastic impact on increasing adenocarcinoma rates or to affect the risk for individual patients with Barrett's. Currently, no biomarkers have shown to be clinically useful in BE, but this continues to be an active area of research. More work is necessary to investigate the many risk factors at play and the populations that they apply to, in order to better understand the contributions to risk for any given clinical situation. Recent advancements in knowledge of risk factors and their contributions to progression have made clinical risk stratification models possible in order to target endoluminal therapies capable of eradicating Barrett's tissue and drastically decreasing risk of progression to adenocarcinoma. Currently, these tools are not widely available. Additional work is required to further develop and validate these tools in order to target patients at the highest risk of progression with either therapeutic intervention or endoscopic surveillance. One risk factor, the presence of LGD, has been very clearly shown to drastically increase the risk of progression to EAC by multiple studies. Given this information along with the known safety and efficacy of radiofrequency ablation and other endoluminal therapies, we believe that there is sufficient data to support the use of RFA in all Barrett's patients with LGD, even in the absence of additional risk factors. Additional stratification tools are required in order to dictate exactly which patients without LGD should receive RFA/endoluminal therapy and which should not, but given the evidence outlined above, patients with very long segment, patients who have had reflux symptoms for time periods of 10 years or greater, or patients who are unable or unwilling to take PPI's or are not antireflux surgery candidates should be considered carefully as potential candidates for endoscopic ablation.

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REVIEW

Endoscopic management of post-liver transplant biliary complications

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Abstract

Biliary complications are being increasingly encountered in post liver transplant patients because of increased volume of transplants and longer survival of these recipients. Overall management of these complications may be challenging, but with advances in endoscopic techniques, majority of such patients are being dealt with by endoscopists rather than the surgeons. Our review article discusses the recent advances in endoscopic tools and techniques that have proved endoscopic retrograde cholangiography with various interventions, like sphincterotomy, bile duct dilatation, and stent placement, to be the mainstay for management of most of these complications. We also discuss the management dilemmas in patients with surgically altered anatomy, where accessing the bile duct is challenging, and the recent strides towards making this prospect a reality.

Key words: Liver transplant; Biliary; Complications; Strictures; Bile leak; Management; Endoscopy; Endoscopic retrograde cholangiography; Biloma; Stone; Cast

Core tip: Biliary complications are being increasingly encountered in post liver transplant patients because of increased volume of transplants and longer survival of these recipients. Overall management of these complications may be challenging, but with advances in endoscopic techniques, majority of such patients are being dealt with by endoscopists rather than the surgeons. Our review article discusses the recent advances in endoscopic tools and techniques which have proved ERCP with various interventions, like sphincterotomy, bile duct dilatation, and stent placement, to be the mainstay for management of most of these complications. We also deliberate the management dilemmas in patients with surgically altered anatomy, where accessing the bile duct is challenging, and the recent strides towards making this prospect a reality.

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INTRODUCTION

Biliary tract complications (BTC) are described as Surgeons' "Achilles Heel" after liver transplantation (LT)[1]. They constitute a major source of morbidity after LT and pose a challenge in both diagnosis and treatment. The incidence of BTC varies from 5% to 32% in various studies and has been decreasing with time; however, newer challenges are emerging with the more widespread use of living donor, donation after circulatory death and split-liver transplants[2,3]. The different complications that can be seen post LT include biliary strictures, leaks, cast formation, papillary stenosis and other less common ones[4,5]. Conventionally, post-LT biliary complications can be referred to as early (within 30 d of LT), delayed (1-3 mo post-LT) and late (beyond 3 mo post-LT). Even though each complication has a predominant manifestation period, for management purposes the clinical presentation and diagnosis are more important. With the advancement of imaging techniques, most of these complications are diagnosed using non-invasive imaging like traditional ultrasound (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) with more invasive techniques like percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiography (ERC) used for therapeutic purposes[6,7]. Over the last decade, there has been significant improvement in endoscopic techniques with an increase in the array of endoscopic assist devices, and consequently most of these complications are managed endoscopically, which will be the focus of this review.

TYPES OF SURGICAL RECONSTRUCTION AFTER LIVER TRANSPLANT

The technique of biliary reconstruction utilized during LT greatly influences the biliary tract complications seen in these patients[8-10]. It is necessary to be cognizant with the anatomy of the liver segments and its ducts, to be able to successfully diagnose and manage these complications. The two most common methods of biliary reconstruction include choledocho-choledochostomy (CC) or duct-to-duct anastomosis; and Roux-en-Y hepaticojejunostomy or choledochojejunostomy (RYC). It is imperative for endoscopists to have a thorough understanding of these anastomotic procedures as the former can be approached *via* conventional ERC whereas for the latter a percutaneous route is preferred. There is also an increasing usage of living, related-donor and split-liver transplants, because of limited availability of deceased donor liver transplants. During this procedure anastomosis is fashioned between donor's right hepatic duct to the recipient's common bile duct, which is even more complex than the traditional methods due to variability of the anatomy.

DIAGNOSIS AND EVALUATION OF BTC AFTER LT

Recognizing the risk factors for development of biliary complications is an important aspect of overall management, because if a risk factor is identified and appropriate remediation steps taken, the natural course of these complications may be altered. The common list factors are listed in Table 1 and discussed in detail at appropriate places in the article. Post-LT, patients with BTC can have varied presentations, which may range from asymptomatic transaminasemia to frank jaundice with abdominal pain and cholangitis. It is imperative to differentiate obstructive cholestasis from a non-obstructive cause like rejection - acute or chronic, drug induced cholestasis or recurrence of primary disease[11]. This is usually achieved with the help of imaging, which includes trans-abdominal ultrasound with Doppler, CT, MRCP, EUS, and HIDA scan (hepatobiliary iminodiacetic acid scan).

US with doppler can diagnose hepatic artery thrombosis in LT patients with a sensitivity of 91% and specificity of 99%[12]. Hepatic artery thrombosis is a risk factor for biliary leaks due to ischemic injury and hence, if detected on Doppler, warrants a confirmatory hepatic angiogram[2]. US can also be used to diagnose biliary strictures with a specificity of 98%; however, normal US findings do not exclude it and require further investigation with MRCP[13,14]. At present, MRCP is the initial imaging of choice to evaluate an LT patient for a biliary tract complications[15]. It provides detailed evaluation of both extra- and intra-hepatic biliary tree and can potentially avoid use of direct cholangiography[14]. It has several advantages over traditional and direct cholangiography, as it is non-invasive, there is no need of sedation, has minimal side effects and can demonstrate ducts both below and above a stricture. Several studies have been conducted to evaluate its role in LT patients with suspected biliary obstruction and in a meta-analysis, which included almost 400 LT-patients, MRCP was found to have a sensitivity of 96%, specificity of 94% with a positive likelihood ratio of 17 and a negative likelihood ratio of 0.04 for diagnosis of biliary obstruction[16-19]. However, it has limited role if LT was performed along with bilio-enteric anastomosis and for diagnosis of malignant strictures[16,20]. CT scan has limited role in evaluation of biliary tract complications in LT patients and maybe used to diagnose abscesses or fluid collections associated with biliary leaks.

TYPES OF BTC AFTER LT AND THEIR MANAGEMENT

Biliary strictures

Biliary strictures are the commonest complications after liver transplantation, with an incidence of 13% following deceased donor liver transplant (DDLT)

Table 1 List of risk factors responsible development of various biliary complications

Risk factor	Mechanism	Resultant biliary complication
HAT or stenosis	Being the main vascular supply to the bile duct, any compromise to integrity of HA or its branches induces acute and chronic ischemia of the biliary system	Anastomotic disruption Bile leak NAS AS Biliary cast syndrome
Type of transplant	Live-donor LT has higher overall biliary complications compared to Orthotopic LT	Bile leak HAT Unplanned re-explorations Portal vein thrombosis
Type of donor	DCD LT has higher biliary complication rate compared to DBD LT. This is because of increased risk of experiencing insufficient organ perfusion. Also increased risk if ABO blood group incompatibility between donor and recipient	Strictures (NAS) Bile duct filling defects (stones/sludge/clots/casts)
Type of anastomosis (biliary reconstruction)	Duct-to-duct CC anastomosis is preferred whenever possible, being simple and prevents enteric reflux into bile ducts, compared to RYC	Comparative biliary complication data is conflicting
Graft related factors	Use of grafts from older donors or grafts with increased steatosis (extended criteria), as well as increased cold (CIT) and warm ischemia times	Strictures (NAS and AS) Bile leak Bile duct filling defects (stones/sludge/clots/casts)
Surgical (or technical) factors-during both donor and recipient surgeries	Excessive dissection of periductal tissue during the procurement of native liver Excessive electrocautery to control bleeding during surgery Tension between the two ends of the biliary anastomosis Suture material used Denervation or injury to sphincter	Bile leak AS Mucocele Sphincter of Oddi Dysfunction
Placement of T-tubes (old strategy)	This increases chances of delayed healing, and may cause bile leaks.	Bile leak Hemobilia Infections (Cholangitis and Peritonitis)
Pre-LT factors	Infections (CMV or intra-abdominal infections) Diagnosis for LT: PSC or AIH	Infections (Cholangitis and Peritonitis) Strictures (NAS and AS) Bile duct filling defects (stones/sludge/clots/casts)
Post-LT factors	Immunosuppression: Emerging evidence that Sirolimus based regimen have higher risk of biliary strictures Infection, Acute cellular rejection, Obstruction, *etc.* Post-operative small bile leak is risk factor for future strictures Early HCV recurrence post-LT also increases inflammation and hence risk of strictures	Strictures (NAS and AS) Biliary cast syndrome

HAT: Hepatic Artery Thrombosis; NAS: Non-anastomotic stricture; AS: Anastomotic stricture; DCD: Donor after cardiac death; DBD: Donor after brain death; CC: Choledocho-choledochostomy; RYC: Roux-en-Y choledochojejunostomy.

but much higher (19%-32%) among living donor liver transplants (LDLT)[8]. They are encountered irrespective of type of anastomosis, although may be more common with Roux-en-Y hepaticojejunostomy or choledochojejunostomy reconstructions than duct-to-duct anastomoses[21]. They can be classified according to time of stricture development from LT as early (within 1 mo post-LT) *vs* late (more than 1 mo post-LT) or classified according to anatomical site into two categories-anastomotic strictures (AS) and non-anastomotic strictures (NAS) or ischemic strictures.

AS are usually single, localized to the site of anastomosis, short in length and occur within a year after LT[6,8] (Figure 1). Recent literature suggests their incidence to be < 10%, and they are formed as a result of ischemia, fibrosis or bile leak during or after the surgery. They are a reflection of intra-operative technical problems or small bile leaks or transient ischemia, resulting in peri-anastomotic fibro-inflammatory response leading to stenosis. Since bile leak is an important risk factor for development of AS, they need to be recognized early and managed appropriately. They can also form due to the sub-optimal surgical techniques like inappropriate suture material and excessive use of cautery for control of bleeding, in which case they are formed relatively early in the post-operative period[8]. Furthermore, there is emerging evidence that type of immunosuppression being used may have a role in development of AS, and need for early ERC for management of AS[22]. Most patients with very early stricture post-OLT may not have true AS, but a stenosis due to post-operative edema and inflammation, which responds very well to single dilatation and/or stenting session. True AS usually occurs between 3-12 mo after LT.

NAS, on the other hand, tend to be multiple, longer in length and are either intrahepatic or in the donor duct proximal to anastomosis, and defined as being present more than 0.5 cm away from anastomotic site. They tend to occur earlier than AS with mean time of presentation 3-6 mo post-LT and have an incidence of 5%-15%[23,24]. Although most NAS are multifactorial,

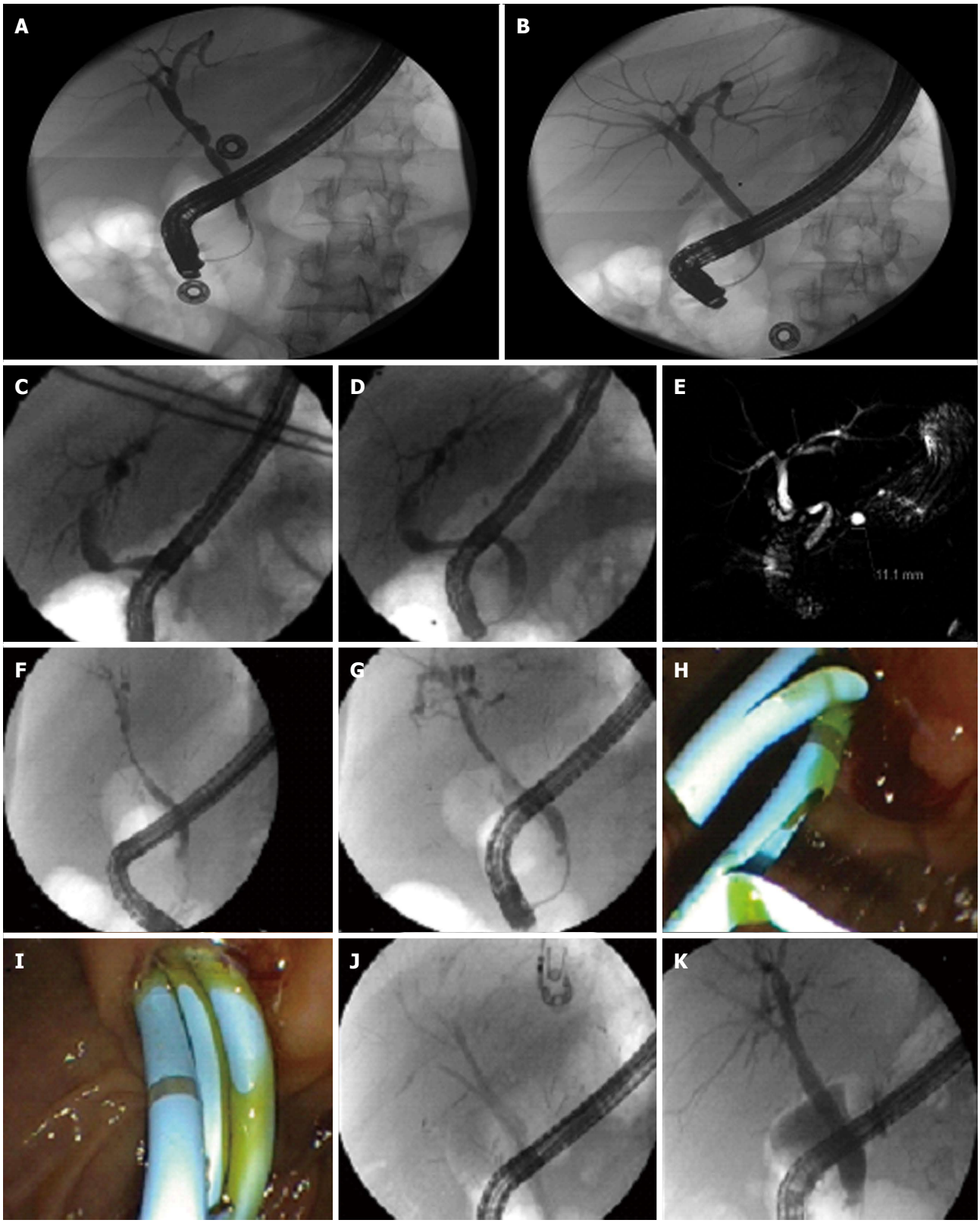

Figure 1 Different management strategies for biliary strictures. A: Post-LT anastomotic biliary stricture (as seen on ERC); B: managed with balloon dilatation only; C: Post-LT anastomotic biliary stricture (as seen on ERC); D: Managed with balloon dilatation; E: MRCP image of the same stricture; F: Long segment biliary stricture due to global hypotension post-LT; G: Dilatation performed with biliary balloon; H: Followed by placement of two plastic stents; I: Due to inadequate effect with two stents, sequential therapy strategy adopted with placement of three stents; J: Fluoroscopic image of three stents in right posterior and anterior hepatic and left hepatic ducts; K: Final cholangiogram suggesting a much improved bile duct diameter. ERC: Endoscopic retrograde cholangiography; LT: Liver transplantation.

they can further be divided into 3 sub-types based on their etiology: (1) macroangiopathic - secondary to hepatic artery thrombosis (HAT) leading to biliary destruction; (2) microangiopathic - secondary to

prolonged use of vasopressors in the donor, donation after cardiac death (DCD), prolonged warm and cold ischemic events; and (3) immunogenic - in patients with primary sclerosing cholangitis, ABO incompatibility, chronic rejection, CC chemokine receptor 5delta32 polymorphism or autoimmune hepatitis, which may act as an independent risk factor[8,23,25]. NAS can also be referred to as type Ⅰ (extra-hepatic), or type Ⅱ (intra-hepatic) and a combination of two[26]. Furthermore, Buis *et al*[27] proposed another classification of the anatomic regions of the biliary tree affected by non-anastomotic biliary strictures: hilar bifurcation (zone A), ducts between the first- and second-order branches (zone B), between second- and third-order branches (zone C) and in the periphery of the liver (zone D). Vascular NAS develops because the blood supply to donor bile duct comes from recipient hepatic artery, which is susceptible to ischemic injury post-transplant, while its native alternative supplies from smaller collaterals and branches of other arteries are transected during organ retrieval. The immunogenic NAS tend to occur later than vascular NAS. Because of their established relationship with ischemia, vascular patency of hepatic artery must be ascertained in these patients with a Doppler ultrasound. Patients who develop manifestations of NAS within the first year of transplant or have recurrent cholangitis, have the most unfavorable prognosis[28].

Management: Historically, post-LT biliary strictures were managed surgically *via* Roux-en-Y hepaticojejunostomy. However, over the past decade there has been tremendous improvement in endoscopic techniques, making endotherapy the treatment of choice for management of these strictures[29-31]. PTC and surgery are less often utilized, and usually reserved for cases where ERC cannot be used or has failed. Although not evidence-based, ursodeoxycholic acid is sometimes used to increase bile flow, and lower the chances of stone formation.

ERC is generally used to perform endoscopic biliary sphincterotomy (EBS) followed by balloon dilation and placement of biliary stent(s) to treat biliary strictures (Figure 1). Balloon dilation, if performed alone, has a high recurrence rate of 62% which decreases to 31% when performed with stent placement[32,33]. However, a recent prospective study by Kulaksiz *et al*[34] showed that dilation alone was as effective as dilation plus stent placement and in fact, stent placement was associated with a higher complication rate. However, more data is needed to clarify this discrepancy.

The most commonly used approach for treatment of AS consists of placement of large-bore 10-French plastic stents after balloon dilation and exchanging them every 3 mo (Figure 1). The median duration of plastic stent patency is around 3 mo (range 2-4 mo), as they are prone to debris deposition in their lumen resulting in obstruction, and risk of cholangitis. This approach has a success rate of 75% to 91% according to different studies for DDLT[32,35-38] but decreases to 37%-71% in patients with LDLT[39,40] because of the more complex duct-to-duct anastomosis. Factors limiting efficacy include peripheral location and presence of smaller and multiple biliary anastomotic strictures. It is also advised that balloon dilation should not be performed for very early strictures and for strictures in the setting of an anastomotic leak to prevent disintegration of biliary anastomosis. Severe complications of this technique are rare, although, a large study showed a complication rate of 6.6% per procedure which increases to 21% per patient as they get more than one procedure[41]. Some of the complications include pancreatitis, cholangitis, stent migration and hemorrhage. There was no death attributable to the procedure itself. An alternative approach to manage biliary strictures is to place maximum number of stents possible, which can then be exchanged at frequent intervals (Figure 1). This method is more aggressive but has shown to achieve a high long-term stricture resolution rate of 90%-94% with less frequent episodes of cholangitis[42,43]. This is a particular advantage of endoscopic therapy, as multiple stents cannot be placed using percutaneous catheter.

Metallic stents are generally useful only for malignant biliary obstruction as they provide effective palliation with a larger diameter (viz. 30-Fr) and longer patency[44]. They are either balloon-mouthed or self-expanding metallic stents (SEMS), but the fact that metal stents cannot be removed makes them less favorable in the setting of benign biliary diseases. Furthermore, possibility of reactive hyperplasia resulting in sludge/stone formation proximal to the stent poses a technical challenge, especially when SEMS cannot be removed. However, covered-SEMS (CSEMS = metallic skeleton with biocompatible and resistant synthetic covering viz. silicon, polyether polyurethane, polyurethane and expanded polytetrafluoroethylene) can be easily removed as the outer coating of the stents prevents tissue ingrowth, seen in about 20% patients. The major limitation with fully covered SEMS, however, is the relatively higher migration rate (6%-10%), which is now counterbalanced by development of partially-covered SEMS (PCSEMS), which provide advantages of covered stent but lower migration rates. Different types of metal stents are currently available, differing in their composition, like stainless steel or nitinol (which is a biocompatible metal alloy of titanium and nickel). Currently available SEMS are either fully covered (Viabil, Wallflex and Niti-S ComVi, *etc.*), or partially covered (Wallstent, Wallflex, *etc.*). Vandenbroucke *et al*[45] showed that Wallstents used in benign strictures after LT can be removed in 66% of patients and offer an option in patients with persistent proximal or anastomotic strictures who have multiple co-morbidities to undergo hepaticojejunostomy or re-transplantation. Similarly, Tee *et al*[46] showed benefit of such SEMSs in patients with refractory post-LT anastomotic biliary strictures. A recent meta-analysis by Kao *et al*[47] inferred that although SEMS appears to be promising

Figure 2 Diffuse non-anastomotic intra-hepatic biliary structuring seen in a donation after cardiac death liver transplant patient, not amenable to endoscopic therapy.

strategy in management of anastomotic biliary strictures in post-LT patients, but current evidence is not enough to suggest clear advantage of SEMS over multiple plastic stents.

NAS are generally more difficult to treat and even though there have been several advancements in endoscopy, overall endoscopic management of NAS remains sub-optimal and endoscopic therapy only acts as a bridging therapy to liver transplantation. This is due to the fact that balloon dilation of all NAS is not feasible (Figure 2) and stent occlusion is rather rapid because of the smaller caliber of the intrahepatic ducts where these strictures are commonly observed. Basic management principles including sphincterotomy and stent placement with scheduled exchange are similar to AS, but endoscopic therapy of NAS typically utilizes smaller diameter balloon dilation (of 4- to 6-mm compared with 6 to 8 mm for AS). Also, just like AS, strategies like use of multiple stents, and stents of progressively increasing diameter have been employed in management of NAS successfully. However, despite all these maneuvers, there is evidence that NAS requires longer time to respond to endoscopic therapy (dilatation + stenting) compared to AS (185 *vs* 67 d)[48]. Use of conventional stents like Amsterdam stent is less satisfactory since these stents are rigid and do not have side holes for draining bile. However, long and large-caliber (up to 20 cm with 10 Fr), flexible and fenestrated stents (Johlin pancreatic wedge stents) can be used. The flexibility helps them to adapt to the tortuous contours of the intrahepatic ducts and multiple side holes allow adequate bile drainage. Endoscopic therapy for NAS, for reasons explained above, has an overall low success rate of 25%-33% in LDLT and 60% in DDLT[40]. In cases of NAS associated with early HAT, aggressive management with either revascularization or early re-transplantation is the key to management, prior to development of intrahepatic complications like biloma and abscess formation.

Endoscopic therapy has generally been reserved for duct-to-duct anastomosis; however, with introduction of single (SBE) and double balloon enteroscopy (DBE), deep ERC can be performed even in patients with Roux-en-Y hepaticojejunostomy[49,50]. A large, multicentric study by Shah *et al*[51] showed that in patients with surgically altered biliary anatomy, SBE, DBE or rotational over-tube enteroscopy can be used to perform ERC successfully in 88% of patients in whom papilla is reachable. Once the duct is accessed, all interventions can be performed like stricture dilatation or stent placement. Another recent advancement has been the use of steerable ERC cannulas like Swing-Tip cannula, which is potentially helpful equipment in management of hilar strictures by using multiple guide wires, and repeated dilation of strictures with placement of stents. These cannulas also help to achieve faster cannulation of the bile duct[52].

Direct cholangioscopy using SpyScope technology has also been utilized to visualize biliary anatomy, and diagnose and manage biliary strictures. It has been studied to be safe and technically superior to conventional cholangiogram in different reports[53-56]. Siddique *et al*[57] demonstrated that direct choledochoscopy also helps in providing targeted treatment to patients. Exciting advancements in this field are happening, although not rapidly enough to make cholangioscopy a consistent tool in management algorithm of post-LT strictures. Balderramo *et al*[58] observed two distinct visual patterns of post-LT AS on direct cholangioscopy, described either as erythema or as edema, sloughing and ulceration, to help predict outcomes after endoscopic therapy. AS patients with only edema responded better with endoscopic therapy, while patients with sloughing and ulceration needed longer duration of stenting[58]. Different types of cholangioscopes (Polyscope) and techniques like use of methylene blue are combined with cholangioscopy to diagnose and delineate features of biliary strictures in patients post-LT[59,60].

Apart from endoscopic therapy, percutaneous transhepatic cholangiography (PTC) can also be used for treatment of AS. However, it is usually reserved for patients with bilio-enteric anastomosis or patients who have failed endoscopic treatment or are at higher risk of complications like bile leaks, infections and hemorrhage[11,61]. Surgery and re-transplantation are reserved for strictures refractory to endoscopic therapy, when all endoscopic and non-surgical options have been exhausted.

Biliary leaks and bilomas

Biliary leaks can be seen in 10%-25% of patients after LT. Although, their incidence has decreased in post-MELD era, it is seen more common after LDLT[62-64]. Biliary leaks mostly occur at 3 sites-anastomotic site, exit site of T-tube and at the site of cystic duct remnant[65]. The bile leaks at anastomotic site are reflection of dehiscence due to technical errors, tension or ischemia and devascularization of the tissue surrounding the biliary tree, in which case hepatic artery thrombosis is a common culprit and must be investigated with

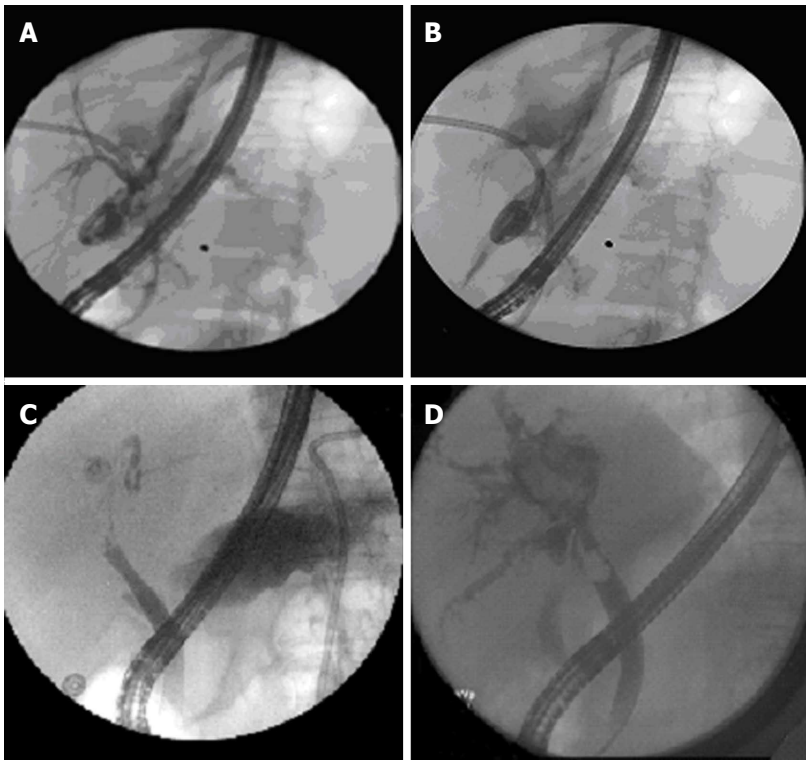

Figure 3 Management strategies for bile leak and biloma. A: Bile leak from split surface of the liver in a patient with split-liver transplant; B: Managed successfully with endoscopic plastic stent placement; C: In a separate patient, bile leak successfully managed by placement of a fully covered metal stent; D: In yet another patient, intrahepatic biloma, which becomes apparent on occlusion cholangiogram.

ultrasound Doppler. Less common sites of bile leak include ischemic injury to extra-hepatic bile duct (at non-anastomotic site), gallbladder fossa, aberrant bile duct (Luschka's duct) and cut surface of liver in LDLT or split livers (Figure 3). If bile extravasation occurs within the liver parenchyma or abdominal cavity, it may form collections called as biloma. Biliary leaks are generally divided according to time of occurrence into[66]: (1) early-occur within a month of the transplant and are usually associated with anastomotic leaks, ischemic injury and leakage around T-tube insertion site[2]; (2) late-occur more than a month after LT and noticed usually at the time of T-tube removal[67,68]. These are less common. Use of steroids or immunosuppressant medications post-LT is also alleged to hamper the healing process after T-tube removal.

Biliary leaks may present with abdominal pain or distension or patient might be asymptomatic, in which case, it is detected accidentally on abdominal imaging. One of the early indicators is the persistence of bile in the operative drain output. This can be confirmed with the help of a T-tube cholangiogram (in patients with a T-tube), or imaging like radionuclide scan (HIDA) or MRCP that can reliably detect a biloma and may localize the level of the leak[69].

Management: Most patients with biliary leaks can be managed endoscopically. ERC is most often used to perform biliary sphincterotomy and placement of biliary stent that can be kept in place for up to 2-3 mo (Figure 3). Although symptom resolution is fast after stent placement, the actual healing of leak may take up to 6-10 wk. Several studies suggest a success rate of 80%-90% using this strategy[8,70,71]. In case of an associated stricture, stent placement across the leak and stricture are prudent. In case of T-tube associated bile leaks confirmed on T-tube cholangiogram, leaving the drain open might suffice, without need for any further interventions. Naso-biliary drainage can also be performed in place of biliary stenting and Saab *et al*[72] in fact suggested that it might be the preferred strategy for management of biliary leaks. Although naso-biliary tubes can be useful for cholangiographic follow-up without further endoscopies and confirmation of leak sealing, however are very poorly tolerated. A small study showed that small leaks can be managed with sphincterotomy alone[73], however this is not the usual practice. In certain circumstances, along with bridging provided with the stent, drainage of the fluid collection might be needed, especially in large biloma with no communication with bile duct. This can be performed *via* EUS guided trans-gastric drainage or the traditional IR-guided drainage. Usually small bilomas resolve spontaneously, if there is adequate communication with duct, and some may require placement of a biliary stent. Despite these endoscopic advancements and options, there may be an occasional case where biliary leak cannot be treated endoscopically and thus requires surgery. These special cases include large anastomotic leaks, cases with Roux-en-Y anastomosis, early biliary leaks (< 1-2 wk after LT), bile duct necrosis or failure of primary therapy[3,69].

Sphincter of Oddi Dysfunction or papillary stenosis

Sphincter of Oddi Dysfunction (SOD) has an incidence of 2%-3.5% after LT. It is an incompletely understood and poorly defined syndrome of questionable significance[74]. It is thought to occur secondary to

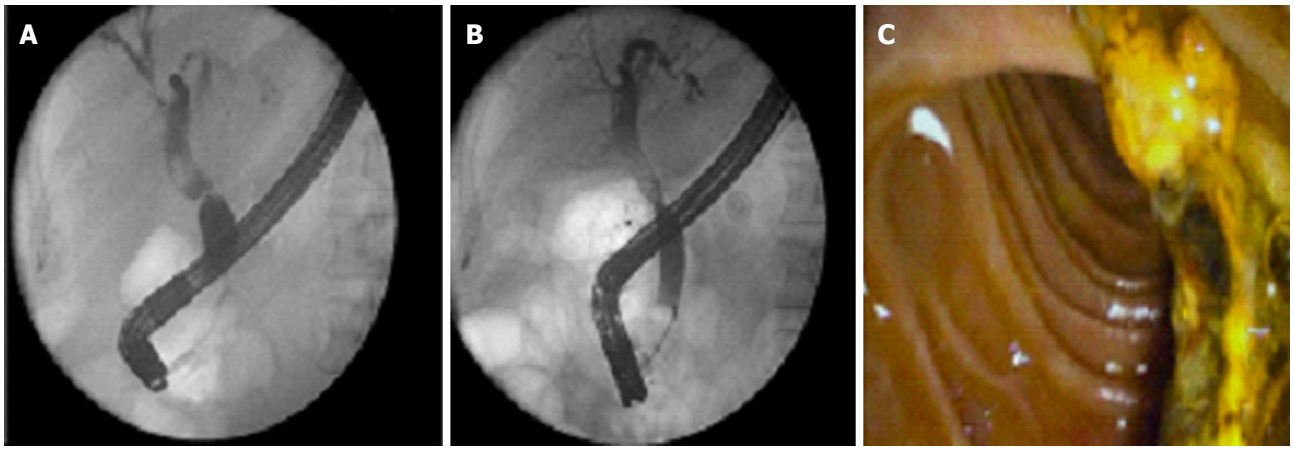

Figure 4 Management of common bile duct filling defects. A: Common bile duct (CBD) filling defect seen proximal to mid-CBD stricture in a post-liver transplantation patient; B: Successful removal of stone after dilatation the stricture; C: Endoscopic image of successfully extracted stone and sludge in this case.

denervation of Sphincter of Oddi during LT leading to a hypertonic sphincter. It can be divided into 2 types based on the mechanism of its pathogenesis: (1) SOD with stenosis - which occurs due to scarring and inflammation. The contributing processes can be CBD manipulation during LT, stone passage through papilla, or infection. Sphincter of Oddi has high basal pressure in this type; and (2) SOD with dyskinesia - which occurs due to functional disturbance of the sphincter resulting in intermittent biliary blockage. The sphincter in these cases has low basal pressure and absent phasic activity[74], and additional neurological or hormonal disturbances may be associated with development of functional disturbance[75].

Both types of SOD can lead to pain, recurrent pancreatitis and cholestasis without any apparent etiology, and hence need a high clinical suspicion for diagnosis. Biliary manometry can be utilized to confirm the diagnosis. Selective patients may be managed endoscopically, and ERC with sphincterotomy is usually reserved for patients with dilated bile duct with cholestasis liver chemistries, without any other obvious cause. It is aimed at cutting the sphincter muscles, resulting in reduction of the intra-luminal biliary and pancreatic hypertension, and symptomatic relief. However, the procedure has high risk of post-procedure pancreatitis and usually pancreatic duct stent is placed prophylactically[76]. In case of failure of endoscopic therapy, choledochojejunostomy is the last resort.

Biliary stones, sludge, casts, and blood clots

Biliary stones, sludge, casts, and blood clots are collectively referred to as "Common Bile Duct (CBD) Filling Defects" and can be seen in 3.3%-12.3% of patients after LT[77,78] (Figure 4). Stricture, infection and ischemia can result in biliary stones and sludge; and sloughed biliary epithelium, chronic rejection, infection, and bile stasis, have been associated with formation of biliary casts. They have been postulated to be related to strictures, bacterial infection, mucosal damage and ischemia[78-80]. These patients might present with abdominal pain, cholestatic liver enzyme pattern or may have recurrent episodes of cholangitis and pancreatitis[11]. However, many patients with choledocholithiasis may be completely asymptomatic, which is often attributed to the fact that transplanted graft is denervated, and may also be afebrile because of steroids and immunosuppressant medications they are on post-LT. Occasionally, CBD filling defects may form due to stagnation of bile proximal to a stricture, in which case management becomes challenging (Figure 4). Because of ischemic etiology to biliary cast syndrome, HAT exclusion with appropriate imaging becomes prudent.

Management: ERC with sphincterotomy has a success rate of 90%-100% in clearing biliary stones and sludge; however removal of biliary casts can be challenging and may require multiple procedures including sphincterotomy, balloon or basket extraction, stent placement and lithotripsy, or may need PTC eventually[77,79]. For removal of biliary casts, endoscopy has shown to successful in 25%-60% of patients across different studies[79,81]. In fact, in cases with severe biliary necrosis and casts, repeated interventions with baskets and dilatations are necessary, and placement of stents is not generally recommended in the early course, for risk of occlusion by biliary debris[82]. On the contrary, biliary duct stones are usually easily removed using ERC with biliary sphincterotomy and balloon sweeps (Figure 4). Occasionally, proximal stones may pose a challenge, and in those cases direct cholangioscopy can be performed to remove biliary stones. Also if filling defect lies proximal to a post-LT stricture, then stricture management becomes first step towards the goal of clearing the duct (Figure 4). Lithotripsy and Holmium Laser can be combined with this procedure for stone dis-impaction. Direct cholangioscopy can be performed using ultra-slim, pediatric endoscopes which can be directly advanced into the bile duct to examine duct anatomy and removal of biliary stones and casts[69]. Again, deep enteroscopy can be utilized to perform

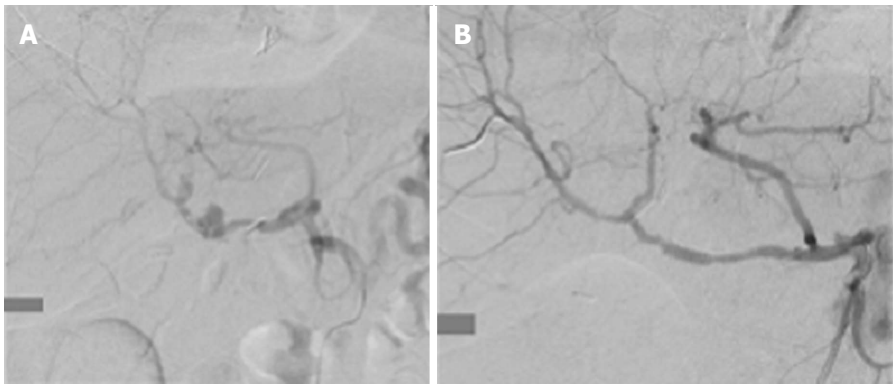

Figure 5 Rare cause of Hemobilia. A: Hepatic artery pseudoaneurysm fistulizing to the common bile duct, resulting in hemobilia; B: Managed with intravascular stent placement by interventional radiology.

ERC in patients with Roux-en-Y anastomosis to remove biliary stones or casts[83].

Mucocele

Mucocele of cystic duct results from collection of mucus from the cells lining the cystic duct remnant, and is an extremely rare entity in post-LT patients. Key to diagnosis is cognizance of this diagnostic possibility in a patient with post-LT obstructive jaundice or cholangitis with no apparent cause, and confirmation with MRCP, which would show an extrinsic mass (fluid collection) compressing the bile or hepatic ducts[84]. Patients usually require surgical or radiological drainage. To prevent this complication, usual operative practice involves either excising the cystic duct, or incorporating the distal end of the transected cystic duct into the suture line of the biliary anastomosis to ensure drainage[85].

Hemobilia

While hemobilia may not be a direct consequence or complication of liver transplant itself, it can happen after liver biopsy or PTC performed in post-LT period for management of various issues. Patients present with abdominal pain, jaundice and gastrointestinal bleeding, and upper endoscopy using regular forward-viewing gastroscope (or side viewing duodenoscope) typically reveals blood extruding from the ampulla. Management goals are hemostasis, as well as confirming clearance of bile duct of any clots, which would otherwise be a source of potential obstruction and cholangitis. Hemostasis may be achieved with a multi-prong strategy of coagulopathy correction, endoscopic therapy with use of epinephrine and electro-cautery if bleeding site is accessible, otherwise localization of bleeding with hepatic artery angiogram followed by embolization of feeding vessel radiologically[86]. Once hemostasis is achieved, clot retrieval and clearance of duct can be achieved with ERC if there is evidence of biliary obstruction. Figure 5 (used with permission from Farshad Aduli, MD) represents a case seen by authors, of post-LT hepatic artery pseudo-aneurysm fistulizing to the common bile duct resulting in hemobilia, which was managed by intravascular stent placement by interventional radiology.

SPECIAL ISSUES AFTER LT

Management of biliary complications in patients with Roux-en-Y Hepaticojejunostomy and Roux-en-Y gastric bypass

With the increase in number of liver transplants being performed and limited number of DDLT, there is increase in use of LDLT and split liver transplant strategies. This has resulted in more complex anatomy post-LT. Roux-en-Y Hepaticojejunostomy and Roux-en-Y gastric bypass are the 2 main altered surgical anatomies that are often encountered in post-LT patients. Roux-en-Y gastric bypass creates a common limb of 150 cm and a bilio-pancreatic limb of 150 cm, which makes conventional endoscopy and ERC challenging. Traditional PTC has been utilized for management of post-LT biliary complications in such patients with altered anatomy. However, as mentioned earlier, development of DBE, SBE and spiral enteroscopy has increased the endoscopic options that permit ERC in these patients[51,87,88]. Details of the success of this technique have been discussed earlier. However, it may not be possible to utilize this strategy in all patients, due to unfavorable surgical anatomy, adhesions, limited maneuverability of the scope around biliary anastomosis, and limited number of small-caliber ERC instruments that can be used through these devices. Also, these procedures require high skill and expertise and the learning curve is steep and hence available only at specialized centers. Another specialized technique that is being tried is formation of gastrostomy, either surgically or percutaneously using EUS, and then performing ERC through the gastrostomy port[89]. A single study using this approach achieved biliary intervention successfully in all patients as compared to 58% success rate with deep enteroscopy, and should be evaluated further[90]. Lastly, an alternative approach that may be potentially used in patients with altered anatomy is the use of direct

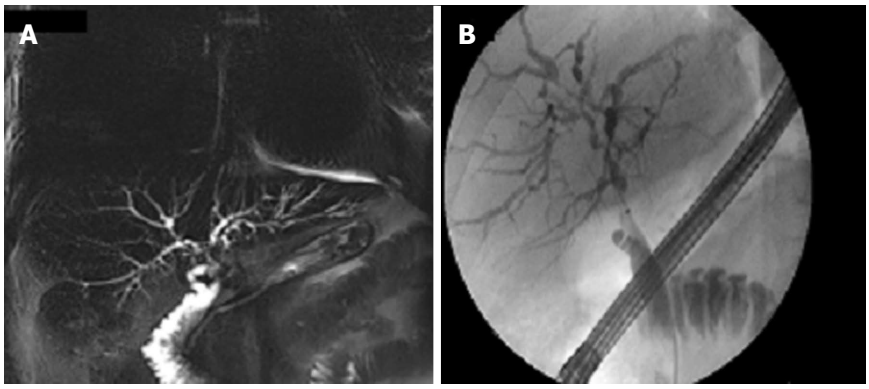

Figure 6 Don't forget the native disease. Recurrence of native disease can mimic biliary complications, hence appropriately investigated with magnetic resonance cholangiopancreatography (A) and/or endoscopic retrograde cholangiography (B). This patient was transplanted for primary sclerosing cholangitis, and had disease recurrence involving the intra-hepatics few years later.

cholangioscopy after percutaneous tract has been created. Direct visualization of bile ducts is possible using this method and can be used for removal of bile duct stones, dilation of stricture and placement of stents.

Biliary complications in recipients of LDLT and DCD transplants

Biliary complications after LT from living donors (LDLT) or grafts from donors after cardiac death (DCD) are more frequent than encountered with conventional donors after brain death (DBD). Complications that occur at a higher rate after LDLT included biliary leak (31.8% *vs* 10.2%), unplanned re-exploration (26.2% *vs* 17.1%), HAT (6.5% *vs* 2.3%) and portal vein thrombosis (2.9% *vs* 0.0%)[91]. However, there is suggestion that these complications may decrease as experience of LDLT center grows. The main reason for higher biliary complications is relatively smaller duct size, making the anastomosis technically difficult, and hence a higher chance of ischemic injury, especially in right-lobe LDLT[92]. Endoscopic management in LDLT recipients may be challenging given the complex nature of their duct-to-duct reconstruction, especially those involving smaller caliber ducts (< 4 mm), than when a hepatico-jejunostomy is used with these duct sizes. If attempted, smaller diameter stents (7.0-8.5 Fr) need to be used in these scenarios, and ERC performed more regularly because rates of re-stenosis are high with shorter duration of stenting. On the contrary, DCD is commonly associated with significant risk for both early and late biliary complications, including strictures, and many patients develop more than one biliary complication[93]. The major difference between pathogenesis of post-LT NAS in DCD is that the contributing mechanism is ischemic injury, which occurs before organ retrieval, rather than ischemia post-anastomosis in conventional DBD NAS[93]. There is also emerging evidence that the type of preservative solution (HTK solution) may also affect future incidence of biliary complications in DCD patients[94]. The endoscopic management principles remain the same, although intra-hepatic and small duct strictures may be more common making them less amenable to endoscopic management. There is evidence that although unilateral and easily approachable strictures may be managed endoscopically (with > 85% long-term survival), most DCD patients have diffuse intrahepatic structuring disease, due to global organ ischemia, which negatively impacts their long-term survival[95].

Sedation for ERC in post-LT patients

The sedation regimen for ERC in non-transplant setting may vary based on country, type of practice, endoscopist preference, age and co-morbidities of patient, and availability of anesthesia support. Conscious sedation (using opioids and/or benzodiazepines) is being increasingly less preferred for ERC, because it is long and uncomfortable procedure, and adequate patient relaxation and sedation is vital for the success of this critical procedure. Data suggests that propofol is superior to benzodiazepines for sedation during an ERC procedure, even in high-risk octogenarians[96]. Further studies proved that the combined use of propofol and midazolam or fentanyl for sedation has some benefits and no safety concerns, compared to using either drug alone[97]. There are adequate safety results for the administration of propofol by nonanesthesiologists[98]. For these reasons, at our center, like most of the other hospitals in the United States, ERC's are usually performed under anesthetist administered general anesthesia or monitored anesthesia care using propofol. Safety of opioids/benzodiazepines as well as propofol based regimens have been adequately demonstrated for GI endoscopic procedures, in several studies[99,100]. However, there is no such data available in post-LT patients, and is an area for further research. Nevertheless, in our experience of performing ERC's on post-LT patients over the last 6 years, we have not encountered any sedation related complication, and we attribute that to proper patient selection and careful optimization of patient co-morbidities before embarking on this critical procedure. Based on our experience, we endorse anesthetist administered anesthesia as a

routine sedation strategy for all post-transplant patients requiring ERC, taking into consideration the overall high-risk nature and length of this procedure, frequent need for multiple therapeutic interventions and patient co-morbidities.

CONCLUSION

Biliary complications are being increasingly encountered in post liver transplant patients because of increased volume of transplants being done and longer survival of these recipients. Overall management of these complications may be challenging, but with advances in endoscopic techniques, majority of such patients are being dealt with by endoscopists rather than the surgeons. ERC with various interventions, like sphincterotomy, bile duct dilatation, and stent placement, remains the mainstay for management of bile leaks, strictures and bile duct filling defects. Recurrence of native disease is the greatest mimicker of post-LT biliary complications, and hence must be investigated thoroughly with advanced imaging or endoscopic means (Figure 6). With increasing number of patients with altered anatomy, whether due to obesity epidemic or use of non-traditional anastomoses in liver transplant strategies like living-donor or split livers, ERC in these patients has been a perplexing issue and many require interventional radiology or surgical procedures. However, with ongoing attempts at developing improved tools and techniques to access the bile duct in patients with surgically altered anatomy, endoscopy will likely become unopposed frontier in this subgroup of patients as well.

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REVIEW

Role of stenting in gastrointestinal benign and malignant diseases

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Abstract

Advances in stents design have led to a substantial increase in the use of stents for a variety of digestive diseases. Initially developed as a non-surgical treatment for palliation of esophageal cancer, the stents now have an emerging role in the management of malignant and benign conditions as well as in all segments of the gastrointestinal tract. In this review, relevant literature search and expert opinions have been used to evaluate the key-role of stenting in gastrointestinal benign and malignant diseases.

Key words: Endoscopic stenting; Stricture; Leak; Complication; Cancer

Core tip: Endoscopic stenting plays an indispensable role in the treatment of benign and malignant digestive strictures and leaks. In this review, we summarize data from randomized clinical trials or prospective studies together with meta-analytical data, when applicable; to present the most updated recommendations in stenting of gastrointestinal diseases.

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INTRODUCTION

Stenting has become an optimal option for the treat-

ment of a variety of gastrointestinal malignant and benign diseases, which plays a vital role in alleviating obstructive symptoms such as dysphagia, pain, and improving patients' quality of life.

Over the past 30 years, dramatic changes have occurred in the composition and design of stents and their application to digestive disorders.

For example, stent composition began with plastic, evolved into self-expandable metal stents (SEMSs) and may soon evolve into biodegradable stents. At the same time, indications for stenting that began with esophageal cancer now include benign and malignant disorders involving a variety of sites in the gastrointestinal tract.

This paper will outline the indications and outcomes of stenting, the techniques of placement, composition and design of stents and prospects for new and improved stents.

TYPES OF STENTS AND PRINCIPLES FOR STENTING

A stent is a cylindrical medical device used to widen a narrow or stenosed lumen in order to maintain the patency of the lumen. The first stents were made of hard plastic and were used for obstructive esophageal cancers. Whereas early stents were mostly composed of plastic, the majority of contemporary stents are metal stents that are composed of either nitinol or stainless steel.

Nitinol mesh has improved the quality of the stents, replacing the other materials. This nickel-titanium shape-memory alloy is soft and flexible, with smoother wire ends, reducing the risk in and overgrowth.

Metal stents are available as uncovered, partially covered (PC), or fully covered (FC). An uncovered SEMS consists of a mesh that is bare and expands into the stenosis. A FCSEMS consists of a mesh stent that is covered by a membrane throughout its length. A PCSEMS consists of a stent with a membrane covering and uncovered proximal and distal ends of the stent.

Recently, FC self expanding plastic stent (SEPS) and biodegradable stent was developed. SEPS is made of woven plastic strands, while biodegradable stent is made from commercially available polydioxanone absorbable surgical suture material. Polydioxanone is a semicrystalline, biodegradable polymer. It degrades by hydrolysis of its molecule ester bonds, which is accelerated by low pH. The amorphous regions of the matrix deteriorate first and the crystalline portion deteriorates later.

Most of the metal stents on the market are mounted on a delivery system that consists of two coaxial tubes, but there is also a type of metal stent mounted on a delivery system with a user-friendly braided-suture release mechanism and it is deployed by pulling a ring attached to the suture string, thereby unraveling the string and slowly releasing the stent (Ultraflex esophageal or colonic stents, Boston Scientific/Microvasive, Natick, Massachusetts).

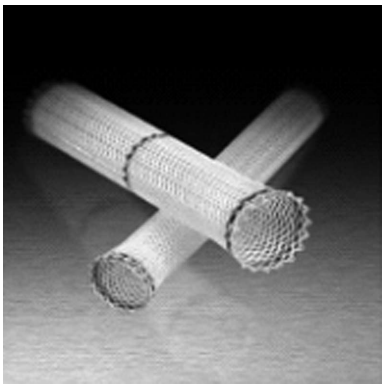

Figure 1 Boston scientific polyflex stent.

There are 2 types of delivery systems: through the scope (TTS), able to pass through the operative channel of the endoscope, and over the wire (OTW) that does not pass through the operative channel of the endoscope. The main differences between the delivery systems are the design of the handles, the lengths and the diameter, which determines the means of deployment.

Although the majority of deployment systems release the stent initially at the distal end of the catheter, there are some types of gastrointestinal stents available in both a proximal and distal release system (*i.e.*, Ultraflex esophageal stent NG/Boston Scientific and the esophageal Nit-S®/TaeWoong). In contrast to most SEMSs, which are sold in a constrained packing, the SEPS requires mounting onto the delivery catheter just before use. One important aspect of deployment is the variable degree of foreshortening that occurs with a majority of SEMSs and SEPS during the transition from the compressed to fully expanded state. The endoscopist must anticipate and allow for this foreshortening to ensure appropriate placement.

Before stenting firstly the lesion should be endoscopically or radiologically evaluated, the proximal and distal aspects of the lesion identified and a guide-wire advanced through the lesion, and the stent positioned across and then deployed under fluoroscopic and/or endoscopic guidance by release of the constraining mechanism.

Esophageal stents: Table 1

The SEPS Polyflex® (Boston Scientific) is a stent of polyester braid completely covered in silicone membrane. The stent need to be loaded prior to insertion into a large diameter delivery device (36-42 Fr) and is available in different sizes (diameters of 16, 18, and 21 mm and lengths of 9, 12 or 15 cm). Are available with proximal flare diameters of 20, 23 and 25 mm, the proximal end is flared for preventing distal migration with radio-opaque markers at the ends and in the middle for a more precise placement (Figure 1).

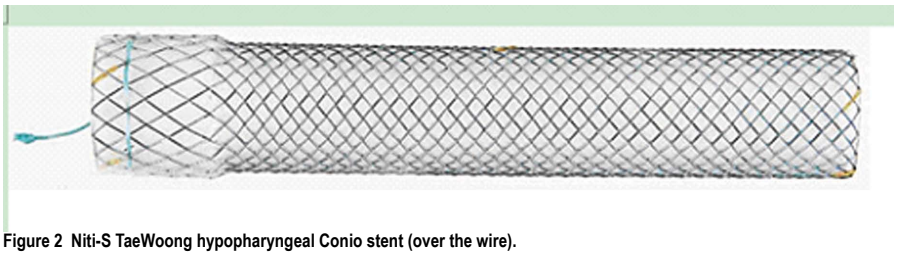

Figure 2 Niti-S TaeWoong hypopharyngeal Conio stent (over the wire).

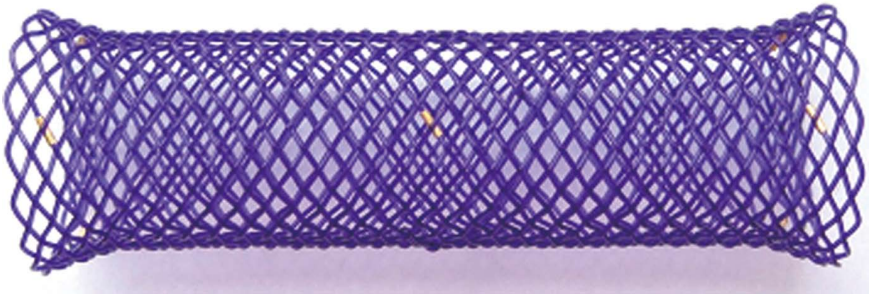

Figure 3 The Ella BD stent.

The most common used esophageal FC-SEMSs are: the Wallflex® (Boston Scientific), Niti-S® (TaeWoong), Evolution® (Cook Medical), Alimaxx-E® (Alveolus, Charlotte, NC, United States), SX-ELLA® stent Esophageal HV (Ella-CS, Hradec Kralove, Czech Republic) and the Hanaro® (M.I. Tech stent) and most of these stents are also available PC.

All these stents are made in nitinol and released OTW, the Alimaxx, Wallflex, Hanaro, SX-ELLA® and Evolution have a distal release, while Niti-S has both distal and proximal release.

The Alimaxx, Niti-S, Hanaro and Evolution are covered in silicone, while the Wallflex stent has the covering made of Permalume®, a particular type of silicone that diminish the food impaction. Actually the only FCSEMS with a possibility of a delivery-system TTS is the Niti-S.

The Wallflex, Alimaxx, Niti-S and Hanaro presents the same OTW release mechanism (the delivery system consists of a coaxial tubing assembly that constrains the stent on the delivery catheter shaft until the stent is released), an innovation, allowing a best control of the release, was recently projected by Cook Medical for the Evolution. The delivery system is composed by a "plastic handgun". With one hand and a squeeze of the trigger, the handle gives a precise control over stent deployment and recapturability. To shift between stent release and recapture, it needs switch the "directional button". There is furthermore a "point-of-no-return" reference mark that alerts when stent recapture is no longer possible.

The Ultraflex (Boston Scientific/Microvasive, Natick, Massachusetts) esophageal stent is another type of prosthesis that has a flared proximal end (23 or 28 mm), available uncovered and PC (the PCSEMS version have 1.5 cm of bare nitinol configured into wire loops at each end, thus sharp elements are absent) and is marketed with both a proximal and distal release design. This stent is highly flexible and is mounted on a delivery system with a user-friendly braided-suture release mechanism, deployed by pulling a ring attached to the suture string, thereby unraveling the string and slowly releasing the stent.

The Taewoong Medical produce specifically designed Niti-S stents. The Niti-S Conio Stent (Taewoong Medical, Seoul, South Korea) is a stent for hypopharyngeal stenosis. The stent have a body with a diameter of 12, 14 or 16 mm, and only the proximal crown has a diameter greater than the body of only 2 mm (14, 16 and 18 mm), to prevent distal migration and reduce the feeling foreign body (Figure 2). The Niti-S Beta stent (Taewoong Medical, Seoul, South Korea) is a newly design OTW stent with distal release with two rings in the body, for the anti-migration mechanism, produced for the treatment of complications of bariatric surgery. The biodegradable implant (ELLA BD stent) (Ella®-CS, Hradec Kralove, Czech Republic) is composed of polydioxanone which is a semi-crystalline polymer biodegradable (Figure 3).

The OTW delivery system has a diameter of 9 mm, the diameter of the stent is 25 mm, while the length varies between 6 and 13.5 cm. After the release in the esophageal lumen, the complete expansion of the stent occurs in 24-48 h. The degradation of the implant begins after 4 wk and the ninth week the radial force (RF) has been reduced by half, therefore the stent does not have to be removed.

The best way to release an esophageal stent is the combined endoscopic and fluoroscopic approach, expecially in presence of a leak, despite some expert endoscopist, only in selected cases, place the stent only with endoscopic control.

Table 1 Characteristics of the most commonly used esophageal stents

Producer	Model	Material	Diameter mm (body/flare)	Length (cm)	Type and characteristics
Merit Endotek	Alimaxx-E®	Nitinol	18/22	7-10-12	Fully-covered with anti-migration system
Merit Endotek	EndoMAXX®	Nitinol	19/24-23/28	7-10-12-15	Fully-covered with anti-migration system
Boston Scientific	Ultraflex®	Nitinol	18/23-23/28	10-12-15	Uncovered and partially-covered Possibility of distal or proximal release
Boston Scientific	Flamingo Wallstent®	Stainless steel	20/30	12-14	Partially-covered
Boston Scientific	Wallflex®	Nitinol	18/23-23/28	10-12-15	Partially and fully-covered
Boston Sientific	Polyflex®	Polyester	16/20-18/23	9-12-15	Plastic stent
Cook Endoscopy	Evolution®	Nitinol	20/25	8-10-12.5-15	Partially and fully-covered
Ella-CS	SX-ELLA® HV	Nitinol	20/25	8.5-11-13.5-15	Fully-covered with collar anti-migration system
Ella-CS	SX-ELLA® Flexella	Nitinol	20/25	8.5-11-13.5-15	Fully-covered Possibility of distal or proximal release Possibility of anti-reflux valve
Ella-CS	FerX-ELLA® Boubella	Stainless steel	20/25	9-10.5-12-13.5-15-16.5-19.5-21	Fully-covered Possibility of anti-reflux valve
Ella-CS	SX-ELLA® Danis	Nitinol	25/30	13.5	Fully-covered (with balloon/specific for variceal bleeding)
Ella-CS	SX-ELLA® Danis Seal	Nitinol	25/30	13.5	Fully-covered (specific for leaks)
Ella-CS	Ella BD stent®	Biodegradable polymer	18/23-20/25-23/28-25/31	6-8-10-13.5	-
Endochoice	Bonastent® ER	Nitinol	18/24	6-8-10-12-14-16	Fully-covered Possibility of anti-reflux valve
M.I. Tech	Hanarostent®	Nitinol	18/24-20/26-22/28	8-9-10-11-12-14-15-16-17	Partially and fully-covered Possibility of double covered configuration, anti-reflux valve and asymmetrical configuration
M.I. Tech	Hanarostent® ECBB	Nitinol	36-30-20-26	18-21-24	Fully-covered (Bariatric surgery)
Micro-Tech	MT® Esophageal stent	Nitinol	(Diameter central/extremities) 18/24-20/26-22/28	8-10-12	Uncovered, partially and fully covered Possibility of anti-reflux valve and radioactive system
Micro-Tech	MT® Cardia stent	Nitinol	16/22-18/24-20/26-22/28-24/30	9-10-11-12-13	Partially and fully-covered
Micro-Tech	MT® Retrievable stent	Nitinol	14/20-16/22-18/24-20/26-22/28-24/30	7-8-9-10-11-12	Fully-covered
TaeWoong Medical	Beta-Stent Niti-S®	Nitinol	18/24-20/26-22/28	10-12-14-15-16-18-20	Fully-covered (Fistula after bariatric surgery)
TaeWoong Medical	Mega-Stent Niti-S®	Nitinol	18/24-20/26-22/28	10-12-14-15-16-18-20	Fully-covered (Stricures or fistula after sleeve gastrectomy)
TaeWoong Medical	Niti-S Conio®	Nitinol	10/12-12/14-14/16	6-8-10-12-14-15	Fully-covered (Hypopharyngeal strictures)
TaeWoong Medical	Niti-S Cervical®	Nitinol	16/18-18/20	6-8-10-12-14-15	Fully-covered (Upper esophageal strictures) Possibility of distal or proximal release
TaeWoong Medical	Niti-S®	Nitinol	16/24-18/26-20/28	6-8-10-12-14-15	Partially and fully-covered Possibility of distal or proximal release for over-the-wire stent Possibility of TTS 10.5 Fr delivery system
TaeWoong Medical	Niti-S® double layer	Nitinol	16/24-18/26-20/28	6-8-10-12-14-15	Fully-covered with additional uncovered nitinol mesh Possibility of distal or proximal release Possibility of anti-reflux valve

Gastro-duodenal stents: Table 2

Different types of enteral stents are actually in use, all with a delivery system TTS (10 Fr) which needs a working scope channel of 3.8 mm.

All the commercialized stent are made in Nitinol, except for the Enteral Wallstent, known as a stainless steel stent, made with a mix of materials called Elgiloy® (Eligoy Inc., Elgin, IL, United States) (cobalt, chromium, nickel, iron, molybdenum, manganese). The Enteral Wallstent is characterized of an excellent RF but with the tendency of straightening, increasing the risk of stent impaction in the angulated sites.

An important role in the gastro-duodenal obstruction is played by two relevant features of the stents: the RF and the axial force (AF).

RF is the expanding force. AF is a force that maintains the stent straight after its placement. Combination of the two forces is more effective than only RF or AF, respectively. The AF straightens the stent, and plays a fundamental role in covered stents. The nature of the nitinol confers to these stents an optimal AF and RF.

Almost all of the TTS SEMS allow re-sheathing of the stent and TTS delivery systems also necessitate a kinking-resistant guide-wire. Delivery systems are

Table 2 Characteristics of the most commonly used duodenal stents

Producer	Model	Material	Diameter (mm) (body/flare)	Length (cm)	Type and characteristics
Boston Scientific	Wallstent®	Elgiloy	20/22	6-9	Uncovered
Boston Scientific	Wallflex®	Nitinol	22/27	6-9-12	Uncovered
Cook Endoscopy	Evolution®	Nitinol	22/27	6-9-12	Uncovered
Ella-CS	SX-ELLA® Eneterella	Nitinol	20-22-25 (no flare)	8.2-9-11.3-13.5	Uncovered
Endochoice	Bonastent® P	Nitinol	20	6-8-10	Uncovered
M.I. Tech	Hanarostent®	Nitinol	20/25-20/26	8-9-11-14	Uncovered and partially-covered
Micro-Tech	MT® Duodenal stent	Nitinol	20/26	6-8-10	Uncovered, partially and fully-covered
TaeWoong Medical	Niti-S® D-type unflared	Nitinol	18-20-22-24	6-8-10-12-14-15	Uncovered
TaeWoong Medical	Niti-S® S-type flared	Nitinol	18/26-20/28- 22/30-24/32-26/34-28/36	6-8-10-12-14-15-16	Fully-covered
TaeWoong Medical	Niti-S® Comvi unflared	Nitinol	18-20-22	6-8-10-12	Partially-covered

available in different lengths (135, 180 and 230 cm). An important characteristic of duodenal stents is the diameter. For obtaining an adequate food transit has to be used stents with a diameter > 20 mm. Some stents have distal flared extremity to improve the anchorage and can be covered and uncovered. The choice of a covered *vs* an uncovered stent depends by the endoscopist, evaluating fatures and site of the lesion. Uncovered SEMS are generally used, in this site, because of the low risk of migration. The flexibility of the uncovered stents allows following duodenal angulations, despite could exercitate high pressure on the angulated strictures. The mesh pressure on the mucosa induces epithelial regeneration, that leads to ingrowth, can contribute to stent occlusion. Then, the placement of a covered-SEMS is preferable in non-surgical patients, or patients with a high risk of mortality and morbidity, with a life expectance > 2-3 mo. Covered stent are generally indicated in the treatment of the tissue ingrowth inside an uncovered stent.

Materials used for covered stent are polyurethane, silicone, and expanded polytetrafluoroethylene. Covered SEMS are conceived to prevent tumor ingrowth and for closing fistula, if present; the only disadvantage of these stent is the tendency to migrate.

Two stents are currently marketed for the closure of fistulas post-sleeve gastrectomy, both over-the-wire (OTW): the Beta-stent® (Niti-S - TaeWoong), with lengths of 15, 18 and 23 cm and a diameter of 24 and 28 mm, and the Hanaro® stent (M.I. Tech) with lengths of 18, 21 and 24 cm and a width of 30 mm diameter. Both the two stents must be placed under fluoroscopic vision, after placing a stiff guide-wire in the duodenum, and present the proximal tourniquet on the crown for removal.

Duodenal stricture evaluation with X-ray enema before the endoscopy is generally not required. The passage of orally administered water soluble contrast through the duodenal stricture is generally delayed because of the gastrectasia, presence of residual food and delayed stomach emptying.

Furthermore, assessment of concomitant proximal jejunal strictures is not satisfactory due to the small amount of contrast that can pass the duodenal stricture. For these reasons stricture assessment during duodenal stenting procedure is preferred. Computed tomography is helpful to exclude the presence of peritoneal carcinosis.

To avoid aspiration, insertion of a naso-gastric tube 24 h before the procedure to empty the stomach, and the prone position during the procedure, are recommended.

Commercially available TTS SEMS require an operative endoscope (3.8 mm diameter working channel). Operative duodenoscopes offer a better visualization of the duodenal stricture lumen, the elevator helps the orientation of the catheter, grips of the guidewire, and the delivery system. Duodenoscopes are also useful for the treatment of a concomitant biliary stricture.

Duodenal stenting placement is performed under fluoroscopic guidance because both endoscopic and radiological controls are preferable. Stricture study is performed by contrast injection above the stenosis to assess diameter and length of the stricture; when the duodenal stricture is passed with an ERCP catheter, with or without a wire, contrast is injected downstream for evaluating the patency of the GI lumen, distally to the stenosis. Another accessory, that could be useful in the angulated stricture, is the sphincterotome. Balloon dilation before stent placement is not necessary (it increases the risk of perforation), and a stiff or super-stiff guide-wire is generally preferred. When the guide-wire is correctly in place distal to the stricture the stent catheter is advanced OTW. It is important the choice of a stent few centimeters longer than the stricture to be sure of a correct stenting of the stricture. If possible, the stricture can be measured by a centimeter guide-wire. The presence of a possible angulation of the bowel, immediately after the stricture, has to be considered. In this case the length of the stent should be chosen to avoid stent impaction on the gut wall. In presence of short stenosis of the upper duodenal genu, it is a 6 cm length stents, with the proximal extremity deployed through the pylorus, has to be chosen, avoiding covering the papilla for a possible further ERCP.

Table 3 Characteristics of the most commonly used colo-rectal stents

Producer	Model	Material	Delivery system and diameter	Diameters (mm) (body/flares-flanges)	Length (cm)	Type and characteristics
Boston Scientific	WallFlex®	Nitinol	TTS, 10 Fr	25 (body)-30 (proximal flange) 22 (body)-27 (proximal flange)	6, 9, 12	Uncovered
Boston Scientific	Ultraflex precision®	Nitinol	OTW, 16 Fr	25 (body)-30 (proximal flange)	5.7, 8.7, 11.7	Uncovered
Boston Scientific	Wallstent®	Stainless steel	TTS, 10 Fr	20 (22/minimal to no flare)	6, 9, 12	Uncovered
Cook Endoscopy	Evolution®	Nitinol	TTS, 10 Fr	25 (body) 30 (both ends flanged)	6, 8, 10	Uncovered
EndoChoice	BONASTENT®	Nitinol	TTS, 10 Fr and 12 Fr	22, 24, 26 (minimal flare)	6, 8, 10	Uncovered and partially covered
Ella-CS	SX-ELLA® Enterella	Nitinol	TTS, 10 Fr	22, 25 (no flare)	7.5, 8, 9, 11, 13.5	Uncovered and fully covered
Ella-CS	SX-ELLA® Enterella	Nitinol	OTW, 15 Fr and 18Fr	22, 25, 30 (no flare)	8.2, 9, 11.3, 13.5	Uncovered and fully covered
Endochoice	Bonastent® C	Nitinol	TTS, 10 Fr	22, 24, 26	6-8-10	Uncovered and fully covered
Leufen Medizintechnik	Aixstent®	Nitinol	OTW, 24 Fr	30 (body)-36 (both ends flared)	8, 10	Uncovered and partially covered
Micro-Tech	MT® Colon and rectum stent	Nitinol	TTS, 10 Fr	25 (body)-30 (both ends flanged)	8, 10	Uncovered
Micro-Tech	MT® Colon and rectum stent	Nitinol	OTW, 24 Fr	30 (body)-36 (both ends flanged)	8, 10, 12	Uncovered and partially covered
Micro-Tech	MT® Rectum stent	Nitinol	OTW, 24 Fr	20, 26, 30 (body)-24, 21, 36 (both ends flanged)	6	Fully covered
M.I.Tech	Hanarostent®	Nitinol	TTS, 10.2 Fr and 10.5 Fr	20, 22, 24 (body)-26, 28, 30 (both ends flared) (flanged and symmetric and asymmetric)	6-16	Uncovered and fully covered
M.I.Tech	Hanarostent®	Nitinol	OTW, 24 Fr	20, 22, 24 (body)-26, 28, 30 (both ends flared) (flanged and symmetric and asymmetric)	6-16	Uncovered and fully covered
M.I.Tech	Choostent®	Nitinol	OTW, 24 Fr	22, 24 (body)-30, 32 (both ends flanged) (symmetric and asymmetric)	6-16	Fully covered
S&G Biotech	EGIS® colorectal	Nitinol	TTS, 10 Fr and 12 Fr	18, 20, 22, 24, 26, 28, 30 (no flare)	6, 8, 10, 12	Uncovered and partially covered
Taewoong Medical	Niti-S® D-Type	Nitinol	TTS, 10.5 Fr	18, 20, 22, 24 (no flare)	6, 8, 10, 12, 14, 15	Uncovered
Taewoong Medical	Niti-S® D-Type	Nitinol	OTW, 16 Fr and 18 Fr	18, 20, 22, 24, 26, 28, 30 (no flare)	6, 8, 10, 12	Uncovered
Taewoong Medical	Niti-S® S-Type	Nitinol	TTS, 10.5 Fr	18, 20 (body)-24, 28 (both ends flanged)	6, 8, 10, 12	Fully covered
Taewoong Medical	Niti-S® S -Type	Nitinol	OTW, 16 Fr, 20 Fr and 22 Fr	18, 20, 22, 24, 26, 28 (body) 24, 26, 28, 30, 32, 34 (both ends flanged)	6, 8, 10, 12, 14, 15	Fully covered
Taewoong Medical	ComVi Niti-S®	Nitinol	TTS, 10.5 Fr	18, 20, 22 (no flare)	6, 8, 10	Partially covered
Taewoong Medical	ComVi Niti-S®	Nitinol	OTW, 14 Fr, 16 Fr and 18 Fr	18, 20, 22, 24, 26, 28, 30 (no flare)	6, 8, 10	Partially covered

TTS: Through the scope; OTW: Over the wire.

The majority of the delivery stent systems allow re-sheathing of a partially deployed stent, permitting further adjustments, before the release, if the position is not correct. If the stent is accidentally released beneath the stricture, it should be immediately replaced with a tooth-rat forceps. If the placed stent is shorter than the stricture, a second stent can be released, with the proximal part inside the first.

The correct position of the stent has to be radiologically documented immediately after the deployment, injecting contrast inside the stent. Completely stent expansion is generally obtained at 48 h.

Colo-rectal stents: Table 3

Over the years have been progressively introduced various types of stent. Material was initially steel (Z-stent® Cook Medical) or Elgiloy (Wallstent®, Boston Scientific) and subsequently the nitinol. The stents actually available are all in nitinol and can differentiate between them for the shape, the size, the type of mesh, the presence or absence of coverage, the catheter carrier (TTS or OTW) and the release system. The stent OTW, typically have a 16 Fr catheter and can be used, in consideration of the length and rigidity of the catheter carrier, only for strictures of the rectum

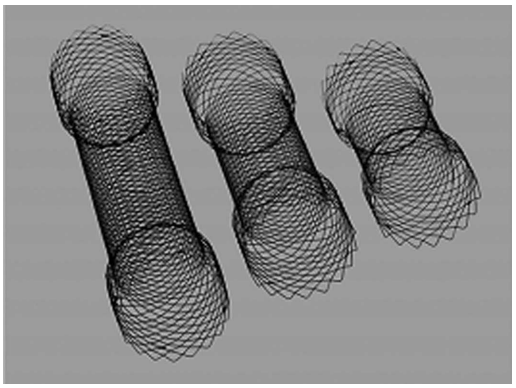

Figure 4 Colonic Evolution® stents.

or sigmoid typically within 30 cm from the anus. For stenosis located further upstream in the bowel, for anatomical reasons, it needs to use TTS stents. The Wallflex® (Boston Scentific) and Niti-S® (TaeWoong) are the most used stents to date and on which there are more data in the literature. The Evolution® stent (Cook) (Figure 4) instead is the most recently introduced on the market and which presents a delivery system that allows a best control of the various phases of the stent placement.

In the study of an occluded patient the diagnostic steps should go include the execution of a contrast medium CT scan that can be extremely useful both to evaluate the seat, the extension and nature of the stenosis, both to obtain a more comprehensive assessment of the situation abdominal (cecal diameter, exclusion of a bowel perforation or evaluation of liver metastases or peritoneal carcinomatosis). In general the onset of symptoms, their severity, and the distension of the cecum are the elements allowing the assessment in how many hours must be executed an attempt of endoscopic stent decompression. In most situations the endoscopic intervention can be performed within 6-8 h from the evaluation, for which reason even if the patient were to arrive later in the evening in the emergency room the stent placement could be deferred to the next morning. Logistically, it is necessary to have an X-ray room, a doctor and one or two experienced nurses or two doctors and a nurse, endoscopic instruments of different sizes to meet all anatomical situations and accessories needed for stent placement (guidewires, catheters, sphincterotome).

Stent TTS have a delivery catheter with a diameter of 10 Fr for which they pass in the channels of 3.8 mm diameter endoscope (standard colonscope, operative gastroscope and duodenoscope). Before placement of the stent is recommended the execution of a rectal enemas toileting which serve to clean the intestinal tract below the stenosis, thus facilitating the endoscopic exploration and identification of the stenosis. The procedure is almost always very well tolerated with minimal sedation with low doses of benzodiazepines. The anesthesia care should be required only for patients very sufferers or those with medical critical conditions.

For the possibility of ab-ingestis polmonitis, it is suggested to leave the stomach in a naso-gastric tube. It is also prudent to work with a very low level of endoscopic insufflation to avoid excessive distension of the colon upstream of the stenosis that could jeopardize the success of the maneuver.

It is preferable the patient lie supine to facilitate the radiological anatomy and identification of markers for the positioning of the stent. After reaching the stenosis, the next step is to cross the stricture with a guide-wire and an ERCP catheter. If the stenosis is very tight, long or very difficult to pass, it is suggested the use of a hydrophilic guide-wire, maybe with curved tip to avoid the risk of making false roads with a rigid (stiff) wire. In some occasional situations, in which the position of the stenosis is very lateralized respect to the endoscopic view for which the catheter fails to be directed in the stenosis, could be use a sphincterotome or, finally, the duodenoscope, having a different viewing angle, which allows to direct the tip of the catheter to the site of stenosis and facilitate the progression of the guide. Once passed the stenosis under radiological assistance, the wire must be withdrawn, injecting contrast medium to identify the correct position of the catheter, check the anatomy of the stricture and colon upstream. After that, a stiff guide-wire will be advanced across the catheter, far beyond the stenosis. This is useful to obtain a sufficient amount of guide-wire beyond the stenosis for all the maneuvers of the wire handling to give tension and straighten to the stent facilitating the advancement on the stricture. Dilation of the stricture before the release of the stent should be avoided because is a risk factor for intestinal perforation.

The choice of the stent will have to keep in mind the location and lenght of the stenosis. It is suggested to use stent with a length of at least 3-4 cm greater than that of the stenosis to allow a good adaptation of the stent also in very angled position where a stent too short might tend to straighten the curve inside and get in tension on the contralateral bowel wall, increasing the risk of dislocation and perforation. Once advanced the stent in the stenosis, the release should be supervised radiological and endoscopic (in the case of stents OTW is suggested to advance a small-caliber endoscope in parallel to the catheter carrying the stent). It is advisable to release the stent in a slow and gradual to always have full control of the maneuver. In the case of TTS stent is important that the endoscopist tends to progressively retract the catheter outside of the stent. Once completed the release, a last check radiological and endoscopic will be necessary to assess the proper expansion of the stent within the stenosis and evaluate the passage of air and fecal material through the stent.

ESOPHAGEAL DISEASES

The SEMSs have acquired a well-defined role in the

Table 4 Classification of dysphagia

Grade of dysphagia	Symptoms
0	No dysphagia
1	Occasional dysphagia for solid foods
2	Dysphagia for solid foods
3	Dysphagia for semi-solid food
4	Dysphagia for liquids

palliation of dysphagia in patients affected by esophageal malignant strictures, with a technical success greater than 95% with regard to their positioning and the ability to quickly resolve the dysphagia in almost all of the patients, reducing the rate of complications during the positioning phase thanks to the small diameter of the delivery catheter, and this, together with the use of an pediatric endoscope, makes unnecessary the preliminary expansion[1,2].

There are several types of esophageal SEMSs actually available for the treatment of malignant and benign esophageal stenosis[3].

The esophageal SEMSs are currently available uncovered, PC (only in the extremes do not have coverage) that FC[4].

The latter have attracted the interest of clinical researchers to evaluate their role in benign stenosis, esophageal mainly because complete coverage would allow their extraction after a certain time. In addition to the FCSEMS is necessary to consider the other two implants which are used in benign esophageal disease, the SEPS (Polyflex®, Boston-Scientific, Natick, MA, United States) and the biodegradable stent (Ella®-CS, Hradec Kralove, Czech Republic).

Benign esophageal diseases

Esophageal strictures: Before starting the endoscopic treatment is necessary to establish the real not malignancy of the stenosis, performing multiple biopsies and, when necessary, using endoscopic ultrasound (EUS) or other radiologic techniques. Essential is the classification of the dysphagia, so as to record the variation in the course of treatment (Table 4)[5].

The benign strictures are relatively frequent finding in clinical practice. In the past peptic strictures were prevalent, but are currently most commonly encountered those caused by caustic and radiotherapy. Esophageal strictures have been recently described in endoscopic mucosal resection, when circumferential and after endoscopic submucosal dissection[6].

Generally most of stenosis responds to a few[7] sessions of endoscopic dilatation, but from 25% up to 30 % requires a larger number of dilatation[8]. There are, however, "complex" strictures that do not respond to dilatation therapy, even if repeated over time (Table 5).

The anastomotic strictures, post-caustic ingestion stenosis and stenosis resulting from radiotherapic treatments, have a low rate of response to endoscopic

Table 5 Characteristic of "complex esophageal stenosis"

Length > 2 cm
Angulated
Irregular edges
Very low diameter

therapy: more than 40% tend to recur[9,10]. The most difficult to treat are the hypopharyngeal strictures, generally refractory.

It was moreover proposed the definition of "refractory stenosis" as: (1) absence of inflammation or motility disorders in presence of stricture; (2) impossibility of maintaining ⩾ 14 mm diameter after 5 sessions of dilation performed with a interval of 2 wk (refractory stenosis); and (3) impossibility of maintaining ⩾ 14 mm diameter for 4 wk after reaching a 14 mm diameter (recurrent stenosis)[11].

In addition to the expansion, have also been proposed other treatments, such as injection, at the level of the four quadrants of triamcinolon and, where appropriate, in particular in the anastomotic stenosis, the incisions of the fibrotic ring with a diathermic needle[12,13]. When these measures fail and dysphagia persists it is mandatory to evaluate the possibility to place a stent that, in addition to determining a laceration of the scarred submucosal layer and muscle of the esophageal wall, it maintains a constant pressure for the entire duration of its stay in the esophagus.

Anastomotic leaks

Total gastrectomy and esophagectomy are generally associated with high rate of morbidity and mortality even in specialized centres. The National Esophagogastric Cancer Audit of England and Wales published a rates of 8.3% of anastomotic leak after esophagectomy and 5.9% after total gastrectomy[14].

Although the improvements in the anastomotic techniques, anastomotic intrathoracic leak is generally associated with bacterial contamination, abscesses, and successive fistulas into pleural cavities. The continuous leakage of gastric juices and saliva into the pleural and mediastinal cavities can be life-threatening, with 30%-40% of post-surgical deaths[15].

Different treatments are described for the management of the esophago-gastric and the esophago-jejunal anastomotic leak. Some authors suggested the surgical treatment, but others prefrer a conservative approach with perianastomotic drainage, parenteral support and nasogastric decompression, and *iv* antibiotic therapy. All of these patients should be treated in appropriate critical care units[16].

The fibrin glue associated to metallic clips has been successfully used in small esophageal leaks[17,18]. An endoscopic stenting remains an attractive option, and SEPS and PC or FC-SEMS ensure good results, although the loading kit device and the delivery of the plastic stent can be difficult in non-expert hands. The leak

closure rates ranges from 60% to 100% with an healing rates > 90%[19,20]. Leak closure should be confirmed by contrast medium injected during the endoscopic procedure. Stents removal is planned at different times, depending by the size of the leak, but the stents are generally removed from 14 to 28 d from the placement with a previous clinical evaluation of healing of the absence or sepsis, radiologically documented.

The majority of the published studies suggest the stent placement immediately after the diagnosis of the leak for minimizing the contamination of the mediastinal cavity[21]. In some cases, the delayed placement can result in the healing of the anastomotic leak. Patients in which a covered stent is placed present an earlier oral intake (11 d *vs* 23 d), short ICU stay (25 d *vs* 47 d), and a less hospital stay (35 d *vs* 57 d). The in hospital mortality ranges from 0% to 20%, in different published series, lower if compared to the groups treated conservatively[22].

Acute and spontaneous esophageal perforations

Esophageal perforation is a life-threatening condition generally requiring surgical intervention. The management of the esopgaheal acute perforation (iatrogenic or spontaneous) is be divided into two groups: conservative and operative. Because of the rarity, the literature on this issue is based mainly on small series and case reports. Surgical repair seems to be the treatment of choice when an early diagnosis is made. The reported mortality in literature ranges from 0% (when the treatment starts within 24 h) to 30% if the treatment is delayed[23].

The conservative treatment is based on broad-spectrum *iv* antibiotic, parenteral nutrition and percutaneous drainage of the collections, when present. Ivey *et al*[24] showed as conservative therapy is appropriate only in presence of a perforation > 5 d; absence of sepsis; wide cavity at radiological imaging draining back into the esophageal lumen and absence of contamination of the pleural space[24]. A recent review advices that conservative treatment is feasible, with a survival rates of 60%-70% if the perforation are promptly diagnosed, but the need of the surgery is mandatory in case of failure[25].

Griffin *et al*[23] showed as in the management of spontaneous esophageal perforation (Boherhaave Syndrom's) they did not use stents. They suppose that the stent may prevent adequate drainage of sepsis, but can be subject to dislocation in absence of a stricture. Moreover, Authors recommend a non-operative management only in selected cases, especially when unfit for surgery[23].

Only three case reports are present in literature about the treatment of spontaneous esophageal perforations with the placement of the SEPS. In the first case the SEPS was placed at 24 h, in another case after 3 wk, in association of chest drainage, broad-spectrum *iv* antibiotic therapy and fibrin-glue injection, and, in the last case, the stent was placed 10 d later. All of the patients survived, and the immediate radiological study after stent placement did not show contrast medium outside from the esophageal lumen[26,27]. Oral intake was started in all of the three patients within 7 d, and were discharged between 7 and 21 d after stent placement.

The stent removal was scheduled between 5 and 10 wk. In two of the three treated patients, the stent was found into the gastric cavity.

Type of esophageal stents and outcomes

Self-expandable plastic stent: The SEPSs (Polyflex®) are usually placed with fluoroscopic assistance, but, in selected cases, deployment only under endoscopic view has been reported. A stent longer from 2 to 4 cm than the stenosis should be used for allowing a 1 to 2 cm extension above the edges of the lesion. Based on the RF of the SEPS, the completely expansion of the stent is obtained from hours to days[28,29].

The delivery device of the SEPS is larger and more rigid, if compared to other delivery system, with a non flexible tip. The assembly of the delivery device can sometimes be difficult in less well trained centres with low volume of cases, than these characteristics increase the challenging of the SEPS placement. The retraction rate of the SEPS is about 18% of the stent length before the release. The delivery system not allows the recapture. Because of the rigidity of the delivery system, it is suggested the neck hyperextension using a super-stiff wire. This may increase the risk of perforation, especially in presence of angulated strictures. This has been demonstrated in a prospective randomized trial (RCT) comparing 3 types of stents (Ultraflex, Niti-S and Polyflex); although dysphagia relief was achieved with all three types of stents, technical problems during stent release are encountered generally during SEPS placement than the other two SEMSs[30].

The SEPS presents some advantages if compared with PC-SEMS, as an easier removal and a less migration[31]. The soft material confers to the stent a well-balanced RF, adapting it to the wall of the esophagus, with a more probability of leak closure. The fully silicone covering does not allow granulation tissue ingrowth with minor overgrowth. It results in a possible successive easier repositioning and removal. The SEPS is available in different diameters and lengths, the exact diameter of stent has to be chosen on the basis of the size and site of the stricture (associated or not with a leak). There is no published evidence that the placement of large-diameter SEPS reduce the migration rate[32].

The SEPS presents other several drawbacks such as: the release takes place very fast, leading to the onset of severe sternal pain which can sometimes persist even 1 wk and the diameter of the introducer system that is excessive, especially in the presence of a "complex

stenosis".

The first study of the placement of SEPS in 15 patients reported a technical success, clinical success and a migration rates of 100%, 80% and 6.6% respectively[33].

Dua *et al*[34] in prospective study including 40 patients reported a clinical success of 40% and a migration rate of 22%, with a death due to a bleeding caused by erosion of the esophageal wall by SEPS[34].

A recent systematic review of the literature that has considered 10 studies with a total of 130 patients evidenced a technical and clinical success of 98% and 52%, respectively. The rate of migration (< 4 wk) was 24%, while complications were observed in 9% of patients with one death (0.8%)[35]. There is no consensus on the time to remove SEPS, but generally it is advisable the retrieval the stent after 6 wk, to prevent the onset of serious complications.

Partially-covered self-expandable metal stent

These stent should be not used in benign pathology because of the proliferation of granulation tissue through the proximal and distal uncovered mesh makes their removal difficult. One study that included 29 patients with benign esophageal strictures, reported the appearance of new stenosis the ends of the prosthesis in 41% of cases, migration in 31%, retrosternal pain and reflux in 21%, trachea-esophageal fistula in 6%[36]. Sometimes, in special cases where it cannot be used a stent completely covered for the high risk of migration, you can insert a PC-SEMS PC. To render its extraction after 6 wk, you can resort to the method indicated by Hirdes *et al*[37] aimed at eliminating the granulomatous tissue ingrowth present at the ends of the prosthesis: in it is placed a SEMS completely covered with similar diameter and length and leaving it up to a maximum of 2 wk. In this way the pressure of the stent will determine the necrosis of granulation tissue between the meshes, thus making possible the extraction of both stents[37].

FC self expandable metal stent

The complete coverage of the stent facilitates the extraction after a predetermined period of time, but could increase the risk of migration. This problem can be reduced if the endoscopist is able to perform an appropriate stent choice, in length and size. The capability of auto-conforming and the diameter should be considered in each individual case. A larger diameter will oppose effectively the migration and in presence of the fistula, and the perfect adhesion of the proximal crown to the wall to effective impermeability to liquids.

Eloubeidi *et al*[38] in 7 patients with benign strictures placed the Alimaxx-E (Alveolus, Charlotte, NC, United States) FCSEMS. The resolution of dysphagia was observed in 29%, while the migration occurred in 36% of the cases, half of the patients developed an ulcer distally to the FCSEMS and the 23% proximally, however these lesions were solved after the removal of the stent[38]. Additional studies have reported a migration rate to 37% up to 50%, a resolution of dysphagia to 21% up to 100 % of cases and the extraction of the stent was possible in all of the cases[39,40].

A meta-analysis that compared SEPS and FCSEMS in esophageal refractory strictures, included 8 studies with a total of 199 patients, found an improvement of dysphagia in the 55.3% patients treated with SEPS and in the 21.8% of the patients treated with FCSEMS, however these data must be accepted with extreme caution because in 6 of the 8 studies was used the SEPS[41].

The FCSEMSs are effective also in the treatment of benign fistulas, perforations and anastomotic leakage.

Van Heel *et al*[42] treated 33 patients with esophageal perforation (19 iatrogenic type, 10 Boerhaave's syndrome and 4 other pathologies), the closure of the perforation was obtained in 32 (97%) patients, recurrence occurred in 37% of cases, which required further stenting (3 patients were treated surgically), and the stents were removed within 6 wk of the placement without major complications[42].

A systematic review, that included 25 studies with a total of 267 patients, showed that the closure of the perforation was successful in 85% of patients, surgery was necessary in 13% and that patients treated with SEPS required a greater number of endoscopic reinterventions compared to patients treated with covered metal stents (26% *vs* 13%, $P < 0.001$)[43].

A particular problem is posed by the hypopharyngeal stenosis resulting from surgery and radiotherapy for cancer ear nose and throat[44,45]. Fibrosis caused by radiotherapy are interested in full thickness bowel and the remodeling of the stenosis is virtually impossible. Expansions of periodic increase fibrosis and therefore the risk of perforation. Generally, the appearance of a fistula requires, when possible, the surgery, with a considerable rate of mortality and morbidity. In these patients has proved useful the use of Niti-S Conio Stent (Taewoong Medical, Seoul, South Korea). The preliminary results are encouraging, but it is necessary to include a larger number of patients to assess the efficacy[46].

Biodegradable stent

The biodegradable implant (Hella® stent - Ella®-CS, Hradec Kralove, Czech Republic) was introduced in the clinical setting in 2008.

One study that included 21 patients with refractory strictures reported a significant improvement in dysphagia at a mean 53 wk of follow-up, 45% of the had not dysphagia at the end of the study, the migration rate was 9.5%, 3 patients complained of retrosternal pain after the release of the stent and one patient presented a slight bleeding after the procedure[47].

Van Boeckel *et al*[48] compared the outcomes

of SEPS (20 patients) and biodegradable stent (18 patients) in refractory strictures. In the group treated with SEPS, 6 (30%) patients were completely free of dysphagia with a median follow-up of 385 d while 10 (50%) had a recurrence of dysphagia, 1 severe bleeding and 1 perforation occurred. In the group treated with biodegradable stent, 6 (33%) patients were free of dysphagia with a median follow-up of 166 d, recurrence was observed in 12 (67%) patients and 2 severe bleeding and 2 cases of severe retrosternal pain occurred. The rate of endoscopic re-intervention was lower in the SEPS compared to the biodegradable stent grosup (15 *vs* 21)[48].

Malignant esophageal disease

Esophageal stents in malignant diseases are mainly placed in presence of unresectable carcinoma of the esophagus, with a short life expectancy, and suffer from marked esophageal stenosis or fistula[49]. Other malignant conditions in which patients are eligible for stent placement are extrinsic esophageal compression or fistula formation as a result of pulmonary cancer, mediastinal cancer or metastatic disease. The main advantages of stent therapy are successful insertion of the device in almost all cases with rapid (24-48 h) improvement of dysphagia. Disadvantages of the stent therapy are the re-occurrence of dysphagia in up to one-third of patients, and other stent related complications, including hemorrhage, pain and fistula[50]. Although most stents are placed in the distal or mid esophagus, insertion in the cervical esophagus is most rarely and it is considered equally effective with dedicated stent[51].

Both SEMS and SEPS are most used in esophageal malignant diseases. Actually to prevent tumor ingrowth PC or FC SEMS were used[51]. Although a FC-SEMS prevents tissue ingrowth over the full length of the stent, it presents a considerable migration risk[52].

Palliative treatment for malignant esophageal strictures

In the last 12 years, only five RCTs comparing different types of stent in patients with malignant esophageal strictures were published[53-56].

The first study randomized 100 patients to treatment with one of three SEMS: the PC-Ultraflex® stent (Boston Scientific, United States), the PC-Flamingo Wallstent® (Boston Scientific) and the FC-SEMS Gianturco Z-stent® (Wilson-Cook, Denmark). The three stents were equally effective in improving dysphagia scores without a significant difference in major complication rate.

The second trial randomized 53 patients with a distal esophageal tumor to a PC-Flamingo Wallstent® (Boston Scientific) or the more flexible PC-Ultraflex® stent (Boston Scientific). Clinical outcome was satisfactory in both groups without significant differences in improvement of dysphagia scores and complication rates.

A third study randomized 101 patients to a Polyflex® (Boston Scientific) or Ultraflex® stent (Boston Scientific), showing similar effectiveness in palliation of dysphagia. However, complications, especially late migration, occurred significantly more often after placement of a Polyflex® stent.

The fourth randomized study with 125 patients evaluated the Ultraflex® stent (Boston Scientific), the FC-double-layered Niti-S stent® (Taewong Medical, South Korea), and the Polyflex stent® (Boston Scientific). The Ultraflex® and Niti-S® stent were equally effective with equal overall complication rates, but recurrent dysphagia generally occurs more frequently with the Ultraflex® stent (52% *vs* 31%), mainly caused by a higher rate of food obstruction. The Polyflex® SEPS was associated with high failure of stent placement (17%) and increased migration risk. Because of a wider diameter of the Polyflex® delivery system, insertion is technically more difficult and dilation had to be performed more frequently. Furthermore, SEPS conform less easily to a stricture, making them more susceptible to slipping.

Observational series had initially demonstrated effectiveness of SEPS in malignant esophageal obstruction; however, the randomized studies revealed an unacceptable high complication rate[57,58].

A recently trial included 80 patients with dysphagia caused by malignant stenosis. Patients were randomized into two groups: PC-Evolution® stent (Cook Medical, Ireland) and Ultraflex® stent (Boston Scientific). The Evolution® stent was related with a significantly lower rate of stent dysfunction (8% *vs* 40%) and major complications (8% *vs* 25%). These data could not be confirmed in another single arm study, which included 44 patients with malignant dysphagia. In this study, the Evolution stent dysfunction rate was much higher (25%), mainly caused by tumor in- or overgrowth[59].

Stent innovations include anti-reflux and anti-migration features. The anti-reflux features were particularly developed for stents bridging the lower esophageal sphincter. This was generally done by attaching a valve to the distal end of the stent, inhibiting backflow from gastric contents into the esophagus. Theoretically, this should prevent reflux symptoms, esophagitis, and possibly aspiration. Although some studies have indicated that anti-reflux stents reduced gastro-esophageal reflux, a recent meta-analysis did not identify a significant difference in adverse events, symptoms and quality of life reflux-related[60]. Therefore, the use of anti-reflux stents has largely been abandoned. Antimigration features include uncovering of distinct areas of the metal mesh and a wider diameter of the stent flares, as well as addition of struts or rings to the outer side of the stent serving as anchoring devices. Both the Alimaxx-E® (Alveolus, United States) equipped with outer antimigration struts and the SX-ELLA® Esophageal HV stent (Ella-CS, Hradec Kralove, Czech Republic), with an anti-migration ring fall in the latter category. Several studies, however, have shown that, in spite of these design modifications, these stents frequently dislocate[61,62]. In addition, the SX-Ella stent

seems to be associated with a major number of adverse events, such as hemorrhage, fistula formation, and severe pain, which likely relate to excessive pressure of the anti-migration ring.

The Niti-S stent has a dog-bone shape to prevent migration. Two design of the stent are present in commerce: a fully-covered self expandable metal stent and a double-layered covering with an FC inner layer made of polyurethane and an outer uncovered nitinol mesh to facilitate the attachment of the SEMS to the wall. Several studies have reported good clinical efficacy and acceptable migration rates (up to 12%) with both types Niti-S® stents[63,64]. In one study, the double-layered version was associated with a significantly lower combined recurrent dysphagia and complication rate than the single layer version (12% *vs* 58%). However, the high complication rate of the single-layered Niti-S® stent used in that study was not confirmed in a recent large single arm study[65]. The FC-Wallflex® stent (Boston Scientific) is characterized by two migration-resistant features: distinct shouldering at both sides and internal covering. This stent has so far only been evaluated in one study for the treatment of neoplastic stenosis. Although the migration risk was low (9%), major complications were commonly seen (30%), which might be associated to the relatively high Wallflex® RF[66].

In summary, the available studies suggest that no major differences in efficacy and safety exist between different stents. However, there is still insufficient evidence to recommend one type of SEMS in the treatment of malignant dysphagia. Specific features reduce migration rates of FC-SEMS; however, they can also induce traumatic injury and lead to major adverse events.

Palliative treatment of malignant fistula

Fistulas usually result from infiltration of esophageal cancer to the respiratory tract or pleural cavity. Additionally, lung and mediastinal cancers can penetrate to the esophagus, also creating fistulas. Multiple series have reported on the use of covered SEMS to seal off fistulas, with closure rates ranging between 73% and 100%[67-69]. At the same time, it is also crucial that pleural and mediastinal fluid collections are drained aggressively. Both PC and FC-SEMS can be used as long as the covering completely seals the fistula. Unfortunately, randomized studies to recommend a specific type of SEMS are lacking. The largest non-comparative series to date reports on 61 patients with esophago-respiratory fistulas treated with covered SEMS. Ten patients also required a trachea-bronchial stent to seal the fistula. Complete fistula healing was reached in the 80% of the cases (49 subjects); the re-intervention was effective in the majority of 17 patients in whom the fistula had re-opened. Based on these data, and in the absence of effective alternative treatments, SEMS is considered the treatment of choice in malignant fistulas[70].

Bridge to surgery and SEMS

Nowadays, neoadjuvant chemoradiotherapy improves long-term survival after esophageal surgery[71]. Stent insertion before neoadjuvant therapy is an interesting new concept in the management of resectable esophageal malignancy. It could be useful as a bridge to surgery during the neoadjuvant chemotherapy, improving nutritional status by ensuring oral solid intake without the need for nasoenteral or percutaneous feeding tubes. Because esophagectomy is scheduled shortly after termination of neoadjuvant therapy, late stent-related complications can be averted. This approach has been evaluated in several studies, using different types of stents and various neoadjuvant regimes[72-74]. Stents were either extracted prior to esophagectomy or removed during surgery. They appear effective in improving dysphagia and maintaining nutrition. However, complications, although rare, may occur. These include esophageal perforation requiring urgent surgery, and stent migration. The latter has in case series been reported to result in small bowel perforation or obstruction. Furthermore, in one study, the number of patients proceeding to curative resection was surprisingly low due to progression or discovery of metastatic disease[75]. These findings indicate that adjunctive studies will clarify the use of the stents meanwhile the patient underwent neoadjuvant chemotherapy before implementing such use in regular practice. These studies should also clarify concerns about the possible spreading of viable tumor cells in the circulation after stent placement.

COMPLICATIONS OF ESOPHAGEAL STENTING

Recurrent dysphagia

Recurrent dysphagia remains a problem after stent insertion and occurs in almost one-third of patients. Endoscopic reintervention is successful in most cases[76]. In cases of tumor over- or ingrowth, insertion of a second stent is effective to restore luminal patency. This can also be considered in cases of stent migration. Conio *et al*[77] in 2010 described the possibility to treat the dysphagia because of the over- or ingrowth by placement of a SEPS. They evaluated 13 patients, previously treated with metal stent developing dysphagia because of tissue in/overgrowth, underwent self-expandable plastic stent (SEPS). Before SEPS placement, the dysphagia score ranged from 3 and 4. After 1 wk from the stent placement the dysphagia score was 0% in 100% of the cases. All of the patients were free of dysphagia till their death. Mean survival after self-expandable plastic stent placement was of 4 mo[77].

However, either endoscopic repositioning or exchanging for a new stent is preferable. Obstruction due to impacted food can easily be managed by endoscopic

stent clearance.

Another rare late complication is spontaneous stent fracture with collapse. The stent-in-stent technique seems safe and effective in these situations and can also be used to facilitate removal of the fractured SEMS[78].

Leak

Esophago-respiratory fistulas are mostly seen several months after stent placement. Due to the RF and resulting pressure necrosis, which is most extreme at the level of the flares, it is usually seen next to the proximal or distal margin of the stent. In these cases, placement of an additional covered-SEMS is an effective method.

Retro-sternal pain

Another complication is the development of retrosternal pain after stent insertion. Didden *et al*[79] found a 60% rate of moderate to severe pain in a prospective assessment of 50 patients after esophageal SEMS insertion for malignant stenosis.

Pain lasted for an average of 10 d and 91% of patients required analgesics, with good effect in all patients without the need for stent removal in any of them.

GASTRIC AND DUODENAL DISEASES

Benign diseases

Complications of bariatric surgery: The sleeve gastrectomy (SG), described for the first time by Gagner *et al*[80] in 2003 is currently a well standardized therapeutic option for the surgical treatment of different degrees of obesity[81,82]. The described complications of the SG include bleeding of the suture line and the stenosis, while the dehiscence of the suture line is the most serious event associated with a high morbidity rate and for whose management have been proposed different therapeutic approaches[83,84].

The re-intervention is often required even if burdened by a high rate of morbidity and mortality.

In recent years some endoscopic methods such as the use of covered-SEMS, have been mostly used for the treatment of anastomotic leakage with the aim of obtaining a non-minimally invasive surgical repair of the fistula[85,86].

The dehiscence of the suture line of the SG could be present in 0.5%-7% of the cases, even if could be underestimated; a detailed review of the American Society for Bariatric and Metabolic Surgery shows an overall rate of complications after SG variable between 0% and 24% with a percentage of dehiscence of 16%-20% of the cases[87]. The esophago-gastric junction and the proximal portion of the stomach near the corner of His are the points where most of you will be dehiscence[88,89].

The use of FC-SEMS in the treatment of dehiscence of the suture line of the SG was proposed by several authors in recent years[90].

The stent constitute a physical barrier between the fistula and the content intraluminal favoring the healing and the closure of the wall defect at the same time allowing the nutrition *per os*. The results of this method are reported in the literature as never variables, even if it is mostly case reports or small case series, so at present there are no extensive data statistically reliable.

Two stents are currently marketed for the closure of fistulas post-SG: the Beta-stent® (Niti-S - TaeWoong), and the Hanaro® stent (M.I. Tech). There are no data about, it is recommended the extraction of the stent between 6 and 8 wk. Currently there are no data comparing the two stents. The migration of the stent is the most common complication, reported in 30% of cases in some papers[87,91] and up to 42%-50% of cases in others[90,92]. The two ends of the stents slightly flared and high profile allow a good anchor. The body of the stents is longer than any of the esophageal stent allowing the opening of the proximal bell at the level of distal esophagus and the distal to the level of the duodenal bulb, by eliminating the pressure gradient, favoring the closure of the wall defect. The large diameter ensures excellent fit of the prosthesis to the wall of the gastric tube.

Malignant gastric outlet obstruction

Gastric outlet obstruction (GOO) is generally secondary to bilio-pancreatic and others. More rarely is due to gastric neoplasia[93]. Gastrojejunostomy (GJ) was the only therapeutic chance till the advent of the SEMS and is characterized by and higher mortality and morbidity, delayed symptoms resolution and longer hospitalization stay when compared to endoscopic stent placement[94,95].

In the last 20 years we observed an emerging role of self-expandable metal stent for palliation of GOO, substituting the GJ. A meta-analysis evaluating nine studies and 307 endoscopic and surgical intervention for palliation of malignant GOO evidenced better clinical success, minor morbidity and mortality, lower time-related procedure and hospital stay for endoscopic stent placement[96]. The rate of endoscopic clinical success was 84%-93%, with a technical success of 93%-97%[97,98].

The correct evaluation of the patients undergoing endoscopic stenting or surgical GJ plays a key role in the management of the malignant GOO. The GJ, in the opinion of some authors, is suggested in patients with a life expectancy more than 6 mo[99] despite a prospective randomized trial suggests GJ when the life expectancy is > 2 mo, and endoscopic SEMS when < 2 mo[100].

During the choice of the stent the endoscopist has to consider the site and the morphology of the stricture. The mean time for endoscopic duodenal SEMS placement is 17.5 min and the use of duodenoscope could

be useful because offer a better view of the duodenal stenosis, moreover, the scope elevator allows also the orientation of the device used, maintaining correctly in place the wire during devices exchange. The use of the duodenoscope is also suggested from some authors in presence of a challenging situation: a concomitant biliary obstruction[101,102].

The concomitant bilio-duodenal strictures are classified in three types: type Ⅰ: involving duodenal bulb/upper duodenal genu in absence of involvement of papillary area; type Ⅱ: involving the medium and distal portion of the duodenum and the papillary area; and type Ⅲ: involving the distal portion of the descending duodenum in absence of involvement of the papillary area[103].

In the type Ⅱ, when a duodenal SEMS is placed, a particular condition is created, the "jailed papilla". ERCP with biliary drainage through the metal mesh of the duodenal SEMS is possible fenestrating the SEMS with argon plasma coagulation (APC)[104]. In case of ERCP failure, percutaneous trans-hepatic biliary drainage is needed.

Actually the reported clinical success rate of duodenal stenting for GOO is 84%-93%, with a technical success of 93%-97%[98,99,101].

Tissue over- and ingrowth, food impaction and stent dislocation are the possible adverse events after SEMS placement, requiring endoscopic intervention in 20%-25% of the patients. Stent migration is more frequent for the covered than the uncovered SEMS[102].

Other complications of enteral SEMS are, bowel perforation and bleeding (< 1%), sometimes due to the uncovered ends of the SEMS[105,106]. The mesh pressure on the epithelium induces tissue regeneration, resulting in the ingrowth of the tissue, conditioning stent failure[107,108]. Then, the placement of a covered-SEMS is preferable in non-surgical patients, or patients with an high risk of mortality and morbidity, with a life expectance > 2-3 mo. Covered stent are usually placed inside of an uncovered stent, in presence of tissue ingrowth or for tumor recurrence and if a leak is present[109,110]. The disadvantage of the covered SEMS is the tendency to migration, even more rare for uncovered SEMS. The migration of a stent might be due to an inadequate stent diameter or after chemotherapy, if a reduction of the neoplastic mass is obtained[111].

COLON AND RECTUM DISEASES

Benign disease

Colo-rectal benign strictures are likely to endoscopic treatment: anastomotic strictures, post-ischemic, Crohn's disease strictures and post-actinic stenosis[112]. Among these, the most frequent is the anastomotic stenosis. It appears on 22%-30% of patients undergoing colorectal surgery and is the most benign colonic pathology treated endoscopically, especially with pneumatic (balloon) or mechanical (Savary) dilation.

Stenting in non neoplastic colorectal stricture is proving to be a viable therapeutic alternative with the intent to bring down the number of endoscopic sessions required to achieve the resolution of the stenosis itself. The data published so far on the use of stents in this setting are still limited and often conflicting.

In the benign stenosis the stents are used with the aim of solving the occlusion or sub-occlusion bowel, which is sometimes an emergency surgical. On the use of stents in benign colorectal diseases are still a few data and with time follow-up is limited, lacking in the literature randomized studies. The results on the efficacy and safety of stents in benign colorectal obstruction is controversial because of the high numbers of adverse events, especially considering the high migration rate[113].

Published studies have demonstrated that colonic stenting in the benign disease has a technical success variable from 85% to 100% with a complication rate of around 30%. The most serious complications observed, although rare, are leaks, bleeding and perforation but the most frequent adverse event is SEMS dislocation[114].

Furthermore, from the "case series" published on colo-rectal inflammatory diseases treatable with SEMS, diverticular stricture are those associated with the higher rate of complications. In fact, as noted by the study of Keränen *et al*[115] the endoscopic stenting in diverticular stenosis is burdened by a considerable risk of adverse events (as leaks, abscesses and perforations) with the need for surgical management in 70% of patients treated with stent[115]. Therefore, the use of stents in diverticular stricture is actually not recommended. The most frequent stricture treated by insertion of stent is than the anastomotic one.

Self-expandable plastic stent

Published data on the use of self-expandable plastic stent in non-neoplastic colonical and rectal diseases consists of case reports and series only[114,116].

Dai *et al*[114] described a series of 14 patients with benign colon and rectal diseases in which SEPS was implanted, anastomotic leak healing in 67% of the patients (4/6) and colonical disobstruction was obtained in the 50% of the patients (7/14). In 2 of 7 patients (28.5%) re-intervention was performed because stricture recurrence at 37 mo[114].

FC self-expandable metal stent

Actually, the biggest series on the use of the FC-SEMS was published in 2013 by the French Society of Digestive Endoscopy (SFED). The study includes 43 patients with bowel obstruction because of anastomotic, post-ischemic or post-radiotherapy stenosis. Stent placement was successful in the 100% of the patients. Clinical success was 81%. Stent migration was in 63% of the cases. The median left in place of the stent was of 21 d. Statistical analysis evidenced that FC-SEMS with a diameter less than 20 mm have a major risk of migration. Recurrence of occlusion was observed in

53% of the cases (23 patients). No predictive factors for occlusive or sub-occlusive symptoms recurrence were individuated at multivariate analysis[117].

Biodegradable stents

Although the use of this stent is limited to benign esophageal strictures, its application on colonic benign stenosis are reported.

Recently was reported its successful use for the treatment of a sigmoid stricture due to Crohn disease[118], however the majority of the published studies on the use this stent in colo-rectal benign strictures is referred to anastomosis.

Pérez Roldán *et al*[119] treated with the biodegradable stent 7 patients with postsurgical colorectal stricture and 3 with rectocutaneous fistula. In 9 patients the biodegradable stents were correctly placed; one early migration was observed. In one patients stent placement was not possible because of the distance to the anal orifice (30 cm) and the deformed anatomy site. Leak healing was obtained in 100% of the cases, despite recurrence was observed in one. Symptoms relief was observed in the 83.3% (6/7) of the occluded or sub-occluded patients; in the other case, the stent migrated 72 h after the placement[119].

Repici *et al*[120] studied 11 patients with anastomotic strictures within 20 cm from the anus, refractory to 3 sessions of endoscopic dilation. They obtained 100% of technical success. In the first 14 d after endoscopic stent placement Authors observed 4 dislocations, with subsequent stricture recurrence. Of the 7 cases with completely meshes biodegradation, 5 had no more symptoms and benign stenosis resolution. In 2 patients surgery was needed. The described clinical success was of 45%[120].

Malignant disease

The endoscopic colo-rectal stenting is indicated for bowel obstruction caused by neoplastic stenosis of the colon-rectum determining a bowel obstruction.

Endoscopic stent placement is also indicated for decompression before of elective surgery (bridge to surgery) in patients affected by colo-rectal neoplasia to avoid emergent surgery and as palliation in presence of patients unfit for surgery candidates because of advanced disease or their poor clinical conditions.

The very low stenosis, which are less than 5 cm from the anus are a contraindication to the stenting. In the case of very low stenosis the use of the stent is invariably associated with the appearance of tenesmus, anal pain and incontinence, making intolerable the presence of the stent in the distal rectum.

More than 20% of patients with acute colo-rectal neoplastic occlusion present metastases and 2/3 of them are unfit for surgery[121,122].

Then, the SEMS placement, especially in patients not suitable for surgery, allows a re-canalization of the bowel patency, avoiding surgery.

In patients with advanced colo-rectal neoplasia causing bowel obstruction surgical intervention with stoma creation is generally performed, with negative implications for patient quality of life[123]. The endoscopic stenting by use of SEMS is nowadays accepted in the palliative therapy of the colo-rectal cancer, becoming a valid alternative to surgical stoma.

Different studies evaluated the role of the SEMS in the palliation of colo-rectal cancer. Three randomized studies are present in literature comparing endoscopic stenting with surgery in patients unfit for surgery affected by colo-rectal neoplasia, causing bowel obstruction.

In these 3 RCTs studies the technical and clinical success was of 92% and 92% respectively, with a morbidity rate of 30% (11/37) in the patients underwent endoscopic stenting and 17% (6/36) in the patients underwent surgery, and a mortality of 8% (3/37) only in the stent group[124-126]. Two of the three Authors of the RCTs suggest superior efficacy and safety of the SEMS group if compared to surgery for palliation of colorectal cancer obstruction, differently to the reported data by the Dutch Stent-in I multicenter RCT. However, in palliated patients with a longer lifespan, SEMS placement in comparison to a colostomy, presents an improvement of the life quality, and with a reduction in cost and length of hospital stay[127,128]. Stents used were the WallFlex (Boston Scientific). The study was closed before the total patients enrollment for the high recorded numbers of perforations related to the SEMS placement, with 3 consequently deaths in 10 patients of the group undergone stenting. Authors had not a clear reason for justifying the high rate of perforations. They supposed a doubtful safety of the WallFlex.

Moreover, no supporting results have been showed by other studies in which WallFlex SEMS was tested as palliative treatment in referral centres. This studies show as the experience of the endoscopist could be an explanation for the high rate of adverse events reported by the Dutch group[129-131].

Bridge to surgery has to be seriously considered in presence of patients with acute obstruction and fit for surgery. SEMS placement provides to bowel patency restoration allowing colonical preparation for surgery and an eventual pre or intra-operative endoscopy for the research of synchronous neoplastic and non-neoplastic diseases. The curative intent for these patients is a single-step intervention with primary anastomosis, especially when a laparoscopic approach is possible.

However, the role of SEMS as bridge to surgery, has been widely debated, because several RCTs studies have shown conflicting and mixed results.

In the 6 RCTs in which endoscopic stenting was evaluated as bridge to surgery (171 patients) compared to emergency surgical resection (169 patients), the technical and clinical success of stenting was 79% and 77% respectively, with a morbidity rate of 33% in the

SEMS group and 53% surgical one with a comparable mortality rate (7% *vs* 8%)[132-137].

Notably evident is the difference in results between RCTs studies carried out in single centers *vs* those carried out in multicenters, particularly with respect to the stent placement outcomes and for the elevated number of stent-related perforations.

An elevated number of stent-related perforations were reported only in the studies specifically designed as multicenter trials and these studies were stopped prematurely.

In these trials, Pirlet *et al*[133] reported 3 stent-related perforations in 35 patients randomized to the stenting strategy and van Hooft *et al*[134] reported 6 stent-related perforations in 47 patients in the stenting group. The elevated number of perforations in these studies remains unexplained.

The worst results in SEMS placement outcomes come from RCTs which are specifically designed as multicenter trials involving low-volume centers. In the of Pirlet *et al*[133], of the nine participating centers, two of them enrolled 3 patients and one only 1 patient; in the study of van Hooft *et al*[134] 21 on 25 endoscopic centers were not referral.

The problem is that in planning RCTs regarding colonic stent placement, the need for involving multiple centers caused the inclusion of endoscopists with limited specific experience and low performance in placing stents. Therefore, this reality could result in confounding data on the real efficacy of the stenting strategy.

Huang *et al*[138] published a recent systematic review and meta-analysis evaluating safety and efficacy of colo-rectal stent placement as bridge to surgery compared to emergency surgery and considered for inclusion the 6 RCTs studies in english language and also another study in chinese language[138].

The technical success of colo-rectal stenting was of 76.9%, in absence of significant statistically difference in the postoperative mortality (10.7% *vs* 12.4%). The study evidenced lower morbidity (33.1% *vs* 53.9%, $P = 0.03$), higher rate of successful primary anastomosis (67.2% *vs* 55.1%, $P < 0.01$) and lower rate of definitive stoma (9% *vs* 27.4%, $P < 0.01$) for the group undergone stent placement[139].

None oncologic adverse events were recorded in the bridge to surgery group, but a major rate of lymphatic invasion was found[140-142]. No significant difference in survival were founded over 5 years (60% *vs* 58%)[143].

Colon stenting procedure does carry some risks, and complications are usually divided into early (within 30 d), including perforation, misplacement, and bleeding, and late, which include migration, reocclusion, tenesmus and delayed perforation.

The most common adverse event described in literature after stent placement as the migration (11%) SEMS obstruction caused by in and overgrowth tissue (12%) and bowel perforation (4.5%), as showed from a systematic review involving 88 published studies[144].

Stent obstruction is generally due to fecal impaction after tissue in or overgrowth, determining the long-term outcomes of the metal stent. The rate of SEMS obstruction by tissue in or overgrowth increases with the time because of the natural tendency of the neoplastic tissue to advance; then, SEMS occlusion is more frequent in patients in which the SEMS is placed for palliation. Literature data evidenced a 16% of SEMS occlusion when the treatment is made with palliative intent[145].

The endoscopic SEMS placement inside a stent is actually the best treatment to solve the stent obstruction due to the tissue in or overgrowth[146].

The migration of a SEMS could be asymptomatic or may cause occlusive or sub-occlusuve symptoms. More rarely is the bleeding. Tenesmus may be present when the SEMS reaches the rectum. Removal of a migrated stents from the rectal ampulla is not a challenging situation and can be also performed manually. Risk factors related to migration are the covering of the stent and the diameter < 24 mm. Some Authors stated that chemotherapy could be also related to the migration because of tumor reduction[147-149].

When the patient becoming symptomatic, the migration of the stent could be treated with the placement of a second one.

Bowel perforation is typically regarded as the only serious complication and is generally procedure or stent related. Most of the perforation occurred within 7 d after stent placement and may be caused by the SEMS delivery insertion into the stricture before the stent deployment, pneumatic dilatation of the stenosis or incorrect advancing of the wire. More rarely the perforation is due to the decubitus of the flared ends of the SEMS on the colonic wall. Over inflation with air can cause a perforation in a yet dilated colon far away from the site of obstruction, usually in the cecum[150-152].

Datye *et al*[152] reviewed the factors involved into the bowel perforation after stent placement, collecting the data from 82 published articles with 2287 patients. They showed a mortality rate related to perforation of 16.2% for patients who had stent-related perforation. The majority of adverse events (> 80%) were recorded within 1 mo from SEMS deployment, and 50% within 24 h from the procedure. Concomitant chemotherapy, steroids, and radiotherapy were significantly associated with perforation[153].

Bevacizumab therapy is considered now a considerable risk factor for post-stenting bowel perforation. The antiangiogenic effect could impair the colonic wall promoting the perforation at the site of maximal stent exercised pressure. Moreover, this perforation risk might be not dependent from the SEMS placement because is nowadays well known that spontaneous bowel perforation can occur during the addition of bevacizumab to chemotherapy.

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REVIEW

Recent advancement of therapeutic endoscopy in the esophageal benign diseases

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Abstract

Over the past 30 years, the field of endoscopy has witnessed several advances. With the advent of endoscopic mucosal resection, removal of large mucosal lesions have become possible. Thereafter, endoscopic submucosal resection was refined, permitting en bloc removal of large superficial neoplasms. Such techniques have facilitated the development of antireflux mucosectomy, a promising novel treatment for gastroesophageal reflux. The introduction and use of over the scope clips has allowed for endoscopic closure of defects in the gastrointestinal tract, which were traditionally treated with surgical intervention. With the development of per-oral endoscopic myotomy (POEM), the treatment of achalasia and spastic disorders of the esophagus have been revolutionized. From the submucosal tunnelling technique developed for POEM, Per oral endoscopic tumor resection of subepithelial tumors was made possible. Simultaneously, advances in biotechnology have expanded esophageal stenting capabilities with the introduction of fully covered metal and plastic stents, as well as biodegradable stents. Once deemed a primarily diagnostic tool, endoscopy has quickly transcended to a minimally invasive intervention and therapeutic tool. These techniques are reviewed with regards to their application to benign disease of the esophagus.

Key words: Per-oral endoscopic myotomy; Per-oral endoscopic tumor resection; Antireflux mucosectomy; Submucosal tumors; Subepithelial tumors; Over the scope clips; Stents; Gastroesophageal reflux disease

Core tip: Antireflux mucosectomy is an endoscopic antireflux procedure showing promising results in patients with refractory gastroesophageal reflux. Over the scope clips and esophageal stents permit safe endoscopic closure of esophagogastric defects, decreasing the requirement for surgical intervention. Per-oral endoscopic myotomy allows the precise performance of endoscopic myotomy for the treatment of spastic esophageal motility disorders with the efficacy of a surgical myotomy without the associated surgical morbidity. Per-oral endoscopic tumor resection enables en bloc endoscopic removal of subepithelial tumors (SETs) and is both a diagnostic and therapeutic intervention for esophageal SETs. These techniques will expand the boundaries of therapeutic endoscopy, decrease the need for surgical intervention, and improve patient outcomes.

Bechara R, Inoue H. Recent advancement of therapeutic

endoscopy in the esophageal benign diseases. *World J Gastrointest Endosc* 2015; 7(5): 481-495 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/481.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.481

ENDOSCOPIC ANTI-REFLUX PROCEDURES AND ANTI-REFLUX MUCOSECTOMY

Background

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal problems with an estimated increasing prevalence of over 25% in North America[1,2]. Consequently, it is a source of significant morbidity as well as considerable healthcare costs. In the United states alone, an estimated 9.3 billion dollars was incurred in direct healthcare cost as a result of GERD[3].

The standard surgical treatment for GERD is the Nissen fundoplication, where the fundus is wrapped around the lower esophagus to reinforce the lower esophageal sphincter (LES). This produces excellent short-term results and is generally safe with a post-operative complication rate of approximately 2%[4]. A recent multicenter randomized trial showed that there was no significant difference in symptom remissions at five years follow-up between oral esomeprazole therapy and laparoscopic Nissen fundoplication[5,6]. Studies with longer follow-up, have reported relapse rates of up to 50% at 12 years post-laparoscopic Nissen fundoplication[7,8]. Furthermore, reoperations in these patients has increased morbidity and relapse is still a possibility[9,10].

Recently, there has been great interest in pursuing endoscopic alternatives to laparoscopic antireflux surgery. There are three categories of such procedures; endoscopic devices for gastric plication, injection/implantable substances at the gastroesophageal junction (GEJ) and ablative therapies.

Endoscopic suturing devices allow plication 1-2 cm below the GEJ with the goal of reinforcing the LES, mimicking laparoscopic anti-reflux surgery. Depending on the device used, total procedure times vary from 30-60 min. However, due to safety, cost, and questionable long-term efficacy, many of these devices are no longer available. One currently available device is EsophyX® (EndoGastric Solutions, Washington, United States) which is marketed to deliver transoral incisionless fundoplication. Due to the fact that long-term efficacy data are not available, significant cost of the device, and the need to confirm safety and define optimal technique, it has not become widely used[11].

Injectable treatments where liquid chemical polymers are directly injected into the LES result in bulking and reinforcement of the natural barrier to reflux. These treatments demonstrated promising early results, but have been removed from the market due to safety concerns related to transmural injection resulting in mediastinits, pericarditis, and death[12-14].

Ablative therapy consists of thermal energy delivered to the GEJ, which results in tissue remodeling that provides reinforcement to the LES. Stretta® (Mederi Therapeutics Inc., Connecticut, United States) is a currently available device which delivers low radiofrequency energy. The Stretta device has been available in the United States since 2000 and has good safety data, contrary to many of the previously mentioned therapies. In short and mid-term follow-up, there is evidence of significant improvement in subjective and objective indicators of GERD. Long-term efficacy has not been consistently demonstrated with some series showing 60% of patients proceed to antireflux surgery, while other series have shown a more durable response[15-19].

Many of the studies on endoscopic antireflux procedures are limited to small single-center case series demonstrating good short-term improvement in symptoms. However, consistent long-term durable efficacy has not been shown, with the few randomized control studies failing to show improvement over sham control arms. Due to the lack of convincing evidence for adequate long-term symptom control, associated high-cost and some safety concerns endoscopic antireflux procedures have failed to become widely used.

With the introduction of strip biopsy by Tada *et al*[20] in 1984, endoscopic resection with local injection of hypertonic saline injection (ERHSE) by Hirao *et al*[21] 1988, cap EMR by Inoue *et al*[22] in 1990 and subsequent development of ESD in Japan, resection of superficial gastrointestinal neoplasia was revolutionized[20-24]. The safety and efficacy of EMR/ESD have been well reported and are now widely applied by endoscopists around the world[23-25]. A known complication of esophageal EMR/ESD, particularly when more than two-thirds circumferential, is stricture development[26-28]. The exact mechanism of stricture formation is unknown. However, from experimental models it has been shown to involve acute inflammation, angiogenesis, fibrous hyperplasia with replacement of the submucosa with dense collagen fibers, and ultimately, atrophy of the muscularis propria[29,30]. In 2003, Inoue *et al*[22] reported a case of circumferential EMR for short-segment Barretts with high-grade dysplasia that was found on endoscopy performed for objectively confirmed (24-h esophageal pH testing) reflux symptoms. A circumferential EMR was performed extending to include a 2 cm wide portion of the gastric cardia. It was hypothesized that this would improve the reflux symptoms by causing fibrosis at the gastric cardia resulting in reinforcement of the LES. As expected, excellent symptomatic and objective (normalization of 24-h esophageal pH testing) improvement resulted and the patient has remained off of PPI for over 10 years[31]. Then in 2014, Inoue *et al*[32] published a series of 10 patients that received the antireflux mucosectomy (ARMs) procedure for

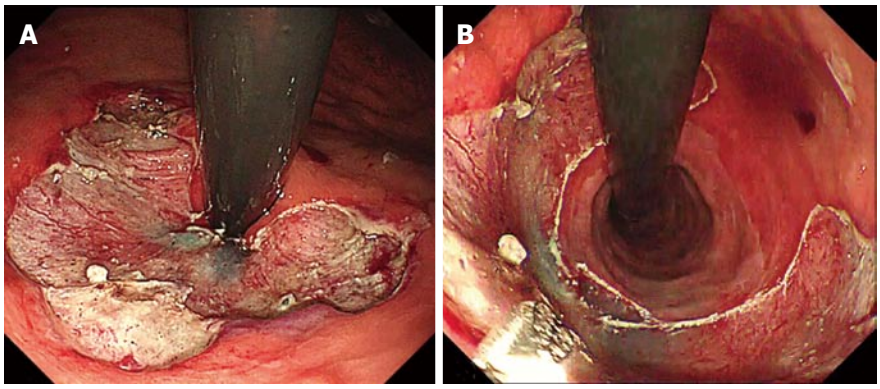

Figure 1 Completed antireflux mucosectomy. A: View on expiration; B: View on inspiration.

refractory GERD showing excellent results both subjectively and objectively.

Indications

Patients with GERD that are considered for ARMs are those without a large sliding hiatus hernia that have been objectively confirmed to be PPI refractory on 24-h esophageal pH testing. The presence of Barrett's esophagus does not preclude the performance of ARMs.

Technique

The ARMs procedure can be performed with ESD or EMR and is generally as follows: Step 1: Marking of area for mucosectomy. Mucosal reduction is planned along lesser curve of the gastric cardia in crescentic fashion (Figure 1A). When retroflexed in the stomach, the length of preserved mucosa on the side of the greater curve is estimated at twice the diameter of the endoscope (approximately 2 cm); Step 2: Submucosal injection. Both EMR and ESD can be used depending on the experience of the operator and the presence of mucosal lesions. Submucosal injection is made along the markings to ensure adequate lift to prevent deep injury or perforation; and Step 3: Mucosectomy. The mucosectomy is performed *via* EMR or ESD (Figure 1B).

Safety

In the first two cases of ARMs, circumferential mucosectomy was performed which resulted in stricture formation, however these were successfully treated with balloon dilation. Subsequently, all ARMS were performed in a hemi-circumferential or crescentic fashion that produced adequate fibrosis to alleviate GERD without stricture formation[32].

Efficacy

All patients had significant improvement in subjective and objective indicators of GERD. The DeMeester, heartburn and regurgitation scores all showed significant impressive improvement. Twenty-four hours esophageal pH testing showed the mean fraction of time at pH < 4 improved from 29.1% to 3.1%[32].

Conclusion

This series of ARMs showed promising safety and efficacy, however, the sample size was small, owing to the low incidence of GERD in Japan. Larger randomized sham-controlled studies with long-term follow-up are required to confirm these findings. Unique aspects of ARMs as an endoscopic treatment for GERD is that the safety of EMR/ESD has already been established, and endoscopists are already familiar with these techniques. These facts would allow ARMs to potentially be performed by most endoscopist with expertise in esophogastric EMR/ESD. In addition, there is no requirement for new, expensive specialized equipment. Thus, if future studies confirm the early promising results of ARMs, it has the potential to become a widely used endoscopic treatment for GERD, as it would meet the demands of safety, efficacy and cost-effectiveness.

OVER-THE-SCOPE CLIPS

Background

The over the scope clips (OTSCs) were initially introduced for closure of perforations and for mechanical hemostasis of complicated arterial bleeds of the gastrointestinal tract. The OTSC consist of a nitinol alloy with a similar shape to a bear trap. The clip, is preloaded on a clear applicator hood which is mounted onto the scope tip. The deployment system is analogous to that of a variceal banding device with the string running through the working channel of the endoscope and is fastened to a rotatable handle that is attached to the port of the working channel.

Indications

Specifically pertaining to the esophagus, the OTSC has successfully been used for refractory bleeds (non-variceal), closer of iatrogenic perforations, Boerhaave's syndrome, anastomotic leaks, tracheaesophageal fistula and securing fully covered self-expandable metal stents (SEMS)[33-43].

Technique

After mounting of the OTSC, the target area is identi-

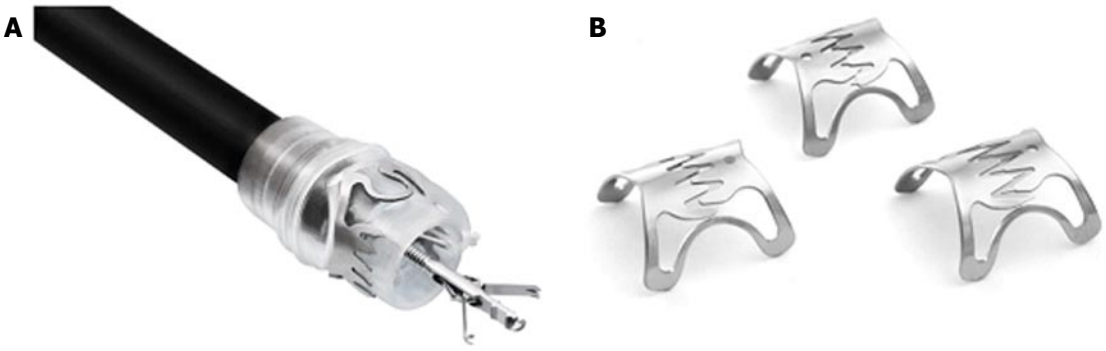

Figure 2 The over the scope clip device. A: Clip mounted onto the distal tip of an endoscope with Twin Grasper projecting from the working channel; B: The different over-the-scope clip tooth configurations available. (With permission from OVESCO Endoscopy, Germany).

fied, suctioned into the hood and the clip is deployed bringing the tissue into apposition. Alternatively, one of the available graspers or anchor can be used, allowing for dimproved apposition of the defect and better visualization of the tissue prior to clip deployment (Figure 2). Once the clip is deployed a permanent closing force of 8-9 Newtons (N) is applied to the tissue without causing necrosis[43]. Depending on the indication, different teeth are available; rounded (type a, Figure 2B left) for atraumatic application, pointed (type t, Figure 2B middle) and long pointed (type gc, Figure 2B right) for more tissue apposition. Some of the challenges with the OTSC device are that it limits sharp angulation which can make maneuverability in the esophagus more challenging and the attached OTSC device slightly impairs the endoscopic view.

Safety

Complications with the OTSC have been uniformly rare in all the published series, the majority reporting no or few complications[33-41,43-52]. However, isolated cases of esophageal perforation, inadvertent tongue piercing and intestinal obstruction (from accidental inclusion of opposing walls into the OTSC) have been reported[44,51,53].

Efficacy

The OTSC device has been shown to be safe and effective for refractory arterial GI bleeding and closure of iatrogenic perforations 20 mm and smaller[47,51]. The successful closure of anastomotic leaks and fistulas in case series has been largely favorable, but efficacy has varied widely between 38%-100% in published series, due to heterogeneity of cases, series size and operators experience[36-38,40-43,45,48-51,54,55]. However, two recent meta-analysis showed success rates of 80%-100% for both perforation and fistula closure, with failure usually associated with chronic fibrotic fistulas[52,56]. Most recently the European Society of Gastrointestinal Endoscopy released its position statement on iatrogenic endoscopic perforations and endorsed the use of the OTSC device for closure of iatrogenic esophageal perforations[57].

Conclusion

Multiple studies have reported that the OTSC device has good clinical efficacy for closure of esophageal, perforations, fistula and anastomotic leaks with few complications. Depending on the expertise available the OTSC device can be considered an early treatment option for esophageal perforation, leaks and fistula.

POEM

Background

Achalasia is an esophageal motor disorder resulting from inhibitory neuron dysfunction causing loss of peristalsis and impaired LES relaxation. This leads to impaired food bolus propulsion and stasis in the esophagus. Patients may experience dysphagia, regurgitation, chest pain, weight loss and heartburn[58-60]. The conventional treatments are laparoscopic Heller myotomy (LHM) and pneumatic dilation (PD). The first account of an endoscopic myotomy dates back to 1980 by Ortega *et al*[61] in Venezuela, where they described two 1cm long myotomies to a depth of 3 mm performed at the LES in 17 patients. In 1997, Pasricha *et al*[62] in the United States, described an experimental technique on a bovine model, where a mucosal incision was made five centimetres above the GEJ and a balloon was placed into the submucosal space to create a tunnel down to the GEJ, where a myotomy of the circular muscle was performed[62]. In 2010, Inoue *et al*[32] in Japan modified the endoscopic myotomy procedure such that it permitted safe and effective human application. Since the introduction of POEM, there has been an dramatic increase in POEM studies and the procedure is now being performed worldwide.

Indications

Currently, there are no universal guidelines for the indication of POEM. It is the opinion of the authors of this review that with the reported efficacy and safety from our center, that POEM can be considered a first line treatment for achalasia. POEM has been safety performed in patients with previous PD, LHM, Botox injection, and even previous POEM. In our center, it

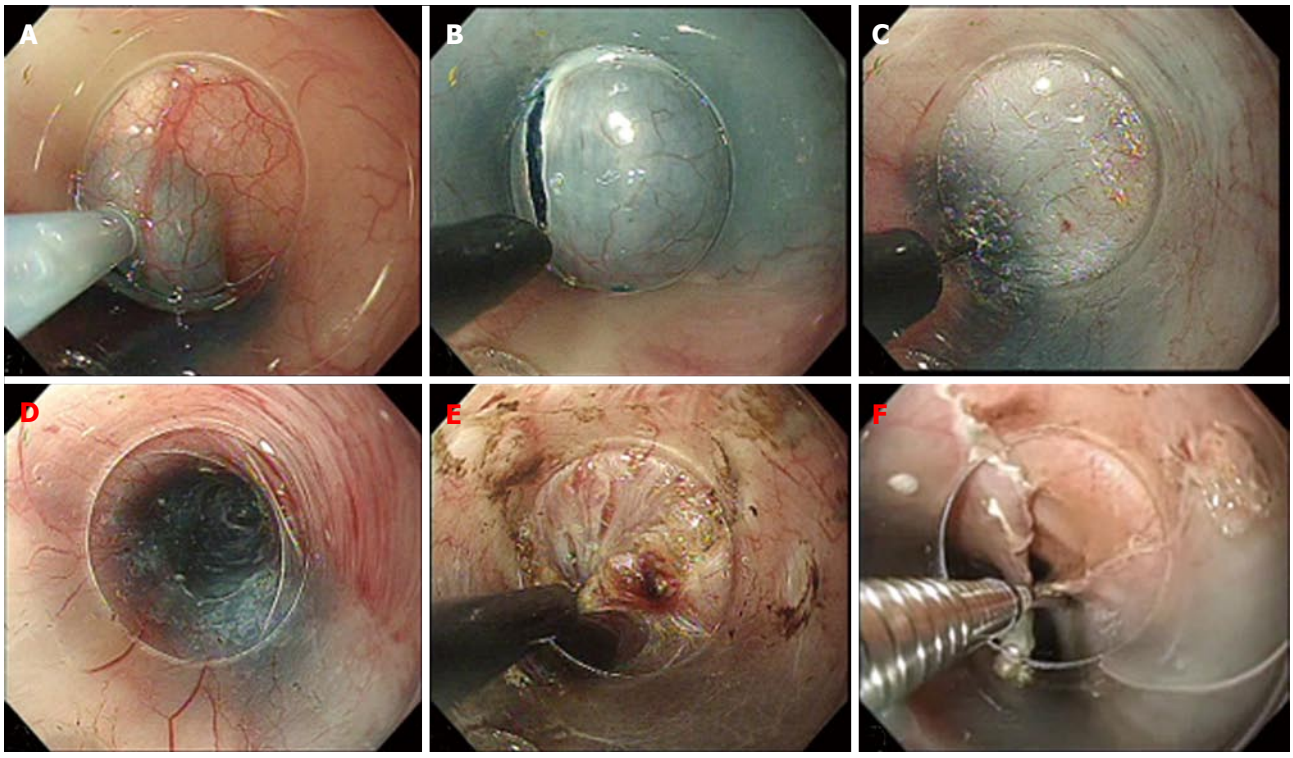

Figure 3 Steps in Per-oral endoscopic myotomy. A: Submucosal injection; B: Mucosal incision; C: Submucosal tunneling; D: Completed tunnel; E: Circular muscle myotomy; F: Closure of mucosal incision.

has also been safely performed in patients with type 1 and type 2 sigmoid achalasia as well as octogenarians. Other motility disorders such as diffuse esophageal spasm (DES), nutcracker esophagus, Jack-hammer esophagus, and hypertensive LES have also been successfully and safely treated with POEM.

Technique

The first successful case of POEM in a human was performed September, 2008 by Haruhiro Inoue. Since then, it has been widely accepted and performed with many slight variations to the original technique. The procedure as performed at our center is as follows (Figure 3): Step 1: Submucosal Injection and Incision. After the area of mucosal incision is chosen (approximately 13 cm above the GEJ for standard myotomy) 10 cc of saline with indigocarmine is injected into the submucosa and a 1.5-2 cm longitudinal incision is made with a triangle-tip knife (KD-640 L; Olympus). To avoid mucosal injury, the submucosal tunnel is dissected as close as possible to the circular muscle; Step 2: Creation of the submucosal tunnel. After enough space is created in the submucosa, mucosal entry is achieved and the tunnel is carefully extended down to the gastric side for approximately 3 cm; Step 3: Endoscopic myotomy. The circular muscle fibers are carefully dissected with the Triangle tip knife. When there is no abnormal contraction of the esophageal body or symptoms of chest pain, the standard myotomy is 8-10 cm; and Step 4: Closure of Mucosal entry. After completion of the myotomy and good hemostasis is confirmed, prophylactic antibiotic is instilled into submucosal tunnel and the mucosal entry site is clipped closed.

The main technical limitation to the performance of POEM is the presence of severe submucosal fibrosis which limits the ability to safety perform the submucosal tunnel and can occur when patients have had severe esophagitis, multiple previous endoscopic treatments, extensive esophageal EMR/ESD in the POEM field or radiation therapy.

Safety

Complications include; capnomediastinum, capnoperitoneum, intraprocedural and delayed bleeding, mucosal laceration/ischemia and GERD. The vast majority of complications reported have been treated conservatively and there have been no mortalities reported or requirement for conversion to open surgical procedure[63-73]. The most robust data comes from the international POEM survey (iPOEMS) database, reporting major complications occurred in 3.2% of 841 cases[74] which were treated conservatively without sequelae. In comparison, the large European trial comparing PD and LHM showed a 4% perforation rate for PD and a 12% rate of mucosal tear for LHM[75].

There is heterogeneity in reporting and classification of complications, partially accounting for the variability in reported complication rates (Table 1). Therefore, a standardized, internationally agreed upon adverse event reporting system for POEM is required. However, it is important to note that all the reported complications

Table 1 Series reporting Eckardt post Per-oral endoscopic myotomy for achalasia

Ref.	Country	No. of patients	Success rate (%)	Complications (%)	Mean follow-up (mo)
inoue *et al*[82] 2010[a]	Japan	17	100	0	5
von Renteln *et al*[79] 2012	Germany	16	94	12.5	3
Swanstrom *et al*[67] 2012	United States	18	100	16.7	11
Ren *et al*[85] 2012	China	119	94	55	3
Costamagna *et al*[65] 2012	Italy	11	100	0	3
Lee *et al*[66] 2013	South Korea	13	100	0	7
Hungness *et al*[76] 2013	United States	18	89	22	6
Teitelbaum *et al*[77] 2013	United States	12	100	NR	9
Zhou *et al*[83] 2013[b]	China	12	92	16.7	10
Von Renteln *et al*[64] 2013[c]	International	70	82.4	14.3	12
Sharata *et al*[84] 2013[d]	United States	31	100	12.5	6
Freidel *et al*[68] 2013	United States	45	95	33	3
Inoue *et al*[80] 2013	Japan	300	100	6	12
Sharata *et al*[73] 2014	United States	75	98	11	16
Bhayani *et al*[78] 2014	United States	37	100	13.5	6
Minami *et al*[63] 2014	Japan	28	96	0	3

[a]Eckard score was not used, but rather a dysphagia symptoms score which decreased from mean of 10 to 1.3; [b]All patient had previous laparoscopic Heller myotomy; [c]European and North American; [d]Included other spastic esophageal disorders, total 31 achalasia cases; Complications rate reported is for all 40 cases performed. NR: Not reported.

have been treated successfully endoscopically, with needle decompression or conservative management without any significant sequelae.

Efficacy

POEM is now being performed globally with excellent clinical results, with patients showing improvement of mean Eckardt scores from 5.4-8.8 pre-POEM to 0.4-1.7 post-POEM[63-68,76-81]. In addition, many series have reported decreases in LES pressure and barium column height[63-67,76-79,82]. Success rates, defined by a post-POEM Eckardt score $\leqslant$ 3, are summarized in Table 1. Multiple comparative studies have shown that POEM is at least as effective as LHM with shorter hospital stay and decreased post-procedure pain[76-78].

POEM has also been shown to be effective in patients with previous LHM. Zhou *et al*[83] reported a mean improvement in Eckardt score of 9.2 to 1.3, and Onimaru *et al*[81] reported a mean improvement in Eckardt score of 6.5 to 1.1. Patients who have failed Botox injections or PD have also seen comparable improvements post POEM[84].

Expanded Indications for other spastic esophageal motility disorders

Generally, other spastic disorders of the esophagus that have been treated surgically require a longer myotomy necessitating thoracotomy. This is another advantage of POEM, where a long myotomy can be performed without increased invasiveness or complications. From the iPOEMS database, the POEM procedure was performed in 25 DES patients, 106 Nutcracker patients, and 58 Hypertensive LES (HTLES) patients. Compared to achalasia, POEM was equally effective in Nutcracker esophagus and HTLES, but less effective for DES[74]. In the recent series by Sharata *et al*[73] that included 12 Nutcracker esophagus, 5 DES, and 8 HTLES patients, complete dysphagia relief was achieved in 70.8% of non-achalasia cases, while chest pain was relieved in 91.5%[73]. There are also two case reports demonstrating successful application of POEM for Jackhammer esophagus[86,87].

Areas of controversy

In our center, the majority of POEM cases were performed at 2 o'clock (anterior-lesser curve) or 5 o'clock (posterior-lesser curve) positions. In some cases, previous procedures such as LHM, POEM, or ESD (for esophageal lesion) had been performed, precluding safe submucosal tunnelling in the normal location and alternate positions were used. At present there are no studies to guide which site of standard myotomy is most optimal. This will hopefully be addressed with a large multicenter, randomized trial in the near future.

A selective circular muscle myotomy is normally performed in our center. Nevertheless, some centers prefer a full thickness myotomy. Li *et al*[88] compared full thickness myotomy with selective circular muscle myotomy and found no difference in either efficacy or adverse events. However, shorter operative times are observed with full thickness myotomy[88]. Until there is more evidence, we suggest an isolated circular myotomy to prevent potential damage to adjacent structures and.

Conclusion

Over 2000 POEM procedures have been performed worldwide. Most of the of the studies show excellent efficacy with low rate of major complications, all of which have been managed without sequelae. There is also growing evidence for the use of POEM for other spastic disorders of esophagus. Over time, POEM may arguably become the standard of care for achalasia and other spastic disorders of the esophagus.

PER-ORAL ENDOSCOPIC TUMOR RESECTION

Background

Subepithelial tumors (SETs) of the upper gastrointestinal tract are generally uncommon with an incidence of about 0.4% of all routine esophagogastric endoscopic examinations[89]. Gastric SETs have a malignancy rate of approximately 50%, in contrast, esophageal SETs are usually benign leiomyomas and only 1%-3% harbor malignancy[89-91]. Generally, SETs are asymptomatic and found incidentally on endoscopic or radiologic examination for unrelated symptoms or screening. However, larger SETs can cause dysphagia, chest pain, regurgitation and bleeding[92,93]. Traditionally, excision of symptomatic SETs has been performed with open surgical, laparoscopic or thoracoscopic techniques. These procedures are invasive, associated with significant health-care cost and morbidity[94-96]. In addition, if the lesion in question is benign it is difficult to justify surgical excision with associated surgical morbidity. With the introduction of POEM, the submucosal tunnelling technique has been subsequently applied for Per-oral endoscopic tumor (POET) resection by Inoue *et al*[97] in 2012. The technique has allowed SETs to be removed from the esophagus and gastric cardia, safety and effectively. Since its first description, multiple series have been published supporting its safety and efficacy.

Indications

Most of the SETs removed *via* POET have been benign. The presumptive diagnoses were made using a combination of endoscopy, endoscopic ultrasound (EUS) and CT scan. Indications for resection were presence of symptoms, enlarging tumor or unclear diagnosis in which resection was diagnostic.

Technique

An essential part of POET (and POEM) is use of low flow carbon dioxide insufflation to prevent complication from barotrauma as noted by Wang *et al*[98], where air insufflation was used in the first half of their series, which resulted in high rates subcutaneous emphysema, pneumothorax and pneumomediastinum. Subsequently, they used carbon dioxide insufflation for the remaining cases and did not have further adverse events related to insufflation[98]. The POET technique can be summarized as follows with the various steps shown in Figure 4: Step 1: Submucosal Injection and Incision. The area of mucosal incision is generally 5 cm proximal to the tumor and is made as described for POEM; Step 2: Creation of the submucosal tunnel. The submucosal tunnel is extended 1-2 cm distal to the tumor to ensure sufficient working space for the dissection of the tumour; Step 3: Tumour Resection. Once the mass is identified and the tunnel is sufficient, resection of the tumor can proceed. Careful dissection of the mass from the muscular layer should be performed to prevent rupture of capsule or perforation of the overlying mucosa. Tumors that extend to the deep muscular layer can be removed with a full thickness resection of the circular and longitudinal muscles. The free tumor can be withdrawn through the mucosal incision using a snare, grasping forceps or suctioning into the transparent hood; and Step 4: Closure of Mucosal entry. The tunnel is re-examined to confirm adequate hemostasis and the mucosal incision is closed with endoscopic clips. There are also reports of using endoscopic staples, OTSCs, as well as covered metal stents to seal the mucosal incision site[99-102].

Patients are managed analogous to post-POEM patients. Patients are kept nil per os for 24 h. Day 1 post-procedure the patient has an endoscopy as well as a contrast study to check for leak. Some centers perform routine post-procedure CT scan to check for insufflation related complications and perforation[103]. The patient's diet is advanced to clear liquids day-1 post-procedure, and advanced to regular diet by day 4 if asymptomatic. Endoscopy and endoscopic ultrasound are generally performed for follow-up on patients that underwent POET resection. If the lesion removed is malignant or with malignant potential, closer follow-up is performed and includes a CT scan to assess for tumor recurrence and the occurrence of distant metastasis[98,104].

Safety

Almost all of the reported complications have been insufflation related (subcutaneous emphysema, pneumoperitoneum and pneumomediastinum). All were managed with decompression or conservatively without sequelae. Analogous to POEM series, there is variability in reporting and classification of complications.

Efficacy

Nearly all series report 100% successful resection (refer to Table 2). With almost all being *en bloc* with intact capsule. A complete resection refers to an en bloc resection of the tumor with intact capsule. This factor is important to prevent seeding especially if the pre-procedure diagnosis is suggestive of a malignant or pre-malignant lesion. The limiting factor for resection of SETs *via* POET is size. The largest SET removed to date was 60 mm × 28 mm × 22 mm[100]. The tumor (known to be a leiomyoma) required fragmentation to be extracted. In addition, the mucosal incision could not be closed and necessitated placement of fully covered SEMS. Anecdotally, it appears that the upper limit for a complete resection is 4-5 cm depending if the shape of the tumor allows for extraction through the mucosal incision site. The efficacy data is summarized in Table 2[97-99,105-111] below.

Conclusion

Subepithelial tumors of the esophagus and cardia are usually incidental findings on endoscopic or radiologic examinations for unrelated symptoms, with

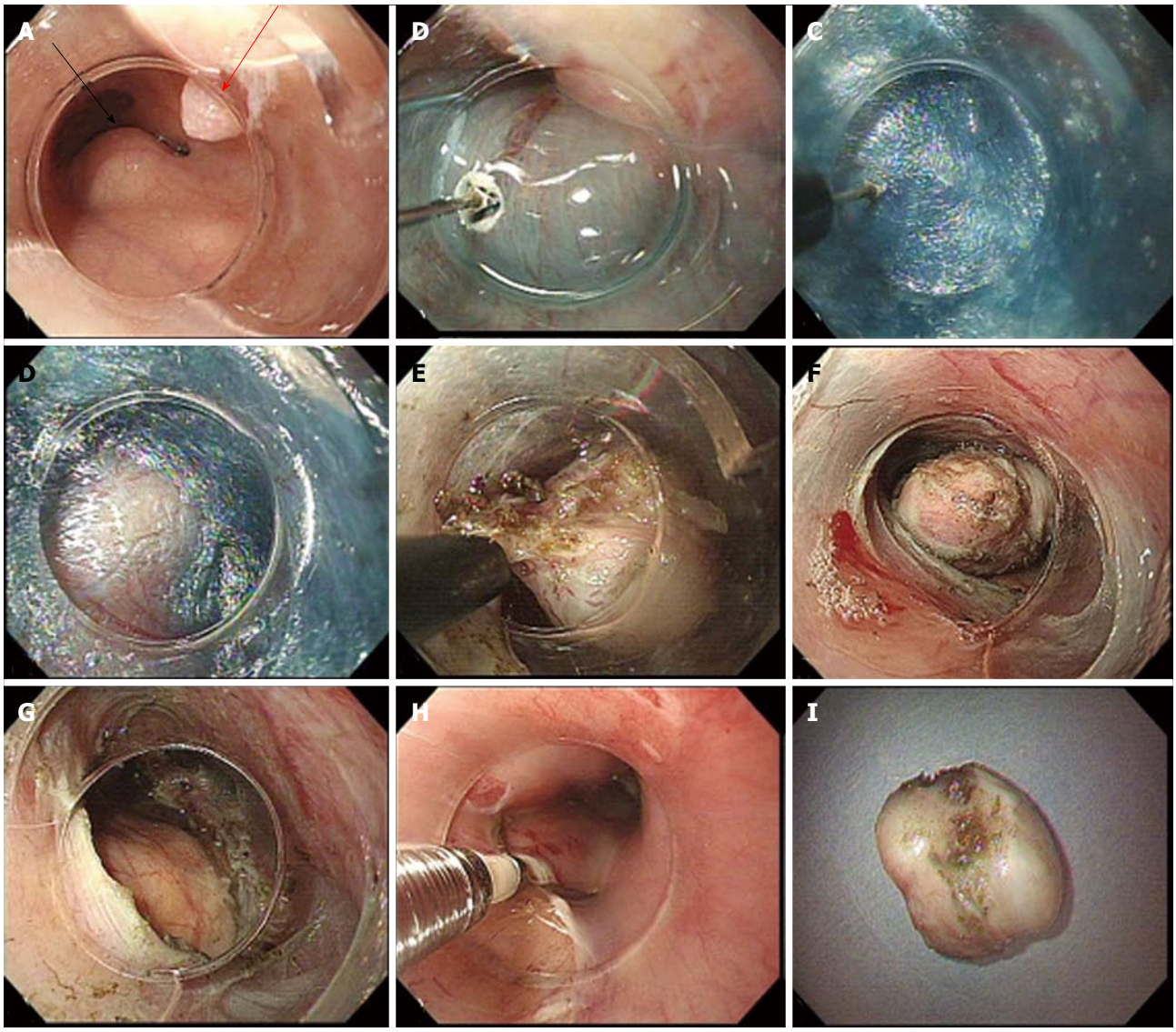

Figure 4 Per-oral endoscopic tumor resection of Leiomyoma. A: Subepithelial tumor (SET) (black arrow) and incidental papilloma (red arrow); B: Mucosal incision with TT knife; C: Creation of submucosal tunnel; D: First encounter with SET in tunnel; E: Dissection of tumor; F: Dissected SET; G: Completed full thickness resection; H: Closure of incision; I: Extracted SET with intact capsule.

the majority being benign. With the moderate yield of EUS, morbidity and costs and surgical resection, a minimally invasive diagnostic and therapeutic procedure is required for the management of SETs. The careful performance of POET is effective and safe, and with continued supportive evidence will likely be performed with increased frequency for resection of most esophageal and gastric cardia SETs, with surgical resection reserved for very large or malignant SETs.

STENTS

Background

When first introduced in 1959, esophageal stents were placed intra-operatively and were indicated only for palliation of dysphagia for non-operable malignant strictures[112]. Endoscopic stents were subsequently introduced in 1977, but were plagued with high complication rates[113]. Since then, SEMS have become widely used for palliation of dysphagia for non-operable malignant esophageal strictures with good safety, efficacy, and cost effectiveness data[114,115]. With the success of SEMS for malignant esophageal disease, there was an effort to expand the use of uncovered/partially covered SEMSS for the use of benign esophageal disease. However, it was found early on that SEMS resulted in increased complications when used for benign disease. Such complications included migration, tissue ingrowth, stent induced stenosis, development of tracheoesogeal fistula, and hemorrhage[116-118].

With the hope to ameliorate the serious issues encountered with SEMS when used for benign disease, manufacturers introduced the fully covered self-expandable metal stents (FCSEMS), fully covered self-expandable plastic stents (SEPS) and biodegradable

Table 2 Series reporting on safety and efficacy of per-oral endoscopic tumor resection

Ref.	Country	No. of patients	Mean tumor size (mm)	Complete resection[b] (%)	Piecemeal or disrupted capsule (%)	Complications (%)
Inoue *et al*[97] 2011[a]	Japan	9	29.4	100 (7/9)	0	0
Cai *et al*[105] 2012	China	1	20	100	NS	100
Gong *et al*[106] 2012	China	12	19.5	83.3 (10/12)	16.7 (2/12)	16.7
Xu *et al*[107] 2012	China	15	19	100	0	13.3
Liu *et al*[103] 2013	China	12	18.5	100	0	66.7
Xu *et al*[108] 2013	China	23	21	100	0	39
Wang *et al*[99] 2013	China	18	33	NS	NS	16.7
Chen *et al*[109] 2014	China	1	#1 = 25 #2 = 30	100	0	0
Kumbhari *et al*[100] 2014	United States	1	60	0	100	NS
Lu *et al*[110] 2014	China	42	12.1	97.7 (44/45)	2.3 (1/45)	15.6
Ye *et al*[104] 2014	China	85	19.2	100	0	9.4
Wang *et al*[98] 2014	China	57	21.5	100	0	21
Lu *et al*[111] 2014[c]	China	18	21	100	0	11.1

[a]The 2 subepithelial tumors (SETs) that could not be resected were 60 and 75 mm in size and an adequate endoscopic field for safe extraction was not possible; [b]Complete resection refers to *en bloc* extraction of the tumor with intact capsule and clear margins; [c]Series included only cardia and gastric SETs. NS: Not specified.

stents (BDS).

Indications

For patients with iatrogenic perforations, tracheoesophgeal fistula, and/or surgical interventions complicated by anastomotic leaks, the treatment has traditionally been surgical. However, with the advent of FCSEMS and fully covered SEPS, these have been increasingly used as means to prevent reoperation and to allow healing to take place. Another emerging use is for refractory benign esophageal strictures in which traditional management with dilation has failed.

Equipment

There are currently a variety of stents available depending on the country. Below is a brief summary (Table 3) of the general differences between the FCSEMS, SEPS and BDS with focus on benign esophageal strictures. Examples of each group are shown in Figure 5.

Technique

Once the stricture has been deemed refractory and stenting is considered, or a defect requires closure, then the choice of stent depends on the position and length of stricture/defect and preference of the endoscopist. The length of the stent should be at least about 3-4 cm longer the stricture/defect. The endoscopist should carefully assess the stricture/defect noting the proximal and distal margins, the distance from the upper esophageal sphincter and LESs. The stricture/defect should be greater than 2 cm distal from the upper esophageal sphincter, as if this distance is less it increase the risk of of pain, globus sensation, aspiration pneumonia or development of tracheoesophageal fistula. If the stent is to be deployed across the LES, a stent with an antireflux valve can be considered if available. Once the location of stent placement is chosen, the proximal and distal margins can be marked endoscopically (submucosal injection of radiopaque substance or placement of clips), by specific anatomic landmarks under X-ray or placement of radiopaque markers on the patient. If simultaneous endoscopic visualization is desired, an ultra-slim scope can be used transnasally. Under fluoroscopic control, the stent is deployed keeping adequate margins on both sides. Endoscopic clips, OTSCs or an endoscopic suturing device can used to decrease the risk of stent migration[34,119-122]. After deployment, the stents will radially expand and shorten reaching their final form.

Efficacy

Efficacy is defined as technical and clinical success. Technical success is defined as successful deployment of the stent and clinical success is the achievement of the intended clinical outcome (improvement in dysphagia, closure and healing of defect). FCSEMS and fully covered SEPS show excellent technical and good clinical efficacy for the closure of benign gastrointestinal disruptions with a technical success of 91% and clinical success of 81%[123]. In the cases where only partial closure fully covered achieved, surgical reinvention is still often avoided[123].

Unfortunately, for benign strictures, the clinical efficacy of FCSEMS and fully covered SEPS is less promising than for benign disruptions with a range of clinical success of 40%-50%[124,125]. Biodegradable stents were introduced with the hopes of improving the shortcomings of modest clinical efficacy of FCSEMS and fully covered SEPS. Unfortunately, the clinical efficacy of BDS has not differed significantly compared to its predecessors, with a mean clinical success rate of 47%[126]. However, in the pediatric population, with the use of custom made plastic stents higher efficacy has been demonstrated. Also, with the stents fastened to a nasogastric tube with an external silicon bar at the

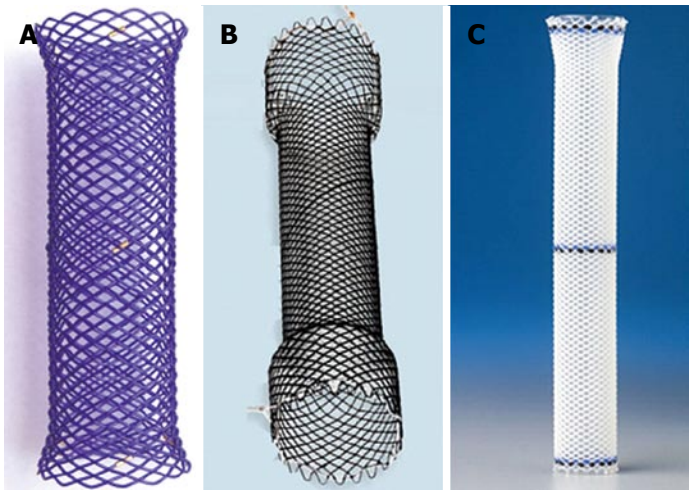

Figure 5 Examples of biodegradable stent, fully covered self-expandable metal stent and self-expandable plastic stent. A: Biodegradable stent (ELLA-CS, Czech Republic) composed of polydioxanone monofilament; B: Fully covered Evolution® stent composed of nitinol silicone coating (Cook, United States); C: Fully covered silicon constructed Polyflex® stent (Boston Scientific, United States).

Table 3 General differences between stents for benign esophageal disease

Stent type	Advantages	Disadvantages
FCSEMS	No requirement for pre-dilation	Expensive
	Recapture is possible	High migration risk
		Increased tissue hyperplasia
SEPS	Cheaper than other covered stents	High migration risk (potentially more than FCSEMS)
	Decreased tissue hyperplasia	Require manual loading
		Require pre-dilation
BDS	No need to remove	Expensive
	Less migration risk	Increased risk of post-procedure pain
		Require manual loading
		Require pre-dilation

FCSEMS: Fully covered self-expandable metal stents; SEPS: Self-expandable plastic stents; BDS: Biodegradable stents.

naris to avoid distal migration, much lower migration rates have been observed[127,128].

Safety

FCSEMS and fully covered SEPS have a modest complication rate, with the most common being stent migration at about 25%-30% with some evidence that the risk of migration is higher with SEPS[129,130]. The risk of migration may also be higher for proximal and anastomotic strictures[131]. Other rare complications of FCSEMS and fully covered SEPS include perforation, tissue hyperplasia, stent induced strictures, hemorrhage, and post-procedure pain. A very rare but dreaded complication is the development of an aortoenteric fistula, which is usually fatal[132-134]. BDS have a lower risk of migration of about 20% and fewer complications overall, but may have increased post-procedure pain[126,135,136].

Conclusion

There is mounting evidence for the efficacy of FCSEMS and fully covered SEPS for closure benign gastrointestinal disruptions with a moderate risk of stent migration. For refractory strictures, the efficacy is less promising likely owing to varying techniques, heterogeneity of patients and the severity of stricture pathology being treated. Depending on the individual case and the experience of the endoscopist, FCSEMS, fully covered SEPS, and BDS are potential options for select patients with refractory strictures. The particular choice of stent depends on the endoscopists preference and experience, perceived risk or migration, tissue hyperplasia and other complications. Hopefully with improvement in stent design, refinement in technique and patient selection, there will be improved clinical efficacy and safety for stents used for benign esophageal strictures.

SUMMARY

Endoscopy has drastically advanced from being primarily a diagnostic tool to becoming the favored modality for treatment of benign disease of the esophagus. Promising efficacy and safety data of POEM and POET is accumulating, and with careful application, these procedures may soon be heralded as the standard of care for various diseases. Despite being a novel procedure, there is extensive experience with the technique used in ARMs in the setting of EMR/ESD. With the early promising results of ARMs, it has the potential to become a prominent treatment of GERD if efficacy confirmed by larger randomized control trials. OTSC usage is becoming widespread and has a remarkably low complication rate with good efficacy in facilitating

the closure of esophageal perforations, fistula, and leaks. At present, the evidence for treatment of benign esophageal disruptions is promising and FCSEMS and SEPS should be considered in their treatment. However, for benign esophageal strictures the evidence for the use of FCSEMS, fully covered SEPS and BDS has been conflicting, but with further improvement in stent design and refinement of technique, there is potential for improved clinical efficacy.

With the ongoing introduction of novel procedures and equipment, it is critical that patient safety remain the top priority. International collaboration in the form of large multi-centered trials provide the opportunity to optimally study safety and clinical efficacy of newly introduced equipment and techniques.

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Peroral endoscopic myotomy

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Abstract

Peroral endoscopic myotomy (POEM) incorporates concepts of natural orifice translumenal endoscopic surgery and achieves endoscopic myotomy by utilizing a submucosal tunnel as an operating space. Although intended for the palliation of symptoms of achalasia, there is mounting data to suggest it is also efficacious in the management of spastic esophageal disorders. The technique requires an understanding of the pathophysiology of esophageal motility disorders as well as knowledge of surgical anatomy of the foregut. POEM achieves short term response in 82% to 100% of patients with minimal risk of adverse events. In addition, it appears to be effective and safe even at the extremes of age and regardless of prior therapy undertaken. Although infrequent, the ability of the endoscopist to manage an intraprocedural adverse event is critical as failure to do so could result in significant morbidity. The major late adverse event is gastroesophageal reflux which appears to occur in 20% to 46% of patients. Research is being conducted to clarify the optimal technique for POEM and a personalized approach by measuring intraprocedural esophagogastric junction distensibility appears promising. In addition to esophageal disorders, POEM is being studied in the management of gastroparesis (gastric pyloromyotomy) with initial reports demonstrating technical feasibility. Although POEM represents a paradigm shift the management of esophageal motility disorders, the results of prospective randomized controlled trials with long-term follow up are eagerly awaited.

Key words: Peroral endoscopic myotomy; Achalasia; Myotomy; Dysphagia

Core tip: Peroral endoscopic myotomy (POEM) is a minimally invasive, scarless approach to Heller myotomy for the palliation of symptoms of achalasia and spastic esophageal disorders. Current data demonstrates short-term success with minimal adverse events. POEM is no longer considered experimental with approximately 5000 procedures performed worldwide. In the future, a personalized approach to POEM will be undertaken with tailoring of the length of gastric myotomy based on intraprocedural physiological measurements. This will allow sufficient reduction in pressure at the lower esophageal sphincter for adequate relief of symptoms but also minimize gastroesophageal reflux.

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INTRODUCTION

Peroral endoscopic myotomy (POEM) is a minimally invasive endoscopic procedure intended for long-term recovery from symptoms of esophageal achalasia. Achalasia is a benign motility disorder of the esophagus which is characterized by incomplete relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophageal body. As the etiology of achalasia is not known, all treatment options are directed at decreasing the resting pressure at the LES.

The first reported endoscopic myotomy in humans was published in 1980[1]. In this report, the myotomy was carried out in an uncontrolled manner by incising the mucosa through to deeper layers of the lower esophageal sphincter with a needle knife. The method achieved technical success in all 17 patients although there was concern as the wound was directly exposed to esophageal and gastric contents and if too deep, there would be a direct perforation to the mediastinum and/or peritoneum. There were three minor bleeding episodes which were controlled endoscopically. The clinical, manometric and radiological postoperative results were promising. However, the direct incision method was not considered a reliable and safe approach and was therefore not adopted by the medical community.

Developments in natural orifice translumenal endoscopic surgery (NOTES)[2] have resulted in a submucosal endolumenal approach for the treatment of achalasia using POEM. Sumiyama *et al*[3] was the first to describe the idea of submucosal tunneling. However, Pasricha *et al*[4] initially described the concept of POEM in 2007 in an experimental preclinical model. This report demonstrated the safety and efficacy of performing a myotomy under endoscopic visualization in 4 pigs after the formation of a submucosal tunnel. Inoue *et al*[5] championed translating this innovative technique into clinical care in 2010 with the first human study reporting favorable results in 17 achalasia patients.

Multiple studies from Asia, Europe and the United States reveal that POEM is a safe and effective therapy for achalasia when performed by expert endoscopists. In addition, the recent white paper summary from the American Society of Gastrointestinal Endoscopy provided substantial data to support the notion that POEM is a promising therapeutic modality[6]. This review illustrates the patient selection and preparation, operative technique, clinical outcomes and future directions for POEM.

PATIENT SELECTION AND INDICATIONS

All patients with symptomatic, manometrically proven, primary idiopathic achalasia are eligible candidates to undergo POEM. Among initial published clinical studies, exclusion criteria included previous esophageal or gastric surgery (including Heller myotomy), sigmoid type esophagus, age under 18 years or inability to undergo general anesthesia. Other less common scenarios that rendered patients unsuitable for POEM included severe erosive esophagitis, significant coagulation disorders, liver cirrhosis with portal hypertension or prior therapy that may compromise the integrity of the esophageal mucosa or could have led to submucosal fibrosis (radiation, endoscopic mucosal resection, radiofrequency ablation, *etc.*). Previous therapy, such as uncomplicated pneumatic balloon dilation and botulinum toxin injection are not contraindications to POEM, although, in these cases inflammatory fibrosis is often encountered during submucosal dissection.

There are now multiple series reporting the technical success, efficacy and safety of POEM in patients who have undergone a prior Heller myotomy[7-9]. Successful POEM in the setting of a Roux-en-Y gastric bypass has also been reported[10] where the extensive adhesions and altered anatomy could have proven challenging for the surgical approach. POEM has also been studied in patients with with sigmoid-type achalasia with similar outcomes as those with a non-sigmoid type esophagus[11]. Age is no longer a contraindication to POEM with successful procedures being performed in those even at the extremes of age. In particular, several series have reported its successful use in the pediatric population[12,13].

Though POEM is classically done for the palliation of symptoms of achalasia, it is being increasingly used for the treatment of other foregut disorders. There are growing reports supporting its use in spastic esophageal disorders such as diffuse esophageal spasm (DES) and Jackhammer esophagus[14-19]. It is potentially more efficacious than even surgical myotomy as it allows myotomy not only of the LES, but also of the esophageal body, where hypertensive contractions occur[15,20,21]. Additionally, POEM has even been reported in the stomach (endoscopic pyloromyotomy) as a treatment strategy for selected patients with gastroparesis[22,23].

EVALUATION AND PREPARATION

It is obligatory that patients have a diagnosis of achalasia or spastic esophageal disorder firmly established based on clinical history, esophageal manometry, contrast esophagram and esophagogastroduodenoscopy (EGD). A standardized validated symptom assessment form is completed by all patients, with the majority of centers using the Eckardt score[24]. The Chicago classification of esophageal motility disorders mandates high resolution

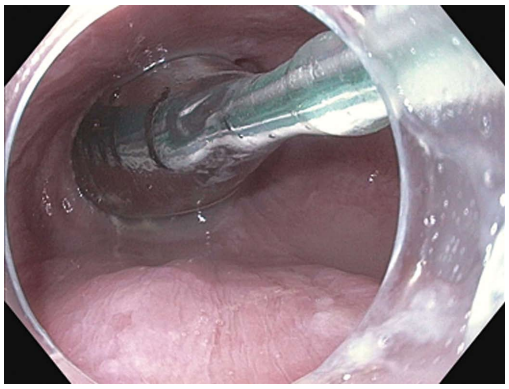

Figure 1 Endosocopic image of the endoluminal functional lumen imaging probe assessing the esophagogastric junction *via* impedence planimetry.

esophageal manometry (HREM) to identify the precise achalasia or spastic esophageal disorder subtype, although the clinical significance of this classification has been recently debated[25]. Computed tomography (CT) is not mandatory, however, some experts find it useful as it provides information on the anatomic features of adjacent structures as well as identifying congenital anomalies or ectopic varices. In addition, CT scan can be an adjunct to contrast esophagram in establishing the presence of a sigmoid-type esophagus.

Our institutional protocol is to perform an EGD on all patients 2 wk prior to their procedure. All patients are placed on a clear liquid diet 2 d prior to this endoscopy and an endoscopic assessment is made of the quantity of residual esophageal contents. If there is persistent solid residue, then even more stringent dietary restriction is advised prior to POEM. This will allow for a clear endoscopic view and may avoid aspiration during induction of anesthesia. Additionally, this evaluation allows for exclusion of underlying malignancy, erosive esophagitis, Barrett's esophagus and Candidal esophagitis. On occasion, a HREM catheter is inserted as passage without endoscopic guidance can be challenging in patients with a tight LES and/or sigmoid esophagus.

In case of use of anticoagulant or antiplatelet therapy, it is generally recommended that these medications be stopped with the exception of acetylsalicylic acid when prescribed as secondary prophylaxis. All patients have a blood type and screen performed on the day of the procedure.

POEM PROCEDURE

Our institutional protocol has been to perform POEM in the endoscopy suite. This is in contrast to most other centers where POEM is performed in the operating room[11,26]. We have performed over 50 cases in the endoscopy unit without a major intraprocedural adverse event. The procedure is performed with the patient in the supine position under general anesthesia with endotracheal intubation and complete paralysis. Our protocol is to use a specialized endotracheal tube that has a taper-shaped cuff with an evacuation port and suction lumen (TaperGuard Evac, Covidien, Mansfield, MA, United States). We have noted that approximately 100mls of fluid is aspirated through this specialized endotracheal tube during each procedure with no episodes of aspiration or pneumonia in our cohort[27].

Carbon dioxide (CO_2) insufflation is mandatory for safe POEM and to reduce the risk of mediastinal emphysema, tension pneumoperitoneum, pneumothorax and air embolization. An arterial line may be inserted such that an arterial blood gas can be performed and CO_2 levels monitored as needed. An indwelling urinary catheter is inserted and a forced air warming blanket is used to cover from the waist down.

The patient's abdomen remains in unrestricted view to allow for an immediate diagnosis of severe pneumoperitoneum. The abdomen is palpated periodically and if tidal volumes begin to diminish or the abdomen is markedly distended, decompression is accomplished using a Veress needle.

A thorough cleansing of the esophageal lumen is performed prior to commencement of the intervention. In certain cases, a therapeutic gastroscope with a 3.8mm working channel (GIF-Q260J; Olympus, Center Valley, PA, United States) equipped with a water jet is necessary. If adherent residue is present on the esophageal mucosa, a soft cleaning cap (Barrx RFA Cleaning Cap - Medium: CP-002A, BARRX Medical Inc., Sunnyvale, CA) can be used to safely scrape off the residue. Broad-spectrum intravenous antibiotics are administered.

Measurements of esophagogastric junction distensibility can be performed using the endoluminal functional lumen-imaging probe (EndoFLIP; Crospon, Galway, Ireland) (Figure 1). This provides a baseline by which the operator can assess the adequacy of the myotomy and may play a role in predicting which patients will likely be non-responders[28-30]. Subsequently, the esophagus is lavaged with 240 mL of sterile saline solution mixed with 180 mg of gentamicin.

A high-definition gastroscope fitted with a transparent cap is used. It is recommend to secure the cap on the endoscope tip with tape as anecdotal reports exist of dislodgement of the cap within the submucosal tunnel. A gastroscope that has a dedicated water jet channel such as the GIF-HQ190/GIF-H180J (Olympus, Center Valley, PA, United States) or EG2990i/EG2990k (Pentax Medical Corp., Montvale, New Jersey, United States) is recommended. For all our procedures, a bottle filled with saline and a second bottle of saline mixed with indigo carmine are attached to the water jet channel *via* a stopcock. Individual foot pedals activate each bottle[31] (Figure 2).

Four step approach to poem

The procedure can be split into four consecutive steps: the mucosal incision, formation of the submucosal tunnel, myotomy and closure of the mucosal incision[32].

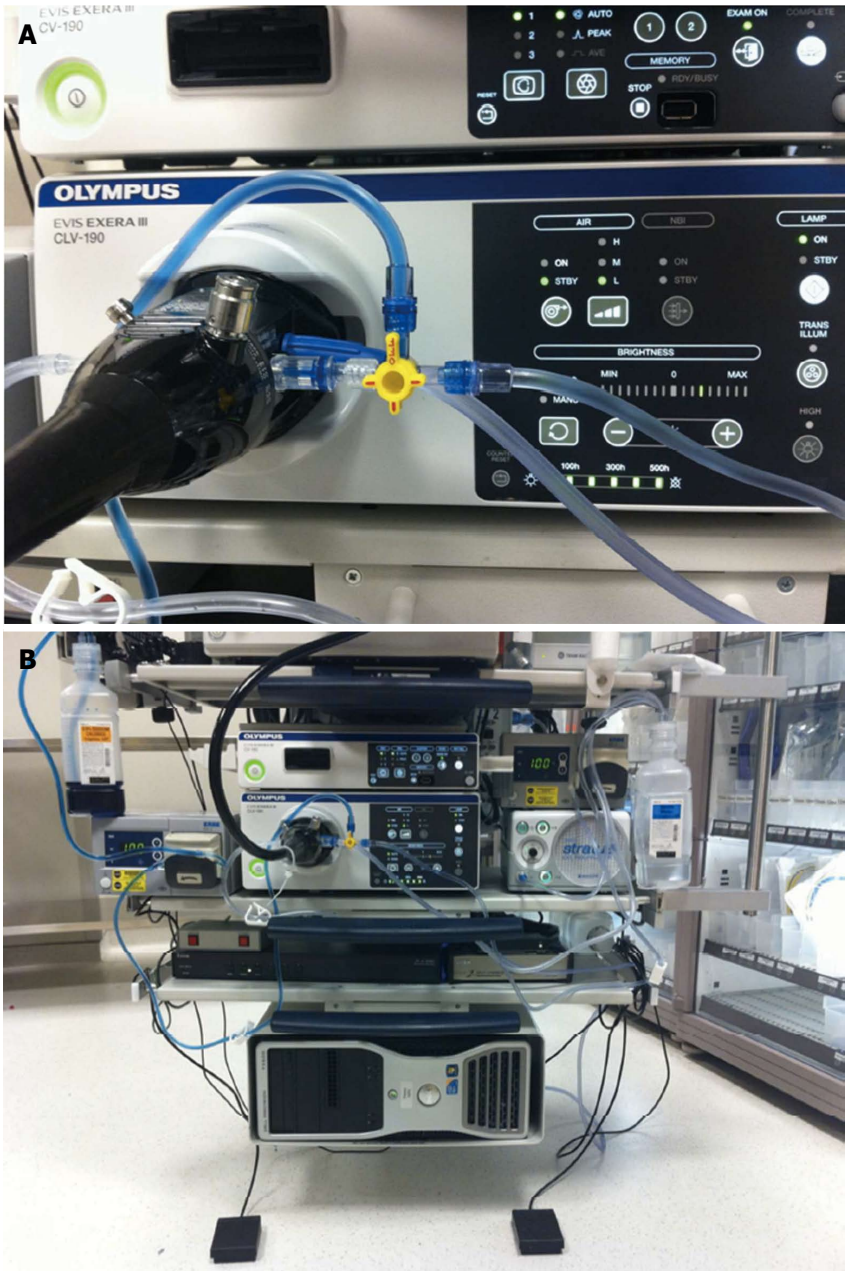

Figure 2 Endoscope setup for jet injection of dyed saline. A: One bottle of saline and a second bottle of saline mixed with indigo carmine are directly connected to the water jet channel *via* a stopcock; B: Separate foot pedals control injection of either pure saline for optimizing visual field or dyed saline for submucosal tunneling.

Step 1: Mucosal incision: The level of the esophagogastric junction (EGJ) is identified and determines the level submucosal tunneling is commenced. In most centers, an anterior (2 o'clock position) is used for the submucosal tunnel and myotomy. However, in some centers a posterior orientation (5 o'clock position) is favored. An anterior myotomy may decrease the damage to the angle of His, a barrier to post-operative GERD. If there is doubt as to the identification of the anterior and posterior walls, water can be injected into the esophageal lumen and will pool on the posterior aspect when the patient is positioned supine.

A submucosal cushion is then made 3 cm proximal to the proposed commencement of myotomy using 0.01% epinephrine, 0.25% indigo carmine and 0.9% saline solution. A 1.5 cm vertical mucosal incision is made using a hybridKnife (HK) (ERBE, Tubingen, Germany) or triangular tip (TT) knife (KD 640 L, Olympus, Center Valley, PA, United States) using a dry cut mode at 50 W on effect 3 (ERBE, Tubingen, Germany) (Figure 3). The gastroscope is then inserted into the submucosal space after dissection of the submucosal fibers at the level of the mucosal incision.

The length of the submucosal tunnel (and hence myotomy) must be determined prior to commencement of the mucosal incision. In patients with achalasia subtype Ⅰ and Ⅱ, a 6-10 cm esophageal myotomy is performed. In patients with spastic esophageal disorders, the length of myotomy is determined based on the proximal extent of the hypertensive contractions on HREM and/or the level of visible spastic contractions seen endoscopically.

Step 2: Creation of submucosal tunnel: The submucosal tunnel is created distally using a technique similar to endoscopic submucosal dissection. Using

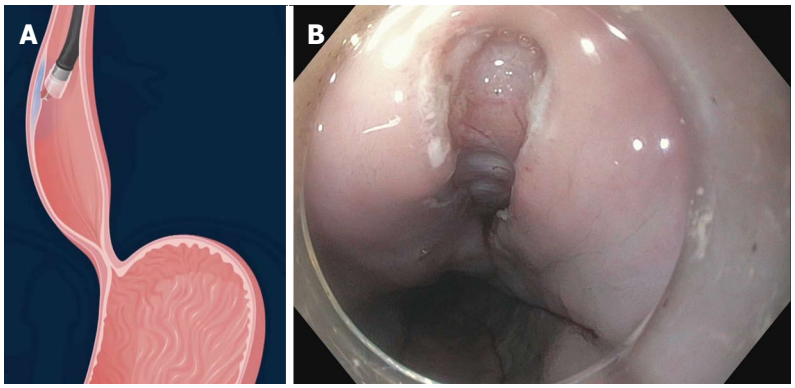

Figure 3 Longitudinal mucosal incision 1.5 to 2 cm on the anterior esophageal wall.

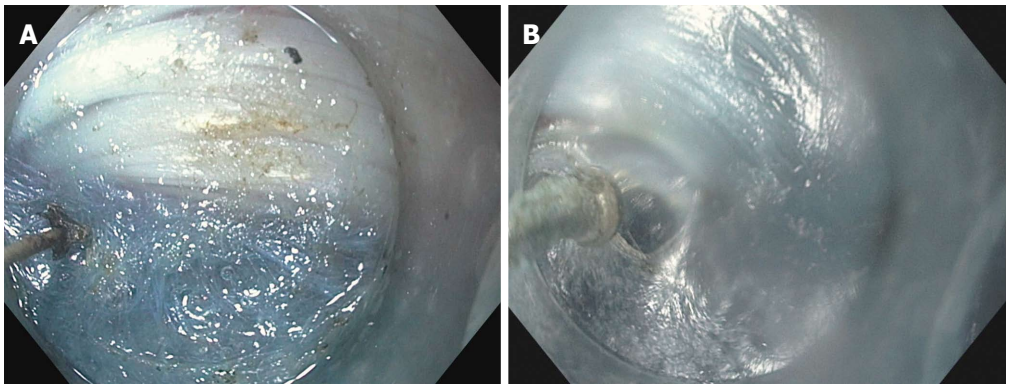

Figure 4 Creation of the submucosal tunnel. A: Dissection of the submucosal fibers using spray coagulation with the triangular tip knife (KD 640L, Olympus, Center Valley, PA, United States); B: Dissection of the submucosal fibers using the hybridKnife (ERBE, Tubingen, Germany) which allows for both submucosal dissection and fluid injection into the submucosal space.

a TT knife or HK, the submucosa is dissected with a no-touch technique using spray coagulation mode at 50 W on effect 2 (ERBE, Tubingen, Germany) (Figure 4). The dissection plane is located nearly on the surface of the muscularis propria. Recurrent jet injection of indigo carmine mixed with saline is done to increase the delineation between the submucosal fibers and muscularis propria whenever the planes become ambiguous (Figure 5). Care must be taken to avoid injury to the mucosal layer during creation of the submucosal tunnel as the mucosal layer is the only barrier between the esophageal lumen and mediastinum after myotomy. Large vessels in the submucosa are coagulated using the Coagrasper (Olympus, Center Valley, PA, United States) in soft coagulation mode at 80 W on effect 5 (ERBE, Tubingen, Germany).

An alternative technique for centers that do not have a water jet for injection is to use the HK (ERBE, Tubingen, Germany). This device obviates the need for multiple accessory exchanges between needle injector and knife as needless submucosal injection using a high-pressure water jet and electrosurgical dissection can both be performed. A randomized controlled trial demonstrated that the HK resulted in statistically significant quicker operating times as compared to using the TT knife. This was primarily the result of a statistically significant lower average number of accessory exchanges during the procedure (2 *vs* 19.2, $P < 0.0001$)[33]. However, the above-described water jet injection method obviates the need for these frequent exchanges as well.

Another technique uses a balloon, such as a standard biliary stone extraction balloon, to dissect the submucosal fibers without the use of electrosurgery. Operators who use this technique claim that it allows for a more rapid creation of the tunnel without substantial bleeding as the vessels are momentarily displaced rather than ruptured using this technique. Proponents of this technique also state that this method is particularly useful at the LES when the space between the muscle and mucosal layer is limited.

The submucosal tunnel is extended 3cm beyond the EGJ (Figure 6). This is essential as an adequate gastric myotomy is considered critical to eradicate the sling and clasp fibers which are considered essential to maintain LES continence[34,35]. The techniques to assess the location of the EGJ include: insertion depth, narrowing of the submucosal space and resistance of passage of the endoscope through the EGJ followed by prompt expansion of the space at the gastric cardia, change in vasculature, visualization of aberrant longitudinal muscle fibers at the EGJ and injection of epinephrine or indocyanine green (ICG)[36,37]. Many of these methods are subjective. Our preference is to use one of two objective techniques: double endoscope

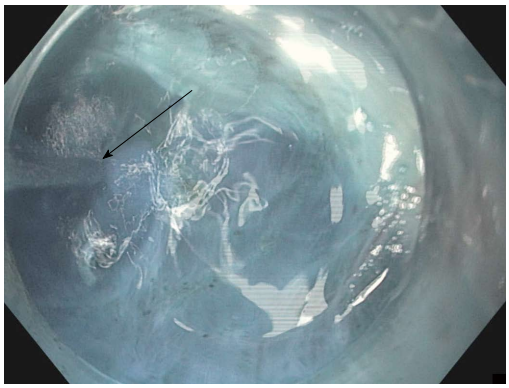

Figure 5 Repeated jet injection (arrow) of dyed saline is performed during submucosal tunneling to improve the demarcation between the submucosal layer and muscularis propria whenever the submucosal dissection plane becomes unclear.

transillumination technique or intraprocedural fluoroscopy[38,39].

Double endoscope transillumination for extent confirmation technique

After the submucosal tunnel is created, the gastroscope is withdrawn and an ultraslim, 5.9-mm endoscope is inserted through the mouth into the stomach and then retroflexed. The cap fitted gastroscope is reinserted alongside the ultraslim gastroscope into the submucosal tunnel. The brightness of the light of the ultraslim gastroscope is reduced while transillumination is switched on for the standard gastroscope within the submucosal tunnel. The transilluminated light is seen by the ultraslim gastroscope and hence allows exact appreciation of the extent of the tunnel into the proximal stomach (Figure 7).

Intraprocedural fluoroscopy

After the formation of a submucosal tunnel, a radiopaque marker (endoscopic clip placed at EGJ on the opposite side to the submucosal tunnel or fluoroscopically guided placement of a 19-gauge needle on the skin) is used to mark the EGJ. The endoscope is then re-inserted to the terminal aspect of the submucosal tunnel. Using a C-arm, a fluoroscopic image is obtained in the anterior-posterior axis. The distance between the jaws of the endoscopic clip or needle, and the endoscope tip is calculated using the known diameter of the endoscope as a scale (Figure 8). This allows for an objective measurement of the length of the submucosal tunnel below the EGJ.

Step 3: Myotomy: Selective myotomy of the inner circular muscle is performed 1cm below the end of the mucosal incision. The HK or TT knife is used to grasp and lift circular muscle fibers followed by cutting with spray coagulation current at 50 W on effect 2 (ERBE, Tubingen, Germany). Selective myotomy of the inner circular muscle, preserving the outer longitudinal esophageal muscular layer is usually preferred during POEM (Figure 9). The selective circular muscle myotomy is intended to prevent the endoscope entering the pleural space and decrease morbidity. However, it can be difficult to accomplish because the longitudinal muscle fibers of the esophagus are very thin, and therefore inadvertent splitting of these fibers often occur during POEM. Either trauma from maneuvering the endoscope in the tunnel, electrocautery damage, or CO_2 insufflation alone can result in splitting of the longitudinal muscle layer and adventitia and hence direct exposure to the mediastinum or peritoneum[32] (Figure 10). Moreover, the ability to differentiate between circular and longitudinal muscular layers becomes particularly challenging at the level of the EGJ and stomach. Therefore, some experts are of the opinion that a full-thickness myotomy at this level is mandated for adequate and long-term reduction of pressure at the LES.

Li *et al*[40] compared the outcomes between 131 patients that underwent selective inner circular muscle myotomy and 103 who underwent full-thickness myotomy. The average procedure times were briefer in the full-thickness myotomy cohort (42 min *vs* 49 min, $P = 0.02$). No difference was found in the frequency of adverse events between the cohorts. During follow-up, clinical success (Eckardt score $\leqslant 3$) persisted for 115/121 (95.0%) of patients in selective inner circular myotomy cohort and 95/99 (96.0%) of patients in full-thickness myotomy cohort ($P = 0.75$). There were no significant differences in absolute (pre and post) or mean reduction in LES pressures between groups (both $P > 0.05$). There was no statistically significant difference in the rate of clinical reflux events (21.2% *vs* 16.5%, $P = 0.38$). The authors concluded that there was no meaningful difference between the two methods in terms of symptom relief and manometric outcomes.

It is believed that selective inner circular myotomy adds an element of extra safety to POEM and hence may lead to easier dissemination, especially when performed by endoscopists with lesser experience. Although the myotomy is not the most challenging part of the procedure, it must be performed carefully such that there is adequate separation of muscle fibers and inadvertent damage to vessels is avoided. Once the myotomy is completed, smooth passage of the endoscope through the area of the LES into the stomach should provide confirmation of complete myotomy.

Step 4: Closure of the mucosal incision: Prior to closure of the mucosal incision, a careful inspection of the submucosal tunnel is performed and any oozing is controlled. Then the esophageal mucosa is interrogated and any laceration or mucosotomy is addressed. Lower esophageal sphincter relaxation is evaluated by retroflexed visualization of the gastric cardia. Repeat EndoFLIP measurements can now be performed to determine post myotomy distensibility.

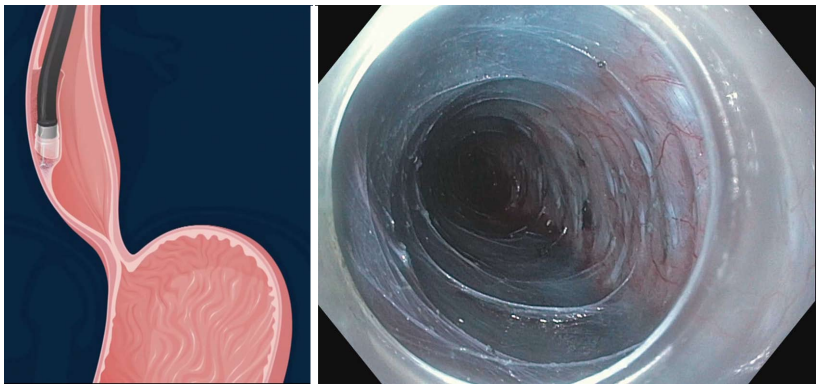

Figure 6 Submucosal tunnel after the submucosal fibers have been dissected away. The myotomy can now be commenced.

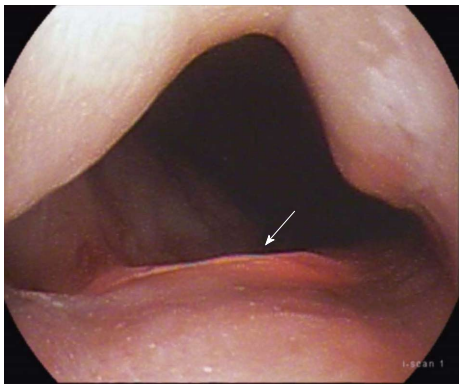

Figure 7 Transillumination can be seen 2 cm below the gastroesophageal junction indicating that the submucosal tunnel can be extended a further 1 cm prior to commencing the myotomy.

The mucosal entry can be closed with endoscopic clips[37,41] or the use of a flexible endoscopic suturing device (OverStitch; Apollo Endosurgery, Austin, TX, United States)[42] (Figure 11). When endoscopic clips are used, the initial clip is deployed at the most distal part of the mucosal incision to facilitate approximation of the incisional borders. Placement of subsequent clips is performed in a proximal direction until complete closure. Salvage closure techniques have been reported when standard methods fail. These include over-the-scope clip and a covered esophageal stent[43-45].

POSTOPERATIVE CARE

Patients are admitted overnight for observation and kept nil per oral. Intravenous prophylactic antiemetics and broad-spectrum antibiotics are prescribed. A contrast esophagram is obtained the following morning and a soft diet is commenced after exclusion of an esophageal leak. Routine thoracic CT scan is not warranted because of the high rate of minor and clinically irrelevant findings[46]. Patients are routinely prescribed broad-spectrum antibiotics for 5 to 7 d. Patients remain on soft diet for 2 wk after which a normal diet can be commenced. In order to avoid any potential damage to the esophageal mucosa, we prescribe twice daily proton pump inhibitor for 2 wk. Follow-up clinic visit to assess for delayed complications and assessment of clinical response (Eckardt score) occur at 3 mo post procedure. Additionally, repeat HREM and esophageal acid exposure testing are ordered routinely.

EFFICACY OF POEM

The published literature to date illustrates that POEM is highly effective in the short-term management of achalasia. In the almost all series, clinical success was defined as postprocedure Eckardt score $\leqslant$ 3. It should be noted that a patient could suffer dysphagia at each meal despite an Eckardt score of 3. Other metrics used are decrease in LES pressure, improvement in esophageal emptying and quality of life. It must be noted that most data are derived from studies that are uncontrolled and open label. Additionally, the follow-up interval is often short and frequently not standardized. Only one prospective multicenter study exists which reports outcomes to 12 mo[41]. The recent white paper summarized data from 14 studies with outcomes based on 804 patients[6]. Clinical success was reported in 82% to 100% of patients with significant reductions in Eckardt score and LES pressure. Several studies have described efficacy based on timed barium esophagram (an objective measurement of esophageal emptying)[42,47,48]. Recent reports have also documented a significant improvement in several measures of quality of life after POEM[42,49].

EndoFLIP has been increasingly reported as a method of assessing the adequacy of myotomy during the POEM procedure. This method involves using a balloon catheter outfitted with a series of electrodes that is placed across the EGJ and allows measurement of luminal diameter, cross-sectional area and balloon pressure *via* impedence planimetry (Figure 12). An index of EGJ distensibility can be determined and this has been shown to correlate better with postoperative symptoms than manometric pressure measurements[50]. Patients within a "sweet spot" of postoperative EGJ distensibility (4.5-8.5 mm^2/mmHg) are almost twice as likely to have optimal symptom outcomes as those outside this window[28].

The literature to date supports the notion that POEM is feasible, safe and efficacious in patients that have undergone prior botulinum toxin injections or pneumatic balloon dilation and is comparable to

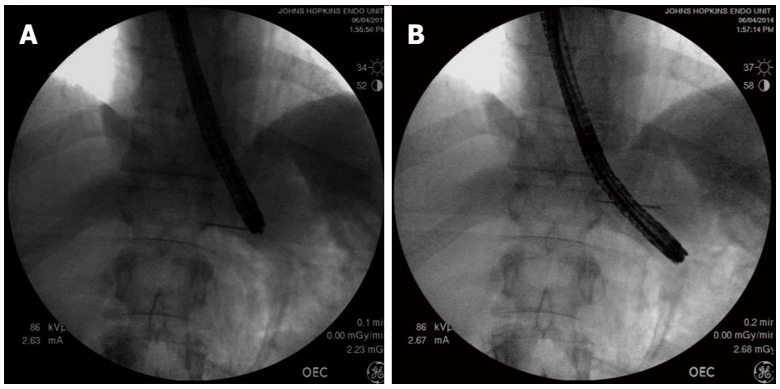

Figure 8 Using fluoroscopy to assess the adequacy of gastric myotomy during peroral endoscopic myotomy. A: The needle is fluoroscopically lined up with the tip of the endoscope and leveled with the EGJ; B: The endoscope has a diameter of 1 cm, and therefore, the endoscope tip is measured to be 3 cm below the needle marking the EGJ. EGJ: Esophagogastric junction.

Figure 9 Selective myotomy of the circular muscle fibers. The longitudinal muscle fibers have been preserved.

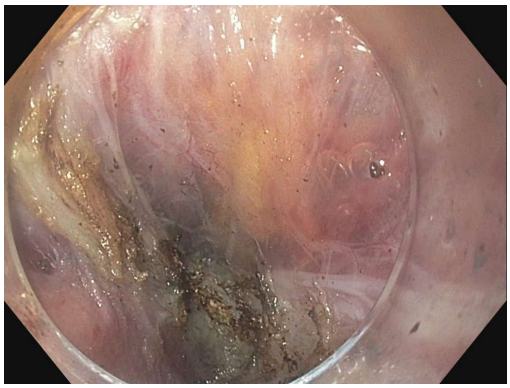

Figure 10 Splitting of the longitudinal muscle fibers despite attempted selective cardiomyotomy. Peritoneal fat can be seen through the translucent adventitia.

patients who are treatment naive[51-53]. In the IPOEMS survey, 40% of patients had undergone POEM after prior endoscopic therapy[36]. The consensus from POEM operators is that botulinum toxin injections injections induce submucosal fibrosis and results in a more challenging dissection (which can be overcome by operator experience) with undiminished efficacy[36]. POEM after prior pneumatic balloon dilation did not render the procedure more technically challenging or increase the rate of complications and the efficacy was undiminished[36].

Relapse or persistence of symptoms after a Heller myotomy happens in 10% to 20% of patients at 2-year follow-up[54]. There are 3 studies that specifically examined the utility of POEM in patients that have undergone a prior Heller myotomy. A prospective study of 12 patients by Zhou *et al*[8] with relapse or persistence of symptoms after Heller myotomy underwent technically successful POEM after a mean of 12 years from the time of the primary Heller myotomy. No major adverse events related to POEM were encountered. Treatment success was achieved in 11/12 (91.7%) patients (mean Eckardt score pretreatment *vs* posttreatment: 9.2 *vs* 1.3; $P < 0.001$) at a mean follow-up of 10.4 mo. Onimaru *et al*[7] reported their series of 11 patients who had relapse or persistent achalasia and had undergone Heller myotomy as initial therapy. Ten patients underwent salvage POEM which was performed successfully without adverse events. One patient responded to pneumatic dilation. At 3 mo follow-up, a significant reduction in Eckardt symptom scores (6.5 *vs* 1.1, $P < 0.001$) and LES resting pressures (22.1 *vs* 10.9 mmHg, $P < 0.01$) were noted. Finally, Vigneswaran *et al*[9] reported 5 patients who had symptom recurrence after Heller myotomy and subsequently underwent POEM. The average procedure time was 149 min. In all patients, there was a significant reduction in average postprocedure Eckardt score (6.8 *vs* 0.6, $P < 0.001$). Therefore, its appears that POEM may be a worthwhile treatment option for patients with relapse or persistent symptoms after Heller myotomy.

While POEM is usually performed for the management of achalasia, preliminary data suggest it is a

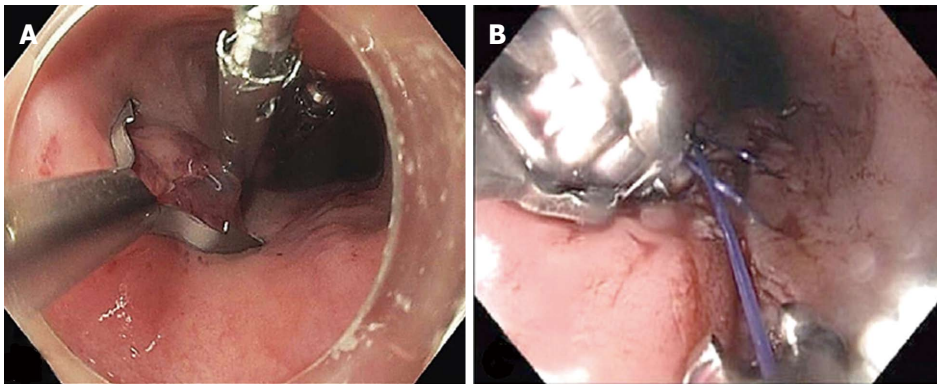

Figure 11 Closure of the mucosal entry after completion of the myotomy. A: A posterior mucosal incision was closed with three endoscopic clips; B: A posterior mucosal incision was closed with a running suture pattern using transoral flexible endoscopic suturing (OverStitch; Apollo Endosurgery, Austin, TX, United States).

viable option for the management of spastic esophageal disorders since it permits myotomy of the proximal esophagus (where hypertensive contractions occur). It is has been suggested that in those patients, a greater improvement in dysphagia is noted compared to chest pain in patients undergoing POEM[21,55]. Based on expert opinion, it is recommended that a longer esophageal myotomy be performed for spastic esophageal disorders and the level of commencement should be based on the findings of HREM and endoscopy[15].

ADVERSE EVENTS

POEM is a safe endoscopic technique associated with a low rate of perioperative and postoperative adverse events when performed by experienced operators.

Intraprocedural adverse events

Subcutaneous emphysema and pneumoperitoneum are often encountered during the procedure and are no longer considered adverse events. Pneumothorax is infrequently encountered and does not usually require treatment as CO_2 is rapidly absorbed. If there is respiratory compromise then a chest tube should be inserted and the procedure continued. In cases of tension pneumoperitoneum a Veress needle can be inserted through the abdominal wall. Excessive hypercarbia resulting from extended CO_2 administration may require the endoscopist to momentarily remove the endoscope from the patient for 5 to 10 min.

The most feared complication is an inadvertent mucosotomy which results in a perforation. As the submucosa and muscle have been dissected, even a small mucosotomy is potentially dangerous. Most mucostomies happen at the level of the LES and cardia as this is the site of narrowing in the submucosal tunnel. If a mucosotomy is identified it should be closed with endoscopic clips. Larger mucosotomies have been closed with a flexible endoscopic suturing device (OverStitch; Apollo Endosurgery, Austin, TX, United States)[56,57]. Other salvage techniques used have included fibrin glue[58] and over-the-scope clips[43]. If the mucosotomy is detected during submucosal tunneling then it should be addressed immediately as delayed closure may result in significant increase is the size of the mucostomy (Figure 13).

Bleeding during submucosal tunneling is not uncommon although the need for specialized interventions is rare (Figure 14). Careful step-wise dissection will allow vessels to be visualized and prophylactically treated using coagulation with the electrocautery knife itself (forced coagulation 25 W effect 2) or hemostatic forceps (Coagrasper; Olympus, Center Valley, PA, United States) for treatment of bigger vessels that are usually encountered in the gastric cardia. If bleeding appears to originate from a vessel along the mucosal surface, hemostasis can be achieved with gentle pressure using the tip of the endoscope for several minutes.

Late advers events

Delayed bleeding has been reported in 0.7% of patients in a large series of 428 patients[59]. Hematemesis with or without chest pain requires an emergent endoscopy and removal of the clips or sutures from the mucosal entry so that the submucosal tunnel and muscle can be assessed. In the aforementioned series, the bleeding point was identified in 2/3 cases and in the third patient there was no focus found and the patient was effectively treated with a Sengstaken-Blackmore tube. It is important to note that hematoma in the tunnel can result in pressure necrosis of the mucosal flap with potentially disastrous consequences. The safety of the Sengstaken-Blackmore tube in this setting is also debated as it can potentially result in pressure necrosis of the already devascularized mucosa.

The most common adverse event with POEM is gastroesophageal reflux (GER). When objective data are reviewed, such as erosive esophagitis on EGD and/or an abnormal acid exposure on a pH study, the prevalence of GER appears to be between 20% to 46%[6]. This is similar to the rates seen with Heller myotomy with partial fundoplication[60,61]. There is no consensus on how to manage patients with objective GER. One center reported the use of transoral endoscopic fundoplication in an patient with GER symptoms refractory to proton pump inhibitor[62].

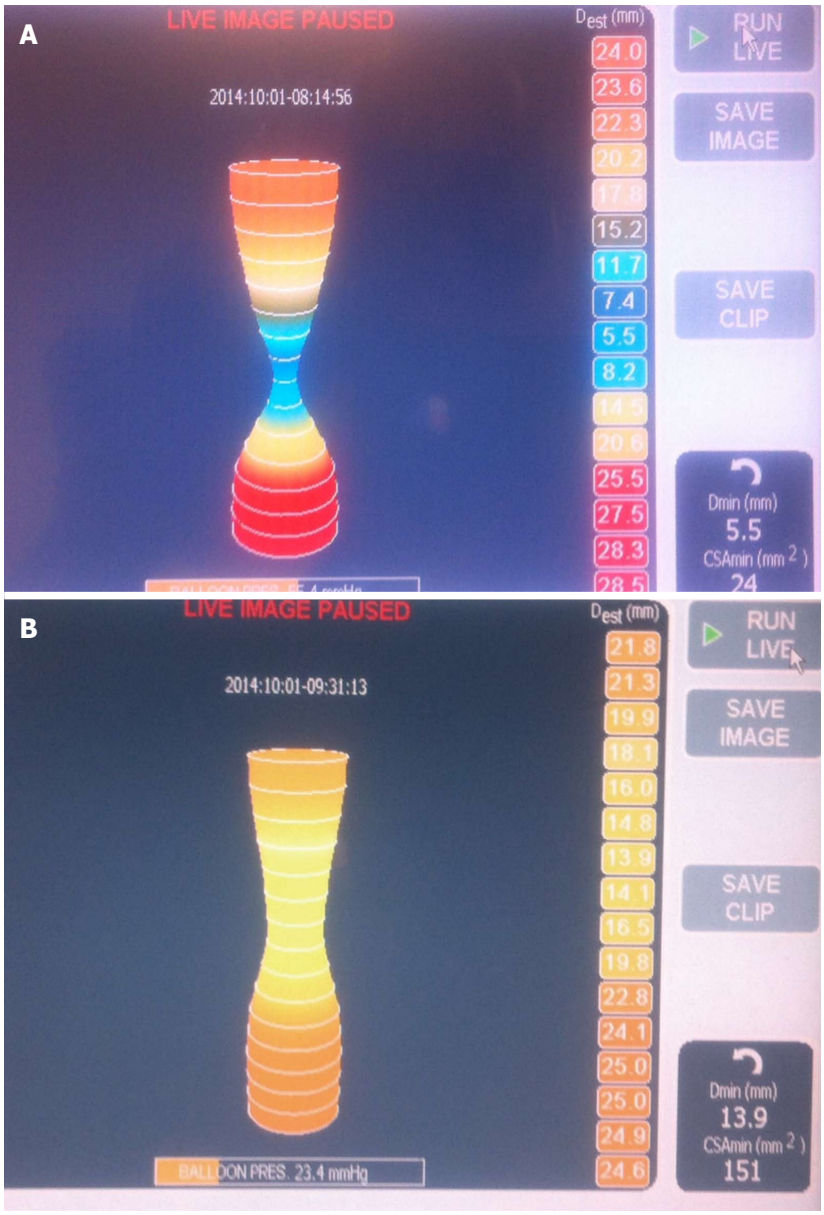

Figure 12 Endoluminal functional lumen-imaging probe (EndoFLIP; Crospon, Galway, Ireland). A: EndoFLIP measurements performed prior to commencement of POEM. A tight hourglass shape at the EGJ can be seen; B: On completion of the myotomy the waist is widened with a corresponding increase in the distensibility index. POEM: Peroral endoscopic myotomy; EGJ: Esophagogastric junction.

POEM IN THE MANAGEMENT ALGORITHM FOR ACHALASIA

For decades, pneumatic balloon dilation and Heller myotomy were the primary methods for the palliation of symptoms of achalasia. POEM appears to have potential advantages over these techniques. POEM appears to be associated with decreased need for retreatment and a lower rate of perforation than pneumatic balloon dilation although no comparative studies exist. There are several uncontrolled studies comparing POEM to Heller myotomy which reveal that they have similar short term efficacy and safety[47,63-65]. Aside from POEM, insertion of self-expandable metallic stents across the EGJ have been studied as an alternative management strategy. Although early reports show promise in terms of symptom palliation, stent migration and intolerance appear to be an issue[66-68].

At this stage, there are no gastrointestinal or surgical society guidelines that have incorporated POEM into their treatment algorithm for achalasia. The American College of Gastroenterology clinical guideline on the management of achalasia cautioned against the use of POEM until the results from further clinical studies are available[69]. Similarly, Vela *et al*[70] in his expert review, comments that POEM should only be performed in the context of clinical trials and that more data is needed before it can be incorporated into the treatment algorithm for achalasia patients. As POEM disseminates worldwide, it is inevitable that it will establish its place in management algorithms of the future.

GASTRIC PERORAL ENDOSCOPIC MYOTOMY (ENDOSCOPIC PYLOROMYOTOMY)

We have published the first human endoscopic pyloromyotomy for medication refractory gastropa-

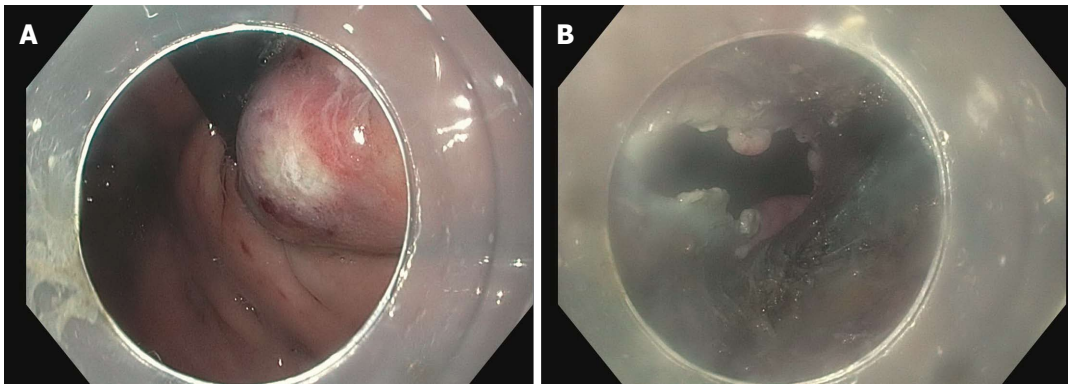

Figure 13 Inadvertent mucosotomy at the gastric cardia. A: Coagulation injury seen on the gastric mucosa at the level of the cardia during the process of submucosal tunneling; B: The procedure continued, however, on completion of the myotomy a frank 12 mm mucosotomy was now present.

Figure 14 Bleeding encountered during gastric myotomy. This was treated with the use of coagulation graspers.

resis[22]. One year later Shlomovitz *et al*[23] reported gastric peroral endoscopic myotomy in 7 patients with gastroparesis. Six of the 7 patients experienced significant improvement in symptoms with normalization of gastric emptying seen in 4 out of 5 patients. This procedure appears viable and can be executed using similar techniques to that of esophageal POEM. It should be noted that only a subset of patients with refractory gastroparesis are likely to benefit from this approach.

COMMENCING A POEM PROGRAM

It is general consensus that institutions commencing a POEM program do it with institutional review board approval[36]. POEM is a technique that requires a unique set of skills combining good endoscopic manipulation and recognition of anatomical structures. In particular, knowledge of the EGJ anatomy and pathophysiology of achalasia is necessary. Of significant importance, is the maintenance of a consistent team throughout the learning curve. This includes nursing as well as anesthetic staff. Additionally, knowledge of the use of accessories necessary to deal with complications is mandatory. Expert operators propose that an efficient training method involves careful observation of POEM by an expert, experience using live animal models and then performing the procedure in humans with a proctor present.

The learning curve for POEM has not been clearly defined. Kurian *et al*[71] used the duration of the procedure per centimeter of myotomy and the incidence of inadvertent mucosotomies and calculated that the learning curve appeared to plateau at approximately 20 procedures. Teitelbaum *et al*[72] found that reduction in time for the mucosal entry and myotomy as well as reduction in the incidence of inadvertent mucosotomies occurred at a "learning rate" of 7 procedures. Expert operators comment that the creation of the submucosal tunnel, particularly at the LES, is likely the most difficult aspect of POEM.

FUTURE DIRECTIONS

Given that achalasia is a chronic disease, long-term outcomes for POEM are essential. Furthermore, POEM needs to be compared to Heller myotomy and pneumatic balloon dilation in multicenter prospective randomized controlled trials.

Progress is being made to simplify POEM in order to increase its efficiency and safety. We published our experience of a novel technique of "auto-tunneling" during POEM in 5 pigs[73]. After creation of the submucosal bleb at the site of the mucosal entry, a proprietary submucosal lifting gel (Cook Medical, Winston-Salem, NC, United States) was injected and resulted in a complete submucosal tunnel to the level of the EGJ. This and other innovative modifications may alleviate current technical challenges.

The most contentious issue surrounding POEM remains the frequency and clinical importance of gastroesophageal reflux. Rigorous evaluations of patients post POEM using pH measurements are required in patients from the East and West. Individualizing the length of the gastric myotomy based on the results of EndoFLIP may reduce the incidence of this problem. Additionally, performing a transoral partial fundoplication in all patients or those that have abnormal acid exposure on post procedure testing may improve outcomes.

Further investigation needs to be performed to

study other technical considerations for POEM. Is an anterior or posterior myotomy the preferred approach? Is it cost-effective and safe for POEM to be performed in the endoscopy unit? Is same day discharge suitable if an immediate contrast esophagram demonstrates no extravasation? These, as well as other questions, will need to be answered by high quality controlled trials.

CONCLUSION

POEM likely represents the first sentinel application in NOTES and has the potential to supplant the current treatment methods for achalasia. It fulfils an important clinical need as both pneumatic balloon dilation and Heller myotomy have their short comings. POEM is an elegant minimally invasive treatment with a short-term clinical response of 82% to 100% and with a low risk of adverse events. The results of prospective multicenter randomized controlled trials are awaited.

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MINIREVIEWS

Current status of peroral cholangioscopy in biliary tract diseases

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Abstract

Peroral cholangioscopy (POC) is an important tool for the management of a selected group of biliary diseases. Because of its direct visualization, POC allows targeted diagnostic and therapeutic procedures. POC can be performed using a dedicated cholangioscope that is advanced through the accessory channel of a duodenoscope or *via* the insertion of a small-diameter endoscope directly into the bile duct. POC was first described in the 1970s, but the use of earlier generation devices was substantially limited by the cumbersome equipment setup and high repair costs. For nearly ten years, several technical improvements, including the single-operator system, high-quality images, the development of dedicated accessories and the increased size of the working channel, have led to increased diagnostic accuracy, thus assisting in the differentiation of benign and malignant intraductal lesions, targeting biopsies and the precise delineation of intraductal tumor spread before surgery. Furthermore, lithotripsy of difficult bile duct stones, ablative therapies for biliary malignancies and direct biliary drainage can be performed under POC control. Recent developments of new types of conventional POCs allow feasible, safe and effective procedures at reasonable costs. In the current review, we provide an updated overview of POC, focusing our attention on the main current clinical applications and on areas for future research.

Key words: Peroral cholangioscopy; Biliary tract disease; Direct visualization; Indeterminate biliary strictures; Bile duct stones

Core tip: Peroral cholangioscopy is a rapidly developing endoscopic technique that provides the possibility to directly explore the bile duct, thereby increasing diagnostic accuracy in selected cases. Less expensive and safer than in the past, the field of applications of peroral cholangioscopy, through the development of new dedicated accessories, has been recently expanded and includes several therapeutic options such as the lithotripsy of difficult bile duct stones, ablative therapies for biliary malignancies and direct biliary drainage.

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INTRODUCTION

Since the 1970s, the dream of all biliopancreatic endoscopists was the ability to directly explore the bilio-pancreatic tree. The first cholangioscopic mother-baby scope system appeared to realize this ambition; however, the technique was too rudimentary, cumbersome, labor intensive and time-consuming because the scopes were very fragile, and two highly skilled endoscopists were required to perform the procedure. Therefore, the effect on clinical practice was marginal and was strictly confined to the research field[1].

In 2005, the advent of new types of peroral cholangioscopes led to renewed interest in endoscopic visualization of the biliary tree. Several technical improvements were introduced, and the leading one was the single-operator system. Furthermore, the endoscopic image quality was progressively improved, and the size of the working channel increased. All these technical improvements have led to an increased diagnostic accuracy.

The aim of the current review is to provide an updated overview on peroral cholangioscopy, focusing our attention on the main current clinical applications and on areas for future research.

TECHNICAL ASPECTS

Currently, two different systems for the direct visualization of the biliary tree are available. The first one, the so-called indirect peroral cholangioscopy, is based on a catheter with an optical probe inside that is inserted within the duodenoscope. SpyGlass® (Boston Scientific, Natick, MA, United States) is the most frequently used and widely diffused probe; the second system is based on an ultraslim upper endoscope (direct peroral cholangioscopy).

Indirect peroral cholangioscopy

The SpyGlass® system is inserted through the instrument channel of the duodenoscope, and the previous placement of a guidewire into the biliary tree is generally recommended. The insertion of the cholangioscope into the bile duct is one of the most challenging aspects of the technique because it can damage the cholangioscope. Once inside, the SpyScope has two dials that allow for four-way tip deflection. The SpyScope has a 10 French outer diameter, is 230 cm in length, and houses four channels: a 1.2-mm instrument channel, two 0.6-mm independent air and irrigation channels, and the 0.9-mm channel used for the fiberoptic probe. This latter channel is a 6000 pixel,

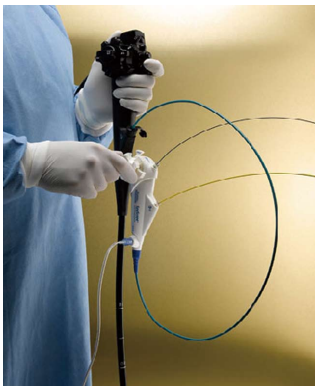

Figure 1 SpyGlass® (Boston Scientific, Natick, MA, United States).

reusable probe with a camera in its distal portion that conducts light and acquires and transmits images. The quality of the endoscopic images can be adjusted by moving the probe forward and backward throughout the procedure. The working channel allows the passage of biopsy forceps (SpyBite®) and dedicated accessories, such as the Holmium laser, for the intraductal fragmentation of non-removable stones (Figure 1).

Similar to the SpyGlass scope is the Polyscope® (Polyscope system; Polydiagnost, Pfaffenhofen, Germany), which consists of a detachable flexible endoscope system available in 8 Fr (185 cm length) with separate optical, working/irrigation (1.2 mm), illumination, and steering channels (Figure 2). There are few differences between the two systems, as summarized in Table 1, but potentially the most important one lies in the image quality because the optical fiber has 10000 pixels of definition; however, the angle of view (70°) is the same as in the SpyGlass scope.

Direct peroral cholangioscopy

Ultraslim endoscopes present larger outer diameters, generally 5-6 mm; therefore, they can be used only after a large endoscopic sphincterotomy and/or sphincteroplasty. The use of this system is definitely more challenging because of the significant difficulties that can be encountered in the initial insertion into the biliary tree as a result of the looping and in remaining anchored inside the duct. Therefore, a 0.025-0.035 inch diameter super-stiff guidewire previously placed within the intrahepatic duct is mandatory to introduce the scope into the acute angle of the biliary system from the second part of the duodenum. Once the duodenoscope is removed, the ultraslim endoscope is then advanced over the guidewire. Large loop development is common, particularly within the gastric fundus and the deep portion of the second part of the duodenal lumen. Hence, several accessories may be useful to successfully advance the ultraslim scope into the biliary tree. Recently, two techniques for an ultraslim endoscopic peroral cholangioscopy (POC) have been reported. The implementation of an intraductal 5 French balloon catheter that is inserted

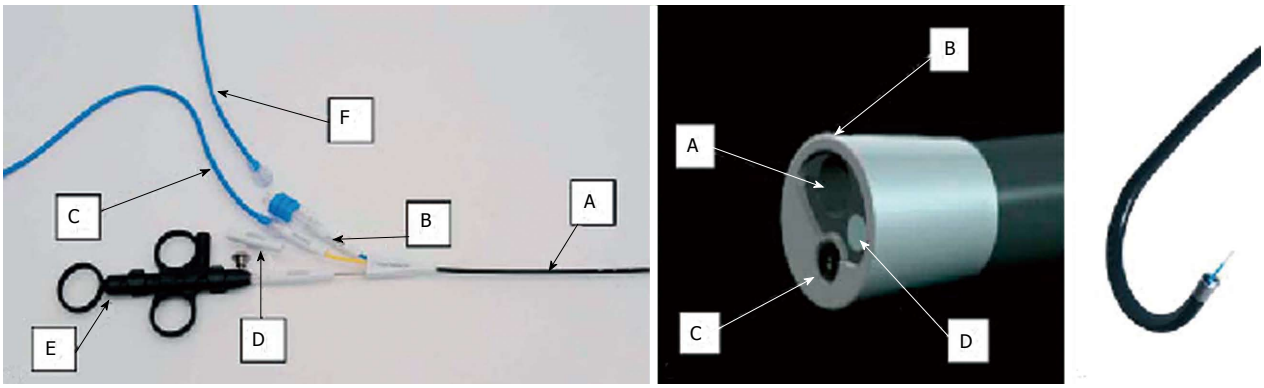

Figure 2 Polyscope system (Polydiagnost, Pfaffenhofen, Germany).

Table 1 Comparison of different equipment for indirect peroral cholangioscopy

Characteristics	Spyglass	Polyscope
Optics resolution	6000 Pixel	10000 Pixel
Working channel	1.2 mm	1.2 mm
Viewing angle	70°	70°
Outer diameter	10 Fr	8 Fr
Re-useable	Yes	Yes
Optical channel hermetically close	No	Yes (The optical fiber doesn't need to be sterilized; this prolongs its life cycle)
Steerability	4 way	1 way (With locking of the bending and rotating of the tip)
Compatibility with existing endoscopy tower	No (You have to buy a complete endoscopy tower system)	Yes (You can use, through adapters an existing endoscopy tower in the Hospital)

and fixed within a branch of the intrahepatic duct or proximally to a stricture has been proposed[2]. This technique facilitates the advancement of the ultraslim scope and the cannulation of the bile duct; however, it presents several drawbacks: the balloon must be withdrawn from the working channel of the scope for interventional procedures, and this maneuver can provide technical difficulties in maintaining the desired position; in addition, the balloon placement within the intraductal branches is not always easily reached. The implementation of the balloon doubles the success rate of direct peroral cholangioscopy from 45.5% with only the guide-wire in place to greater than 95% using a 5 F balloon catheter.

Notably, an anchoring balloon produced by Cook Medical (Winston-Salem, NC, United States) was removed from the market after a fatal complication because of an air embolus[3]. This development represents the most worrisome complication that can develop during a cholangioscopy; therefore, the use of CO_2 rather than room air is mandatory.

An overtube balloon-assisted cholangioscopy has also been proposed with successful results[4-9]. This device is generally adapted from the overtube of either a single or double-balloon enteroscope; however, these overtubes are too large in diameter for an ultraslim scope, making the manipulation cumbersome[4,10].

An overtube allows the right position to be obtained by securing the endoscope and preventing loop formation during advancement; it also provides an easier access to the papilla. Several techniques have been described to achieve easier cannulation of CBD, including the inflation of the overtube balloon in the distal gastric antrum rather than in the duodenal bulb, which may or may not make a J-turn maneuver right in front of the papilla[11].

CLINICAL APPLICATIONS

Twenty-five years ago, endoscopic retrograde cholangiopancreatography (ERCP) was the gold standard for the diagnosis of biliary diseases. Currently, that role has been almost completely replaced by other imaging modalities, including endoscopic ultrasound, magnetic resonance (MRI) and computed tomography (CT). However, the accuracy of these methodologies does not always allow for a definitive diagnosis. Therefore, the necessity of direct viewing and tissue sampling has always been claimed as a demanding goal in selected cases. Both direct and indirect cholangioscopy offer great advantages in terms of diagnostic and therapeutic options, as reported in the details in Table 2. Nevertheless, the main field of application of cholangioscopy is the work-up of indeterminate biliary strictures and, less frequently, the treatment of difficult bile duct stones.

Indeterminate biliary strictures

Direct visualization of biliary strictures is one of the most interesting applications of cholangioscopy, and it allows the physician to improve the diagnosis to plan the most suitable treatment. Indeterminate biliary strictures, in which a diagnosis has not been reached after standard procedures have been performed (*i.e.*, CT, RMN, or ERCP with brushing), is the initial and natural field of application of cholangioscopy.

Table 2 Diagnostic and therapeutic applications for cholangioscopy

Diagnostic applications		Therapeutic applications	
Common	Uncommon	Common	Uncommon
Indeterminate biliary strictures	Biliary cyst evaluation	Lithotripsy for choledocholithiasis	Biliary guidewire placement
Verification of bile duct stone clearance	Bile duct ischemia evaluation (post-liver-transplant)		Transpapillary gallbladder drainage
Staging of cholangiocarcinoma	Ductal involvement in ampullary adenoma		Foreign body removal (*e.g.*, stent)
	Hemobilia		

Currently, the visual criteria for malignancy are not fully standardized, and clinical experience interpreting cholangioscopic visual findings is still limited[12].

Criteria highly suggestive for malignancy include dilated and tortuous "tumor vessels" (also known as "capillary signs"), intraductal nodular or papillary masses, and oozing and irregular vascular patterns with an irregular surface. A benign condition should be considered when a smooth or fine granular surface structure without neovascularization or intraductal mass is observed[13,14]. The diagnostic accuracy of the "tumor vessel" sign for malignancy has been evaluated in 63 patients with indeterminate strictures, reporting a sensitivity of 61% and a specificity of 100% with excellent interobserver agreement (100%)[15].

A definitive diagnosis requires histological assessment. Several prospective trials have shown enthusiastic diagnostic accuracy results achieved with cholangioscopic-direct tissue sampling. Draganov *et al*[16] compared three sampling techniques during the ERCP: standard cytology brushing *vs* standard forceps biopsies *vs* SpyBite miniforceps biopsies. The authors enrolled 26 patients with biliary strictures, and the sample quality was adequate in 25 of 26 of the cytology brushings (96%), in 26 of 26 of the standard forceps biopsies (100%) and in 25 of 26 of the SpyBite miniforceps biopsies (96%). Three high-quality prospective trials showed a diagnostic accuracy of SpyBite forceps biopsy for indeterminate biliary lesions ranging from 72% to 85%, with a sensitivity of 49% to 82%, a specificity of 82% to 100%, a positive predictive value of 100% and a negative predictive value of 69% to 100% (Table 3)[12,16,17].

Although the high values of both the positive predictive value and specificity did not differ from those observed with traditional sampling techniques (*i.e.*, brushing and standard forceps biopsies), the interesting finding was the high sensitivity and negative predictive value, likely because of the possibility of directly targeting the altered mucosa. Although the SpyBite miniforceps biopsy showed expected disappointing

Table 3 Results of cholangioscopic-guided biopsies in indeterminate lesions

Ref.	Sensitivity	Specificity	Negative predictive value	Accuracy
Ramchandani *et al*[17]	82%	82%	100%	82%
Chen *et al*[18]	49%	98%	72%	75%
Draganov *et al*[16]	76.5%	100%	69.2%	84.6%

results for extrinsic lesions, with a sensitivity of only 8%, the sensitivity of the SpyGlass visual impression alone was less severely compromised (62%)[12].

Concerning extrinsic compression, the specificity is unavoidably reduced when direct visualization is solely used because it can be secondary to benign conditions, and in the case of several benign intraductal diseases, such as primary sclerosing cholangitis (PSC), it can present irregular biliary mucosa without harboring malignancy[18].

Nevertheless, it should be noted that in a prospective trial enrolling 53 patients with PSC and dominant stenosis, cholangioscopy, which was performed using a 9 Fr cholangioscope, was found to be significantly superior to ERCP for detecting malignancy in terms of its sensitivity (92% *vs* 66%), specificity (93% *vs* 51%), PPV (79% *vs* 29%) and NPV (97% *vs* 84%), respectively[19]. In patients with PSC, the main limitation is that the small diameter of their ducts frequently does not allow endoscope passage[19,20].

Image-enhanced cholangioscopy techniques have been proposed to improve diagnostic accuracy, particularly through new techniques that are currently being investigated, including chromocholangioscopy and narrow band imaging. Only limited experiences with chromocholangioscopy have been reported[21,22]. Hoffman *et al*[22] prospectively enrolled 55 patients who underwent chromoendoscopic cholangioscopy for biliary strictures or filling defects as a result of various etiologies (orthotopic liver transplantation, PSC, idiopathic). After the initial inspection of the bile duct, 15 mL of methylene blue (0.1%) was administered *via* the working channel of a Pentax "baby" cholangioscope, and the lesions were judged according to the macroscopic type and staining features. The authors identified characteristic surface and staining patterns in chronic inflammation, dysplasia and ischemic-type biliary lesions; in particular, they found that homogeneous staining predicted the presence of normal mucosa, the absence of staining predicted circumscribed lesions, and the diffused staining of such lesions represented neoplastic changes or inflammation. Unfortunately, these findings have not been confirmed by other studies, and their clinical usefulness remains limited.

Narrow band imaging (NBI) was developed by the Olympus medical system and is based on narrowing the bandwidth of spectral transmittance, resulting in optical color separation. In particular, the shorter band

(415 nm) is thought to provide information regarding the capillary and pit patterns of the superficial mucosa, whereas the longer band (540 nm) provides more information regarding thicker capillaries in slightly deeper tissues. NBI is available on a few models of cholangioscopes. The literature concerning NBI application in cholangioscopy is limited to case reports and small case series[23-25].

Based on these preliminary experiences, it appears that the addition of NBI to the usual inspection with conventional white light cholangioscopies increases the ability to identify unknown strictures and might be helpful in differentiating benign from malignant strictures. Azeem *et al*[26] recently published the results of a prospective study conducted on a total of 30 patients with PSC using NBI and high-resolution peroral video cholangioscopy with NBI-directed biopsies of suspicious lesions. The goal was the early detection of cholangiocarcinoma and high-grade dysplasia and the identification of candidates for liver transplantation. Even if there was a 48% increase in suspicious lesions biopsied with NBI compared to white-light imaging, the NBI-directed biopsies did not improve the dysplasia detection rate. Additional experience is required to assess the exact role of NBI in detecting dysplasia.

Theoretically, systems with a higher image quality definition should allow a better identification of such alterations; however, comparative studies focusing on this issue have not been conducted. In 2012, we published a case-series describing the clinical usefulness of peroral cholangioscopy that implements a new type of cholangioscope, the Polyscope®, which enhances image quality as a result of the 10000 pixel definition[27]. Peroral cholangioscopy was performed in 12 patients with different indications: 4 patients with strictures that developed after orthotopic liver transplantation and were suspected of being ischemic biliary lesions; three patients in which the indication was indeterminate biliary strictures, three patients in which retained bile duct stones were suspected, and finally two cases in which a cholangioscopy was performed for evaluating the intraductal spread of adenomatous tissue after ampullectomy. All the peroral cholangioscopies were successful, no procedure-related morbidity was reported and a correct diagnosis was reached in all the patients.

Missed stones and difficult bile duct stone treatment

The diagnosis of biliary stones is easily obtained using imaging techniques that are routinely available. However, these techniques are often insufficient because small stones can be missed and larger stones can block a duct, thus preventing the passage of contrast and avoiding detection during an ERCP. Indeed, it has been shown that previous ERCPs failed to correctly identify choledocholithiasis in 8%-16% of cases that were referred for a SpyGlass choledochoscopy[17,28]. In a study conducted in patients with primary sclerosing cholangitis, stones were not detectable in a cholangiography in approximately 30% of cases (7 out of 23 patients)[20]. In a multicenter study, stones were missed in 29% of cases that underwent an ERCP for different indications[12].

The most interesting feature of cholangioscopy is the possibility of fragmenting difficult-to-remove stones for which conventional techniques have failed. The "difficult stones" may result from several factors related to size, shape, texture or position. In these cases, intraductal electro-hydraulic (EHL) or laser lithotripsy (LL) under direct vision may be performed. Probes that pass through the accessory channels of cholangioscopies for EHL or LL are commercially available. These probes must be positioned close to the stones to increase effectiveness and reduce possible complications, thereby avoiding potentially dangerous shock waves delivered to the bile duct wall. Several studies have reported high success rates in clearing the bile ducts of stones after a cholangioscopic EHL or LL, ranging from 80% to 100%; these results are frequently achieved in only one session[12,29]. In the case of intrahepatic stones, the thinner LL probe is generally preferred to the EHL probe, whereas the EHL is the most widely used technique, particularly with the SpyGlass system, because of the dedicated irrigation channel providing the flowing water that is required to perform the EHL.

Uncommon applications of cholangioscopy

Several infrequent applications of cholangioscopy have been described, such as the study of cystic lesions of the biliary tree[30], the evaluation of ductal involvement in ampullary neoplasms[27], the diagnosis and treatment of cases of hemobilia as a result of rare causes[31,32], the identification of biliary varices in patients suffering from portal hypertension[33] and the use of different ablative therapies for intraductal tumor lesions, such as Nd-YAG laser photo-ablation, argon plasma coagulation or brachiotherapy for mucin-producing bile duct tumors[24]. Anecdotal cases of the cholangioscopy-assisted removal of stents that migrated proximally, targeted placements of guide-wires, transpapillary gallbladder drainage in cholecystitis and foreign body extractions have also been reported.

One interesting field of application of cholangioscopy is the evaluation of the biliary tract lesions in liver transplant patients or the treatment of liver complications after surgical resection or anti-tumoral therapies (*i.e.*, transarterial chemoembolization, TACE). In a study of 20 liver transplant patients, direct cholangioscopy helped identify the biliary stricture etiologies, such as ischemia, scar tissue, intraductal clots and retained suture material, that were otherwise missed by the ERCP[34].

The usefulness of cholangioscopy in the management of complications after the anti-tumoral treatment of hepatocarcinoma has also been reported by our group. In 2011, we described a choledochoscope-assisted percutaneous fibrin glue sealing of a bile leak

complicating a TACE of a nodule of hepatocellular carcinoma after conventional ERCP treatments had failed[35]. An inverse rendezvous procedure was successfully performed, allowing the insertion of the percutaneous wire-guided choledochoscope (Polyscope system) into the biloma and the injection of fibrin glue around the distal opening of the bile leak, allowing the direct closure of a fistula.

SAFETY

Peroral cholangioscopy is generally considered a safe procedure; however, cases of cholangitis, pancreatitis, bleeding and infection have been reported[15,36,37]. In particular, the most commonly reported complication is cholangitis, which is reported in up to 14% of cases[36]; hence, prophylactic antibiotics are mandatory. Chen *et al*[12] conducted a large, prospective, international, multicenter study using the SpyGlass system and reported an overall complication rate of 7.5% (17/226); the most frequent adverse event was early onset cholangitis. All the episodes were resolved without sequelae. Aspiration pneumonia is theoretically possible because of the large amount of normal saline generally used. Air embolism is a rare but fatal complication associated with direct peroral cholangioscopy[3]; therefore, CO_2 insufflation is strongly recommended rather than room air.

FUTURE APPLICATIONS

Cholangiocarcinoma has one of the worst prognoses of virtually all tumors, with a 5-year survival rate lower than 5%[38]. The early diagnosis of biliary preneoplastic lesions could reasonably identify patients who are at an increased risk of developing cholangiocarcinoma. Biliary duct pathology may be evaluated by intraductal endoscopy, but feasibility studies are required to test the diagnostic accuracy of cholangioscopy in the identification of preneoplastic lesions of the extrahepatic biliary tree. The improvement of image quality and the development of dedicated accessories will further promote the diffusion of peroral cholangioscopy.

Endoscopic drainage can be performed by direct cholangioscopy using a 5-Fr catheter or stent inserted in the 2.0-mm working channel, particularly in patients who require "ultra" selective guidewire access, such as for the orifice of the cystic duct or major intrahepatic branches[39]. Additionally, proximally migrated biliary stents, which cannot be removed *via* conventional ERCP, can be removed using 5-F baskets or other accessories under direct visual cholangioscopic control[40].

Cholangioscopy have been reported for the evaluation of recurrent pancreatitis because of T-tube remnants in the cystic duct stump that were previously not detected *via* ERCP, CT or MRI[41]. Although there are no published data on the therapeutic applications of cholangioscopy for the resection of a biliary lesion, a biliary polypoid lesion could be removed using a 5-F snare.

CONCLUSION

The introduction of peroral cholangioscopy has constituted a turning point for biliary endoscopy. In particular, the single-operator systems are able to address a new, enthusiastic approach to biliary tract diseases, with great advantages in everyday practice. The greatest interest has centered on the evaluation of indeterminate stenosis, in which a diagnosis has not been reached after standard procedures; this is the main field of application of POC. The development of standardized criteria for the differential diagnosis between benign and malignant strictures is the main goal for the future. Prospective multicenter studies are required to define criteria with high intra- and inter-observer agreements and adequate diagnostic accuracy. Peroral cholangioscopy currently remains a challenging and expensive technique in expert hands. However, the renewed interest of researchers, clinicians and the medical device industries, and the substantial technological improvements in image quality and dedicated accessories, might contribute in the near future to the dissemination of this technique.

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Endoscopic management of bariatric complications: A review and update

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Abstract

With over a third of Americans being considered obese, bariatric procedures have now become the most performed operation be general surgeons in the United States. The most common operations are the Laparoscopic Roux-en-Y Gastric Bypass, the Laparoscopic Sleeve Gastrectomy, and the Laparoscopic Adjustable Gastric Band. With over 340000 bariatric procedures preformed worldwide in 2011, the absolute number of complications related to these operations is also increasing. Complications, although few, can be life threatening. One of the most dreaded acute complication is the anastomotic/staple line leak. If left undiagnosed or untreated they can lead to sepsis, multi organ failure, and death. Smaller or contained leaks can develop into fistulas. Although most patients with an acute anastomotic leak return to the operating room, there has been a trend to manage the stable patient with an endoscopic stent. They offer an advantage by creating a barrier between enteric content and the leak, and will allow the patients to resume enteral feeding much earlier. Fistulas are a complex and chronic complication with high morbidity and mortality. Postoperative bleeding although rare may also be treated locally with endoscopy. Stenosis is a more frequent late complication and is best-managed with endoscopic therapy. Stents may not heal every fistula or stenosis, however they may prevent certain patients the need for additional revisional surgery.

Key words: Bariatric surgery; Bariatric complications; Endoscopic treatment; Sleeve gastrectomy; Roux-en-Y gastric bypass; Anastomotic leak; Self-expanding metal stent

Core tip: The majority of general surgeons and all bariatric surgeons will be faced with complications related to bariatric surgery. Understanding the new anatomy and most frequent complications is paramount to treating these patients appropriately. The use of endoscopic self-expanding stents alone or in combination with an operation can stabilize and occasionally completely heal anastomotic leaks and fistulas. Endoscopy can also be useful in the diagnosis and treatment of bleeding, stenosis, and ulcerations. This review will summarize the current literature on endoscopy for bariatric complications.

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INTRODUCTION

Obesity is a complex and chronic disease that is attributed to a combination of genetics and environmental factors. In the United States in 2011-2012, 69% of adults aged over 20 were considered overweight, 35.1% were obese, and 6.8% were morbidly obese. Similar trend are also seen in children (2-19 years) with obesity rate of 16.9% during the same period[1]. It is the second leading cause of preventable death in the United States, second only by smoking. The gap between these two has be diminishing and obesity is thought to overtake smoking in the near future[2]. Although lifestyle modifications have good short term results (1 year)[3], longer follow up has demonstrated a significant advantage to patients who have undergone a bariatric procedure[4]. The number of bariatric procedure performed worldwide in 2011 is estimated at 340768. The most commonly performed operations are the [Roux-en-Y gastric bypass RYGB (46.6%)], sleeve gastrectomy [SG (27.8%)], bilio-pancreatic diversion with duodenal-Switch [BPD/DS (2.2%)], and the Adjustable Gastric Band [AGB (17.8%)][5]. Over 90% these procedure are performed laparoscopically. The mean percentage of excess weight loss is 61.6%, 57%, 70.1%, and 47.5% respectively[6,7]. With an increase in the number of procedure being performed worldwide, as will the complications. These can be divided into intraoperative, perioperative, and late. The two latter can be further subdivided into local and systemic (Table 1). The sleeve gastrectomy is noteworthy as is does not create any mesenteric defects, thus the potential for internal hernia is eliminated.

Perioperative complications, although rare, are life threatening and must be diagnosed and treated promptly. Many of the clinical signs and symptoms are vague and subtle and can easily be overlooked. Late complications, although less life threatening, can be a diagnostic dilemma. Endoscopy is an excellent first line tool and may be simultaneously diagnostic and therapeutic. We will explore the pathophysiology, incidence and management of anastomotic/staple line leak, fistulas, stenosis, ulcers, and bleeding.

Table 1 Postoperative complications

	Local	Systemic
Intraoperative	Iatrogenic splenectomy (0.41%)	
Perioperative	Anastomotic leak (1.1%) GI hemorrhage (2.5%) Trocar injury (0.1%)	Deep vein thrombosis (1%) Pulmonary embolism (0.5%) Bowel obstruction (1.7%) Wound infection (3%) Pneumonia (0.2%) Cardiac event Mortality (0.2%-1%)
Late	Anastomotic stricture (3%-12%) Marginal ulcer (0.5%-20%) "Candy Cane" syndrome Gastroesophageal reflux	Bowel obstruction (2.5%) Incisional hernia (0.5%-8%) Internal hernia (1%-3%) Dumping syndrome (up to 30%) Cholecystitis (up to 30%) Anemia Vitamin deficiencies

ANASTOMOTIC AND STAPLE LINE LEAKS

Leaks occur when there is discontinuity of tissue apposition at the site where the tissue has been stapled and divided. It is generally felt that leaks within 48 h are caused by a technical failure. This can be a result of stapler misfire, wrong staple size for the tissue, or tissue trauma. Leaks occurring after several days are more likely due to tissue ischemia cause by tension on the anastomosis, distal bowel obstruction, or hematoma. In both situations, the intraluminal pressure exceeds the strength of the staple line[8]. Risk factors for leaks are increased age, male gender, sleep apnea (SA), and reversional surgery[9]. The incidence of leaks after RYGB has been as high as 8.3%, however most recent data would suggest the incidence to be closer to 1.1%[8,10,11]. The most common sites for anastomotic leak in the Roux-en-Y gastric bypass is the gastrojejunal anastomosis (GJA) 42.2%-67.8%, gastric pouch 10.2%, excluded stomach 3.4%, jejunojenual anastomosis 5.5%-7.8%, or in a combination or these sites in 14%[11,12]. As for sleeve gastrectomies, the most common location of staple line leak is the proximal third of the stomach occurring at the level of the cardiac notch in approximately 75%-87.5%[13,14]. Overall leak rate-related mortality is low (0.6%) in RYGB, however leak associated mortality is significantly higher (14.7%-17%)[9,15]. The results are similar in the sleeve gastrectomy population with an incidence of 1%-2.7%[14,16-18], overall leak-related mortality 0.14%, and leak associated mortality 9%[14].

Anastomotic leaks can be classified as acute < 7 d, early 1-6 wk, late 6-12 wk, chronic > 12 wk[17]. Regardless of the time at which the anastomotic leak occurs, a thorough clinical assessment must me performed. Diagnosis of these leaks can be quite difficult with the most commonly found abnormality being sustained tachycardia > 120 bpm[19,20]. Other symptoms that have been reported are abdominal pain, use of more analgesics than expected, no ambulation within 2 h of surgery, and shortness of breath[11]. Laboratory abnormalities may show leukocytosis or an elevated C-reactive protein, although these are not always present. The use of an upper gastrointestinal series with water-soluble contrast or computed

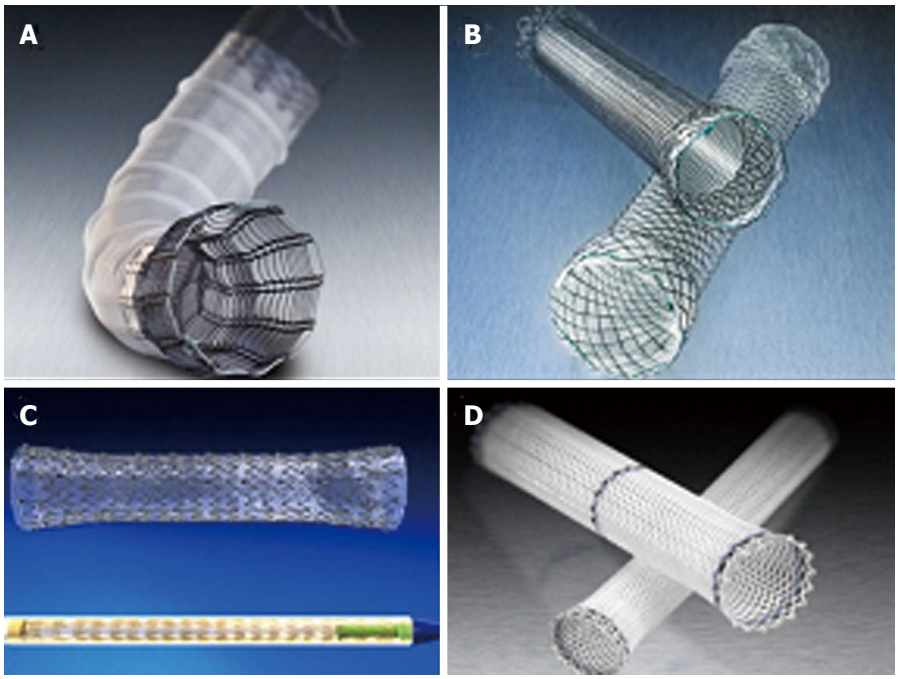

Figure 1 Self-expanding metal stents. A: Partially covered self-expanding metal stent; B: Partially and fully covered self-expanding metal stents; C: Fully covered self-expanding metal stent; D: Self-expanding plastic stent. Images courtesy of BostonScientific.com and Endotek.merit.com.

tomography may confirm the diagnosis, however these tests should not delay a return to the operating room. Most surgeons (86%) would take the patient to the OR with an unconfined and persistently symptomatic patient[17]. The majority (39%-81%) of patients with acute or early anastomotic leaks will ultimately return the the OR[11,12,19,20]. In the subgroup of patients who have minimal symptoms, are hemodynamically stable, and have a contained leak, conservative management may be warranted. Traditionally this management was NPO status, broad-spectrum antibiotics, percutaneous drains, and parenteral nutrition[11].

Endoscopic stents were initially designed as a tool of palliation for obstructing esophageal, gastric, and colorectal cancer. Some of the first published data for using stents across an anastomotic leak was in the thoracic population after esophageal resections. Leak rates as well as mortality after re-operation in this population was much higher therefore prompting a more conservative solution[21]. Most endoscopic stents used today are covered self-expanding metal stents (SEMS), partially covered self-expanding metal stents, and covered self-expanding plastic stents (SEPS) (Figure 1). These stents will provide a barrier between endoluminal bacteria and the acidic enteric content and the anastomotic disruption. Having an intraluminal device that will keep the anastomosis patent may also prevent wound contraction and the subsequent development of stenosis. The presence of these stents also confers the advantage of early enteral feeding. Healing success is defined as radiological confirmation of no leak after removal of stent. Stents are successful in 80%-94% of acute anastomotic leaks with stents left in place ranging from a mean of 41 d to 3.2 mo. Most patient may resume an oral liquid diet within 1-3 d. The most common side effects of the stent are early satiety, nausea, epigastric pain, and hypersialosis[22-24]. In a recent international expert panel consensus including 24 centres and over 12000 cases of laparoscopic sleeve gastrectomy (LSG), 93% of responders found the use of a stent for and acute proximal leak is a valid treatment option[17]. The most frequent complication of stent placement is stent migration seen in 16.9%-59%[25]. Most migrations are only a few centimetres, however this is enough to uncover the leak. The stents may also migrate distally with most passing per rectum. Only a few require an elective operation for stent retrieval. An urgent OR for erosion through the gastrointestinal wall and laceration of a blood vessel has also been described. Partially covered SEMS, larger diameter (18-22 mm), and longer length (15 cm) seem to have the least potential to migrate. The procedure of stent placement is most commonly performed in the operating room under general anesthesia with edotracheal intubation. The endoscope is use to identify the location of the leak and mark the location with radio-opaque clips. A guide-wire is also placed through the Roux limb. Under fluoroscopy, the stent deployment system is positioned across the leak and released. The length of the procedure can range from 23-47 min[24,26,27]. Endoscopic extraction is easiest with fully covered SEMS or SEPS. They can be grasped with large toothed graspers and extracted with firm steady pressure. Partially covered SEMS may have tissue ingrowth at either end. Two common techniques from removal are argon plasma coagulation and insertion of SEPS within the SEMS to induce tissue necrosis and easy extraction at a later date.

Figure 2 Resolution clip. Image courtesy of BostonScientific.com.

BLEEDING

Early bleeding after surgery can be intraluminal or extraluminal. The most frequent site of bleeding is the site of the anastomosis of staple lines. A risk factor for early bleeding is the presence of diabetes mellitus. The minority of bleeds will require an intervention more involved than a simple blood transfusion, and even fewer will require reoperation (21%)[28]. Bleeding is most often diagnosed with a postoperative decrease in hemoglobin. Uncommon clinical findings are hemoptysis, bright red blood pre rectum, or melena. A patient with hemodynamic instability, a distended or tender abdomen, or falling hemoglobin should be managed with an expeditious return to the operating room.

The gastroscope may be used may be used cautiously in the early post op with minimal air insufflation to avoid undue tension on the fresh anastomosis. The use of endoclips (Figure 2) alone or in combination with epinephrine is preferred to electrocautery[29].

FISTULAS

Anastomotic disruption with a more indolent and contained leak may ultimately form a fistula. A theory for the formation of a gastrogastric fistula is an incomplete transection of the gastric pouch and gastric remnant. The most common locations of an enteric fistula after bariatric surgery are gastrogastric, gastrocutaneous, duodenocutaneous, gastroperitoneal, and more rarely gastro-bronchial[8,26,30]. The incidence of gastric fistulas after bariatric surgery has not been well described, it may be in the order of 14.2% after an anastomotic leak[19]. The presence of a fistula will increase mortality with an order of magnitude of 8%-37.5%. It will also increased morbidity associated with a prolonged hospital stay, frequent hospital/clinic visits, and home care[31]. Success after stenting has been much less favourable than in the acute leaks. The success ranges from 19%-81%[19,26,32]. During an international expert panel for LSG, 89% of centres agree that stenting has a limited utility for chronic leaks (> 12 wk)[17]. Bège *et al*[25] have described a series of interventions starting with endoscopic drainage and debridement (± Amikacin 500 mg into the cavity), placement of a nasocystic tube, and placement of a plastic double-pigtail stent. A stent was inserted if the opening was more than 1 cm in diameter. The stent was secured proximally with endo-clips. If there was no resolution after 6 wk, therapeutic endoscopy was performed with placement of clips and/or injection of synthetic glue (N-butyl-2-cyanoacrylate) within the fistula cavity. Success after the first intervention was 64% of patients with late leaks/fistulas. Eisendrath *et al*[26] had a 61.9% success after stent alone, and an increased success rate of 80.9% the use after biologic glue, fistula plug, or clips.

ULCERS

Marginal ulceration may be seen in 0.49%-20% after RYGB[33-35]. The most common symptoms include epigastric pain, nausea, vomiting, food intolerance and bleeding. It is one of the most common finding on endoscopy in patients presenting with abdominal pain (52%)[36]. Risk factors include smoking (OR = 30.6), NSAIDs (OR = 11.5), diabetes (OR = 5.6), ischemia, increased stomach acid, bile acid reflux, *Helicobacter pylori* (*H. pylori*), steroids, alcohol, and foreign body[35,37-40]. Management is largely directed to the suspected etiology. Cessation of smoking, NSAIDs, and good blood glucose control is paramount. Proton pump inhibitors taken twice daily and tapered for 3-6 mo have had good results. If sampling of gastric fluid reveals normal or alkaline pH, sucralfate four times daily may have better results[41]. Biopsy proven *H. pylori* should be treated and visible suture should be removed. Non-healing ulcers should raise the possibility of a gastrogastric fistula.

STENOSIS/STRICTURE

This late complication can present with early satiety, nausea, vomiting, dysphagia, obstruction, retrosternal or abdominal pain[35]. These most commonly occur at the GJA and have an incidence of approximately 3%-12%[42-45]. Less frequently, stenosis can be seen at the enteroenteric anastomosis, the passage of the Roux limb through the mesocolon (Retrocolic approach only), and the Petersens defect. They most commonly present after 4-8 wk post op[46,47]. GJA with a linear stapler has a lower stricture rate of 2% compared to the 21 mm circular EEA stapler with a rate of 14%[19]. Risk factors include small (< 25 mm) circular stapler and marginal ulcers. The majority (90%) of patients will be amenable to endoscopic dilatation[47-49]. Dilatation may be attempted cautiously in as early as 4 wk post operatively. Frequently two, three or more dilatation may be required. With conscious sedation, the endoscope is passed to the level of the GJA. The diameter of the stricture is frequently be smaller than 3 mm and precludes passage of the endoscope. Caution must be applied when passing a guide wire

and the balloon dilator through the stenosis blindly. If any resistance is encountered, it should raise the possibility of passage into the blind limb. The balloon dilator is passed through the structured segment until its midpoint is at the maximal level of the stenosis. The smallest balloon is used initially and the size is progressively increased with every successful dilatation. This is felt to reduce the risk of perforation reported to be 3%-5%[46]. Dilatations of up to 15 mm, even in the first procedure, have been shown to be safe. The use of stents for treating strictures that have failed dilatation has not been fruitful. Puig *et al*[32] have had minimal success with only 2 of 16 patients not requiring and operative revision.

CONCLUSION

As the number obese patients increases, as will the number bariatric procedures. We will be left with a large number of patients with complications requiring adequate diagnosis and treatment. The surgeon is expected to promptly identify and appropriately manage early and late complications. Only surgeons who have performed the operations truly understand the new anatomy. Diagnostic and therapeutic endoscopy should be considered a first line tool in stable patients with perioperative complications such as anastomotic/staple line leaks, and bleeding. The placement of self-expanding metal or plastic stents in a patient with an anastomotic leak has shown favourable results. Late complication often present with vague complaints such as nausea, vomiting, or abdominal pain. Endoscopy is an excellent instrument for early diagnosis and treatment. SEMS, SEPS alone or in combination with metal clips, biologic glues, and biologic fistula plugs for treatment of fistulas should be considered first line therapy despite modest results. This strategy should greatly decrease the morbidity and mortality by reducing the rate of a revision surgery.

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Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions

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Abstract

The prognosis of early gastric cancer (EGC) is good if there is no concomitant lymph node metastasis. Therefore, the early detection of EGC is important to improve the prognosis of patients with gastric cancer. In Japan, 40% to 50% of all gastric cancers are EGC, and endoscopic submucosal dissection (ESD) is widely accepted as a local treatment for these lesions, particularly for large lesions that at one time were an indication for gastrectomy because of the difficulty of *en-bloc* resection. Consequently, this procedure can preserve the entire stomach and the patient's postoperative quality of life. ESD has become a general technique with improved procedures and devices, and has become the preferred treatment for EGC rather than gastrectomy. Therefore, ESD may demonstrate many advantages in patients who have several comorbidities, particularly elderly population, patients taking antithrombotic agents, or patients with chronic kidney disease, or liver cirrhosis. However, it is not yet clear whether patients with both EGC and comorbidities are feasible candidates for ESD and whether they would consequently be able to achieve a survival benefit after ESD. In this review, we discuss the clinical problems of ESD in patients with EGC and those comorbid conditions.

Key words: Endoscopic submucosal dissection; Gastric cancer; Elderly person; Antithrombotic agents; Liver cirrhosis; Chronic kidney disease

Core tip: Endoscopic submucosal dissection (ESD) is widely accepted as a local treatment for gastric cancer, particularly for early gastric cancer. Consequently, this procedure can preserve the entire stomach and the patient's postoperative quality of life. Therefore, ESD

may demonstrate many advantages in patients who have several comorbidities. However, it is not yet clear whether patients with both early gastric cancer (EGC) and comorbidities are feasible candidates for ESD and whether they would consequently be able to achieve a survival benefit after ESD. In this review, we discuss the clinical problems of ESD in EGC in elderly patients and patients with comorbid conditions.

Nishida T, Kato M, Yoshio T, Akasaka T, Yoshioka T, Michida T, Yamamoto M, Hayashi S, Hayashi Y, Tsujii M, Takehara T. Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J Gastrointest Endosc* 2015; 7(5): 524-531 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/524.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.524

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death in both sexes worldwide[1,2]. The incidence of gastric cancer has declined in younger populations along with decreasing infection rates of *Helicobacter pylori (H. pylori).* The infection rate of *H. pylori,* however, remains high in elderly Asian populations. In 2002, nearly 1 million new cases of gastric cancer were diagnosed, and more than half of these cases were from East Asia, including 41% from China and 11% from Japan[3]. Therefore, gastric cancer remains one of the most common cancers in Asian countries[4]. Patients with advanced gastric cancer have a poor prognosis; however, the prognosis of early gastric cancer (EGC) is good[5,6], and the 5-year gastric cancer-specific survival rate was reportedly 99% in cases that lacked concomitant lymph node metastasis[7]. EGCs account for 40% to 50% of all gastric cancers in Japan. Endoscopic resection (ER) is an alternative to surgery for treatment of mucosal neoplasms[8]. The criteria for ER for EGC was classified into the following three groups proposed by Gotoda *et al*[9] based on the characteristics of the initially detected tumor: "guideline group", "expanded guideline group" and "non-curative group". The guideline group was defined as mucosal differentiated cancer with the largest diameter measuring ≤ 20 mm. In Japan, ER is definitely indicated for this group. The expanded guideline group was defined as the following: (1) mucosal differentiated cancer measuring > 20 mm in diameter; (2) mucosal differentiated cancer with ulceration and measuring ≤ 30 mm in the largest diameter; and (3) differentiated cancer measuring ≤ 30 mm in the largest diameter with a submucosal invasion depth of < 500 μm. If the lesions did not meet these criteria, they were classified as the non-curative group. ER includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)[10]. EMR has been a standard technique for early gastric cancer with no risk of lymph node metastasis. EMR is, however, reportedly difficult to achieve *en-bloc* complete resection for the removal of lesions with the extended indication[11]. ESD is widely accepted as a treatment for EGC, particularly for larger lesions that at one time were an indication for gastrectomy because of the difficulty of *en-bloc* resection. Consequently, this procedure can preserve the entire stomach and improve the patient's postoperative quality of life. Moreover, ESD has become a standard technique with improved procedures and devices. Now, EMR has been replaced by ESD.

Because most patients with EGC are elderly, these patients commonly have several comorbidities that involve medical treatment, such as antithrombogenic agents to combat thrombosis, chronic kidney disease, or liver cirrhosis. In this review, we discuss the clinical problems associated with ESD in patients with EGC and comorbid conditions.

ELDERLY PATIENTS

Most patients with gastric cancer are diagnosed between their late 60s and 80s[12]. Therefore, most patients with EGC are elderly and therefore have an increased risk for procedure-related complications or events. EGCs generally grow slowly, and thus, we must determine a therapeutic strategy that considers the presence of comorbid diseases.

Most of elderly individuals have multiple chronic medical conditions[13]. Therefore, any indication for elderly patients with EGC must account for both life expectancy and concomitant conditions or diseases. However, there is little evidence that endoscopic resection is well tolerated in the elderly EGC patients who are most likely to benefit from resection.

Kakushima *et al*[14] previously reported the safety and efficacy of ESD for EGC in elderly patients aged 75 years or older (average age, 79 years old). Indeed, 57% of these patients also presented with comorbid diseases, but the *en-bloc* plus R0 resection rate and the complication rate in elderly patients were not significantly different from those of younger patients. Kakushima *et al*[14] concluded that ESD for gastric neoplasms is safe and effective in both elderly patients and younger patients. We also retrospectively validated whether gastric ESD was feasible even for elderly patients. In a study of 459 patients aged 75 years or older among 1188 EGC patients, perforation occurred in 20 patients (4.4%), and bleeding occurred in 12 patients (2.6%)[15]. The incidences of those complications were similar to those in the younger patients. Advanced age (*i.e.,* older than 75 years), however, is associated with an increased risk for postoperative pneumonia. Toyokawa *et al*[16] reported that the rate of late bleeding rate was significantly higher in elderly patients aged 75 years or compared with

Table 1 Endoscopic submucosal dissection in elderly patient *n* (%)

Ref.	Age (yr)	Patients *n*, lesions *n*	En-bloc resection, with R0, %	Perforation	Late bleeding	Pneumonia
Hirasaki *et al*[53]	≥ 75	53, 53	96, 81	1 (1.9)	(43%)[1]	NE
Kakushima *et al*[14]	≥ 75	42, 49	NE, 96	1 (2)	3 (7)	NE
Akasaka *et al*[15]	≥ 75	459, 459	NE	20 (4.4)	12 (2.6)	15 (3.3)
Toyokawa *et al*[54]	≥ 75	200, 229	92, 80	4 (1.7)	22 (9.6)	2 (0.87)
Abe *et al*[55]	≥ 80	440, 470	NE, 77.9	12 (2.8)	14 (3.2)	NE
Park *et al*[17]	≥ 70	132, 132	NE	6 (4.5)	5 (3.8)	6 (4.5)
Zhang *et al*[56]	≥ 75	171, 187	98, 94.1		(15.2%)[2]	NE

[1]Bleeding was defined in cases that required endoscopic management with methods such as clip placement and/or monopolar electrocoagulation to stop the bleeding, including early and late bleeding. One patient required surgery to treat the bleeding; [2]Immediate bleeding. NE: Not evaluated.

younger patients (9.6% *vs* 5.3%, $P = 0.0473$). After a multivariate analysis, the size of the resected specimen was the only significant risk factor for delayed bleeding. Recently, Park *et al*[17] reported that with expanded criteria as proposed by Gotoda *et al*[18], overall survival did not differ between elderly patients with EGC who underwent ESD and those who underwent surgery, although the risk of metachronous lesions was higher in patients who underwent ESD[17]. A propensity-matched analysis indicated that all of the adverse events observed in the ESD group were successfully treated and did not result in mortality. In contrast, two patients in the surgery group died of operation surgery-related complications, although no significant difference was observed between the two groups. Based on these data, we believe that gastric ESD in elderly patients is feasible and that EGC is manageable with this treatment (Table 1).

PATIENTS TREATED WITH ANTITHROMBOTIC AGENTS

In the last few decades, the number of patients treated with oral antithrombotic agents, including antiplatelet agents and anticoagulants, has increased worldwide in an effort to prevent or reduce thromboembolic events[19]. Recently, many novel oral anticoagulant drugs have been presented as alternatives to vitamin K antagonists and are either currently available or in the early or advanced stages of clinical development[20].

In patients who undergo minor surgical procedures, the discontinuation of antithrombotic therapy may not be required. However, patients who undergo major surgical procedures are required to discontinue the use of these drugs to minimize their risk for perioperative bleeding, as the continuation of antithrombotic agents in the perioperative period may lead to an increased risk of bleeding. In endoscopic procedures, antithrombotic agents may be discontinued when a patient is judged to have a low risk of thrombosis. The appropriate cessation of antithrombotic therapy has recently been reported to not increase the rate of delayed bleeding[21,22]. However, when gastric ESD is scheduled in a patient treated with oral anticoagulants (*e.g.*, warfarin) and judged by the prescribing doctor to have a high risk of thromboembolism, he or she will also undergo heparin replacement (HR). Similarly, when gastric ESD is scheduled in a patient treated with antiplatelet agents (*e.g.*, aspirin, ticlopidine, clopidogrel and cilostazol) and judged to have a high risk of thromboembolism, he or she will be placed on a continuous aspirin or cilostazol regime according to recently published guidelines from the Japan Gastroenterological Endoscopy Society[23]. In patients at high risk of thrombosis, the risks of both bleeding and thrombosis are unclear in patients who undergo endoscopic invasive procedures, such as gastric ESD.

Regarding antiplatelet agents, the continuous use of aspirin during the perioperative period of ESD has been reported to be acceptable, although the rate of delayed bleeding is slightly higher[24,25]. In an analysis of the combination of antiplatelet agents and anticoagulants, Koh *et al*[26] reported that antithrombotic therapy increased the risk of delayed bleeding. Takeuchi *et al*[27] also reported that the rate of postoperative bleeding in patients taking antithrombotic agents was 23.3%, which is significantly higher than the 2.0% observed in patients not treated with antithrombotic agents. Despite the discontinuation of antithrombotic agents, the authors found that combination therapy of low-dose aspirin (LDA) plus warfarin was a significant predictor of post-ESD bleeding (OR = 14.83, $P < 0.001$).

We believe that not only is LDA plus warfarin combination therapy a risk factor for late bleeding but also that HR is a risk factor for this condition. HR therapy is used as a bridge therapy along with invasive treatments to prevent antithrombotic events. We previously showed that the rate of delayed bleeding was high during gastric ESD (38%)[22] or colon polypectomy (20.0%)[28] under HR therapy.

However, few studies on the relationship between thrombotic events and endoscopic procedures have been conducted. The incidence rates of thrombotic events related to gastric ESD have been reported to range from 0 to 4.2%[21,22,24,27] (Table 2). We encountered one patient (4.2%) with delayed bleeding in the HR group who experienced a thrombotic event[22]. The patient's activated partial thromboplastin time was sufficiently prolonged under HR after successful endoscopic hemostasis for late bleeding. Although the patient discontinued the use of all antiplatelet agents, a cerebral infarction developed on post-operative day 13. Therefore, thrombosis during bleeding should be carefully considered, despite the presence of a sufficient anticoagulant effect during the perioperative period (Table 2).

Table 2 Endoscopic submucosal dissection in patients treated with antithrombotic agents *n* (%)

Ref.	Patients *n*, lesions *n*	En-bloc resection, with R0, %	Perforation	Late bleeding	HR No., bleeding	Thrombogenic event
Ono *et al*[21]	47[1], 56	96.4/82.1	1 (1.8)	6 (10.7)	1, 3 (33)	0 (0)
Lim *et al*[24]	274, ND	NE	0 (0)	26 (12.6)[2]	NA	1 (0.5)[3]
Koh *et al*[26]	175, ND	NE	NE	17 (9.7)[4]	NA	0 (0)
Takeuchi *et al*[27]	90, 90	NE	NE	21 (23.3)[5]	12, 21 (57)	1 (1)
Yoshio *et al*[22]	24, 24	100/100	0 (0)	9 (38)[6]	9, 24 (38)	1 (4.2)

[1]Forty-four low-risk patients stopped treatment with antithrombotic agents for 1 wk before and after endoscopic submucosal dissection (ESD). Three high-risk patients underwent intravenous heparin replacement during the cessation period; [2]A total of 274 patients were treated with antiplatelet medication, 102 of whom discontinued the use of these drugs for 7 d or more before ESD, whereas the remaining patients continued use; [3]One (1%) of the 102 patients who discontinued the use of antiplatelet medication developed an acute cerebral infarction; [4]Antithrombotic drug therapy was principally interrupted preoperatively and restarted when hemostasis was confirmed by second-look endoscopy. The rate of early postoperative bleeding during the first 5 postoperative days was 4%, and the rate of subsequent bleeding was 5.7%; [5]All patients commenced treatment with proton pump inhibitors immediately following surgery. Antiplatelet agents were discontinued for 7 d preoperatively until postoperative day 1, and anticoagulants were discontinued for 5 d preoperatively until postoperative day 1. A total of 46 patients received low-dose aspirin (LDA) only, 23 received LDA + thienopyridine, and 21 received LDA + warfarin. Anticoagulants were discontinued from preoperative day 4 to postoperative day 2. Heparin was substituted for anticoagulants after the latter were discontinued; [6]All patients underwent intravenous heparin replacement during the cessation period because of an increased risk of thromboembolism. HR: Heparin replacement; NA: Not applicable; NE: Not evaluated.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is associated with significant morbidity and mortality and is now recognized as a worldwide problem because the number of patients with CKD is sharply increasing[29]. In Japan, clinical practice guidelines have reported that the frequencies of stage 1, 2, 3, and 4/5 CKD in adults were 0.6%, 1.7%, 10.4% and 0.2%, respectively, in 2009. The total number of patients in stages 3 to 5 was estimated to be approximately 10.97 million[30]. Renal function linearly deteriorates with age. Therefore, the number of patients with CKD is higher in elderly populations, and consequently, the number of patients with gastric cancer and CKD is also believed to be increasing. Patients with CKD are more likely to experience multiple complications during the surgical procedure, such as procedure-related bleeding due to uremic platelet dysfunction and tissue vulnerability, compared with patients without CKD[31,32]. The safety and feasibility of gastric ESD for patients with CKD, however, are unclear.

Mannen *et al*[33] reported no significant risk factors for complications from gastric ESD among 17 patients with CKD. Goto *et al*[34] reported complications from gastric ESD in 7 patients with CKD who underwent hemodialysis (HD), one patient experienced delayed bleeding that required a blood transfusion, followed by shunt occlusion. Although all of the lesions were resected *en-bloc* with R0 resection, the authors concluded that ESD in patients with CKD should be carefully considered for substantial risks because late-onset complications may turn out to be severe. Kwon *et al*[35] also conducted a single-center retrospective study in which 17 patients with CKD were compared with 894 control patients who received gastric ESD. They reported no significant differences in *en-bloc* resection and perforation rates between patients with CKD and patients without CKD, but a tendency to hemorrhage was observed in patients with CKD. Numata *et al*[36] reported that the rate of post-ESD bleeding was 33% in 15 lesions in 12 patients with HD among the 63 patients with CKD, whereas the rate of post-ESD bleeding was only 9% in patients without HD. In addition, 2 deaths related to the ESD procedure were reported, but no deaths due to EGC occurred. Both of these patients were receiving HD, and the deaths occurred subsequent to the bleeding. The authors concluded that the cause of the bleeding was associated with other comorbidities, such as the use of anticoagulants during HD[36]. To focus on the eGFR, we also evaluated 144 patients with CKD in a multicenter survey that included municipal hospitals, where many patients with CKD were among those who underwent ESD[37]. In our study, we included patients with gastric cancer under the expanded criteria[7], and found that 20 patients did not achieve curative resection (13.9%), whereas additional surgeries were performed in 14 patients (9.7%). No ESD-related deaths were reported in these 144 patients. With respect to short-term outcomes, late bleeding was observed in 1.1% of patients in stage 3 (1/92), 13.0% in stage 4(3/23), and 13.8% in stage 5 (4/29). All incidences of bleeding were controlled by endoscopic hemostasis, but 5 patients required a blood transfusion (3.5%). In a univariate Poisson regression analysis including CKD stage, HD, diabetes mellitus, use of antithrombogenic

Table 3 Endoscopic submucosal dissection in patients with chronic kidney disease *n* (%)

Ref.	CKD, *n*/ lesions, *n*	Hemodialysis, *n*	HR, *n*	En-bloc resection, with R0, %	Perforation	Late bleeding
Goto *et al*[34]	7/9	7	ND	100/100	0 (0)	1 (14)
Kwon *et al*[35]	17[1]/19	8	ND	94.7/94.7	0 (0)	3 (17.6)[2]
Numata *et al*[36]	63 /79	12	2	89.9/89.9	3 (4.8)	11 (17.5)[3]
Yoshioka *et al*[37]	144/ 144	19	7	95.8/86.1	6 (4.2)	8 (5.6)

[1]Includes 2 patients with peritoneal dialysis; [2]Original paper reported 15.5%, which represented the percentage of perforation per lesion; [3]The rate of late bleeding was 33.3% (5/15) in hemodialysis patients and 9.4% (6/64) in non-hemodialysis patients; the difference was significant ($P < 0.05$). ND: Not described; HR: Heparin replacement.

Table 4 Endoscopic submucosal dissection in patients with liver cirrhosis

Ref.	Patients N (Child-Pugh A, B, C) /lesion, *n*	*En-bloc* resection, with R0, %	Perforation *n* (%)	Late bleeding *n* (%)	Median observation period (mo) Prognosis
Ogura *et al*[51]	15 (9, 6, 0)/18	88.9, 77.8	0 (0)	3 (20)	21.4 mo No recurrence but 3 patients underwent additional ER or surgery
Kwon *et al*[35]	18 (13, 3, 2)/22	90.9, 86.4	1 (5.6)	ND (approximately 9)	NE
Choi *et al*[57]	23 (20, 3, 0)/23	86.2, 82.6	0 (0)	1 (4.3)	17.5 mo (range, 2 to 72 mo) No local recurrence was found in either group during the follow-up period
Repici *et al*[58]	5 (4, 1, 0) /5	100, 100	0 (0)	2 (40)	22 mo (range, 18 to 36 mo) No recurrence
Kato *et al*[52]	69 (53, 15, 1)/69	99, 90	1 (1.5)	4 (5.8)	33.4 mo (range, 0.5-96.9 mo) The 5-yr overall survival rates were 60%

ND: Not described; NE: Not evaluated.

agents and HR, the critical factors related to bleeding were CKD stage and HD. In multivariate Poisson regression analyses, the risk ratio of bleeding was 11.4 in patients with stage 4 CKD and 11.0 in patients with stage 5 CKD. Thus, we concluded that CKD calculated from the eGFR would be an independent risk factor regardless of whether a patient undergoes HD[37].

Gastric ESD in patients with CKD is technically feasible, even in patients undergoing HD. However, bleeding in patients with CKD may lead to death due to other comorbidities, such as conditions that require the use of anticoagulants. Therefore, particular attention should be paid to late bleeding in patients with CKD, particularly patients with advanced CKD (Table 3).

LIVER CIRRHOSIS

Liver cirrhosis (LC) is a common disease, especially in Japan and other East Asian countries, due to the high prevalences of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections[4]. *H. pylori* and HBV/HCV, respectively, are the leading causes of bacterial and viral diseases in humans worldwide, particularly in East Asian. Consequently, it is not rare for patients to be affected by these two diseases. Patients with LC have a poor prognosis because of liver failure or the development of hepatocellular carcinoma (HCC)[38], esophagogastric varices[39], compromised host[40], or glucose intolerance[41]. In contrast, the prognosis of patients with EGC is good[7]. Therefore, it is difficult to determine whether patients with cirrhosis and EGC are suitable for ESD because this procedure may not increase the survival benefit for patients with LC. Until now, several studies have focused on the clinical outcomes of radical gastrectomy in patients with gastric cancer and comorbid LC[42-47]. These studies indicate that 10%-20% of patients with LC develop postoperative intractable ascites, and that the perioperative mortality rate is approximately 10%. However, few investigators have reported whether gastric ESD can be performed safely in patients with poor liver function or gastric varices. During gastric ESD, the rate of bleeding rate may increase because LC is frequently accompanied by complex alterations in the hemostatic system[48,49], and patients with LC have fewer platelets and a prolonged prothrombin time. More specifically, it is technically difficult to perform ESD when a varix is located near a gastric lesion. Kim *et al*[50], however, reported a successful ESD adjacent to a fundal varix after treatment with endoscopic variceal obturation using N-byutyl-2-cyanoacrylate (Histacryl®).

Ogura *et al*[51] performed a case series study on short-term ESD outcomes for 18 patients with LC. The authors reported that *en-bloc* resection was achieved in 88.9% of patients with EGC and cirrhosis but that the rate of late bleeding rate appeared to be higher (20%). Kwon *et al*[35] reported that the procedure time and short-term outcomes in patients with cirrhosis, such as the rates for *en-bloc* and complete resections, did not differ from those of the control group, even though the results of endoscopic mucosal resection were included. Immediate bleeding tended to occur more frequently in patients with both LC and CKD than in controls (47.5% *vs* 33.9%, $P = 0.077$). However, no significant difference was observed in the incidence of perforation[35]. We also evaluated outcomes of gastric ESD among 69 patients with LC. Based on a propensity-matched analysis, 53 (77%) of these patients had Child Pugh Grade A (CP-A) and 16 (28%) had Child Pugh Grade B/C (CP-B/C) compared with patients without LC[52]. In that study, short-term outcomes did not differ between the patients with LC and controls or between the patients with CP-A and those with CP-B/C. This study, however, revealed that the CP grade and HCC history were significantly independent risk factors for poor prognoses according to a Cox proportional hazards model. Patients with cirrhosis and CP-A demonstrated an overall survival that was nearly equivalent to that of patients without cirrhosis; however, patients with cirrhosis and CP-B/C or with histories of HCC had significantly worse long-term outcomes (the overall 3- and 5-year survival rates after ESD were 58% and 26%, respectively). Therefore, the long-term outcomes of patients with cirrhosis were likely influenced by liver

function or cirrhosis-related conditions rather than by gastric cancer. We concluded that patients with cirrhosis and CP-A appear to be good candidates for ESD but that patients with CP-B/C or with histories of HCC benefit less from ESD (Table 4).

CONCLUSION

This review demonstrated that gastric ESD could be performed safely, even in medically complex patients, such as elderly patients, those who are being treated with antithrombotic agents, and those with CKD or LC regarding the risk of complication, particularly bleeding. Although the short-term outcomes were not inferior, ESD was less beneficial to the survival of patients with a poor prognosis.

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Is it time to replace propranolol with carvedilol for portal hypertension?

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Abstract

Beta-adrenergic receptor antagonists (β-blockers) have been well established for use in portal hypertension for more than three decades. Different Non-selective β-blockers like propranolol, nadolol, timolol, atenolol, metoprolol and carvedilol have been in clinical practice in patients with cirrhosis. Carvedilol has proven 2-4 times more potent than propranolol as a beta-receptor blocker in trials conducted testing its efficacy for heart failure. Whether the same effect extends to its potency in the reduction of portal venous pressures is a topic of on-going debate. The aim of this review is to compare the hemodynamic and clinical effects of carvedilol with propranolol, and attempt assess whether carvedilol can be used instead of propranolol in patients with cirrhosis. Carvedilol is a promising agent among the beta blockers of recent time that has shown significant effects in portal hypertension hemodynamics. It has also demonstrated an effective profile in its clinical application specifically for the prevention of variceal bleeding. Carvedilol has more potent desired physiological effects when compared to Propranolol. However, it is uncertain at the present juncture whether the improvement in hemodynamics also translates into a decreased rate of disease progression and complications when compared to propranolol. Currently Carvedilol shows promise as a therapy for portal hypertension but more clinical trials need to be carried out before we can consider it as a superior option and a replacement for propranolol.

Key words: Portal hypertension; Chronic liver disease; Non-selective beta-blockers; Propranolol; Carvedilol

Core tip: Carvedilol is a promising agent among the beta blockers of recent time that has shown significant effects in portal hypertension hemodynamics. For primary prophylaxis of variceal bleeding, the effects of carvedilol were compared to band ligation in a few trials and showed some promise, but there has been no comparison with propranolol. Patients not responding to propranolol have shown clinical response to carvedilol, opening a new window of clinical application. For secondary prophylaxis of variceal bleeding, carvedilol has been shown to be effective. However no head-to-head trials comparing propranolol and carvedilol for variceal re-bleeding were found in literature.

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INTRODUCTION

Liver cirrhosis remains the 12th leading cause of death worldwide according to estimates by the Global Burden of Disease Study[1]. Portal hypertension is an inevitable consequence of cirrhosis and underlies most of its complications like: variceal bleeding, ascites and hepatic encephalopathy[2]. Portal hypertension is characterised by a pathologic increase in the portal pressure gradient (the pressure difference between the portal vein and the hepatic veins) y greater than 5 mmHg. This causes the creation of porto-systemic collaterals leading to shunting of portal blood to the systemic circulation, bypassing the liver parenchyma. It has been shown that therapeutic reduction in portal pressure has been shown to improve clinical outcomes and reduces the incidence of recurrent haemorrhage, ascites, encephalopathy, and death[3-5].

Beta-adrenergic receptor antagonists (β-blockers) have been well established for use in portal hypertension for more than three decades. Non-selective β-blockers (NSBB) have been widely utilized since 1980, when the first article on their role in portal hypertension was published by Lebrec *et al*[6]. Portal hypertension results from fibrosis or regenerative nodules in the liver parenchyma increasing resistance to flow and causing mechanical obstruction; contraction of sinusoidal and perisinusoidal contractile cells (stellate cells and vascular smooth muscle cells) with intrahepatic imbalance between vasoconstrictors (such as endothelin 1 and angiotensin) and vasodilators; and splanchnic vasodilatation in secondary to a relatively ischemic liver or extrahepatic excess of NO, with sGC-PKG signalling and smooth muscle cell relaxation[7] (Figure 1).

NSBB have a dual mode of action decrease portal pressure, *i.e.*, reduction of cardiac output and splanchnic blood flow by β-1 receptor blockade, and β-2 receptor blockade, resulting in splanchnic vasoconstriction caused by unopposed effect of alpha 1 receptors[7]. NSBBs have been proven to decrease incidence of bleeding (primary prophylaxis) and re-bleeding (secondary prophylaxis) from esophageal varices[8-11]. It has been demonstrated that they also prevent bleeding from portal hypertensive gastropathy and development of spontaneous bacterial peritonitis[4,12,13]. Due to their widely diverse effects in patients with cirrhosis and widespread use, they have been dubbed as "aspirin" in clinical hepatology[14].

Different NSBBs like propranolol, nadolol, timolol, atenolol, metoprolol and carvedilol have been in clinical practice in patients with cirrhosis. Propranolol was the first, most widely studied NSBB and mainstream for treatment of portal hypertension. Carvedilol is a nonselective beta-blocker with intrinsic anti-alpha1-adrenergic activity. It has been a relatively newer addition to the NSBBs, in the arena of portal hypertension and has demonstrated promising results in terms of clinical outcomes.

Carvedilol has proven 2-4 times more potent than propranolol as a beta-receptor blocker in trials conducted testing its efficacy for heart failure[15]. Whether the same effect extends to its potency in the reduction of portal venous pressures is a topic of ongoing debate.

The aim of this article is to compare the hemodynamic and clinical effects of carvedilol with propranolol, and attempt assess whether carvedilol can be used instead of propranolol in patients with cirrhosis.

HEMODYNAMIC EFFECTS

To achieve successful protection against gastrointestinal bleeding, the portal pressure [usually measured as the hepatic venous pressure gradient (HVPG)] has to be decreased to ⩽ 12 mmHg or by 20% of baseline values[16]. Long-term follow-up of cirrhotic on beta blockers has shown that decrease of HVPG of above mentioned values results in lesser risk of developing variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome and hepatic encephalopathy[4].

Comparison of carvedilol to propranolol for portal hypertension was made in a recent systematic review with meta-analysis which included five head-to-head randomised trials[17-22]. This analysis favored carvedilol against propranolol, in terms of: (1) acute effects on reduction in HVPG [mean weighted difference in % of reduction in hepatic vein pressure gradient; -7.70 (95%CI: -12.40--3.00)]; (2) long term effects [mean weighted difference in % of reduction in hepatic vein pressure gradient was -6.81 (95%CI: -11.35--2.26)]; and (3) overall effects [(mean weighted difference in % of reduction in hepatic vein pressure gradient -7.24 (95%CI: -10.50--3.97)].

Additionally the same metaanalysis showed that Carvedilol had a lower relative risk of failure to achieve hemodynamic response than propranolol. The number of patients who achieved a reduction in HVPG to ⩾ 20% or to ⩽ 12 mmHg was reported in 4 of the 5 studies and was also markedly higher with carvedilol *vs* propranolol (57/94 *vs* 33/87). However, this favourable difference for carvedilol did not reach statistical significance.

Carvedilol caused more reduction in arterial blood pressure resulting in orthostatic hypotension as compared to propranolol. Propranolol caused a - 6.66 mmHg (95%CI: -10.17--3.15) mean reduction in arterial pressure whereas carvedilol caused a mean reduction of -10.40 (95%CI: -13.9--6.9). The reduction in mean arterial pressure was found to be significant

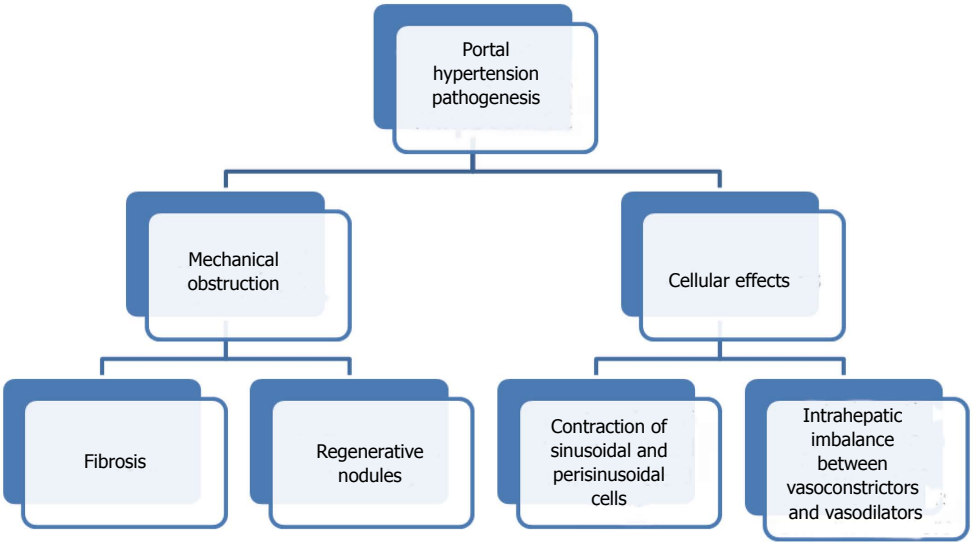

Figure 1 Pathogenesis of portal hypertension.

with both drugs, but the degree of reduction was in the order of one-third more with carvedilol compared to propranolol[17] (Figure 2).

Therefore carvedilol has been shown to be superior to propranolol in causing of acute, long-term and overall reduction of the hepatic venous pressure gradient, *i.e.*, portal venous pressure. The proportion of patients who demonstrated an adequate response is also higher for carvedilol.

Although the translation of these effects in terms of clinical benefit of reduced gastrointestinal bleeding events is significant, these changes in hemodynamic parameters come at the cost of orthostatic hypotension and fluid retention including ascites, with the use of carvedilol. However carvedilol can be a safe alternative in patients who are not hypotensive. In addition carvedilol has achieved significant hemodynamic response in more than half of the patients who were resistant to propranolol[23].

CLINICAL EFFECTS

Variceal bleeding

Pre-primary prophylaxis: Prevention of development of varices in patients with portal hypertension is known as pre-primary prophylaxis. Experimental models of portal hypertension have shown that B-Blockers delay the development of collaterals[24,25]. Escorsell *et al*[26] demonstrated that administration of β-blockers (timolol) to patients without varices caused a greater reduction in portal pressure than the reduction seen in patients with varices[26]. However this effect of use of timolol did not translate into prevention of variceal formation and variceal hemorrhage in a randomised study by Groszmann *et al*[27] which compared timolol with placebo in patients without varices. The study by Calés *et al*[28] using propranolol, for pre-primary prophylaxis did not show clinical benefit in terms of variceal development. To-date there were no studies using carvedilol for pre-primary prophylaxis.

Due to lack of any demonstrated clinical benefits of β-blockers in patients with portal hypertension without varices and adverse effects of these medications, none of the current guidelines (including Baveno V consensus[2], AASLD[29], and EASL/AASLD consensus[30]) recommend their use for pre-primary prophylaxis.

Primary prophylaxis: NSBB are recommended for use in primary prevention of variceal bleeding, as they have been associated with decrease in incidence of first bleeding episode and mortality benefits[2].

A meta-analysis of published randomised controlled trials on primary prophylaxis including 1859 patients, revealed pooled risk difference of 11% in incidence of variceal bleeding with use of propranolol against controls[31]. In another meta-analysis, D'Amico *et al*[32] demonstrated that in patients with varices of any size, β-blockers reduced the risk of a first bleeding episode from 25% to 15% within 2 years. The absolute risk difference was 9% (15% *vs* 24%) as compared to placebo. Moreover, the absolute risk reduction in mortality was found to be 4% (from 27% to 23%)[32].

Another meta-analyses has reported the usage of Beta blockers as primary prophylaxis to be associated with a 40% reduction in bleeding risk and a trend towards improved survival[33]. In a double-blind randomised trial, the Boston-New Haven-Barcelona Portal Hypertension Study Group compared propranolol with placebo for primary prophylaxis. There was significant difference in incidence of bleeding between the study groups favouring propranolol (incidence of bleeding 4% *vs* 22%; $P \leqslant 0.01$) during a mean follow-up of 16 mo. However there was no difference in mortality rates between the two groups[34].

Propranolol has been compared to esophageal band ligation (EBL) in terms of bleeding prevention

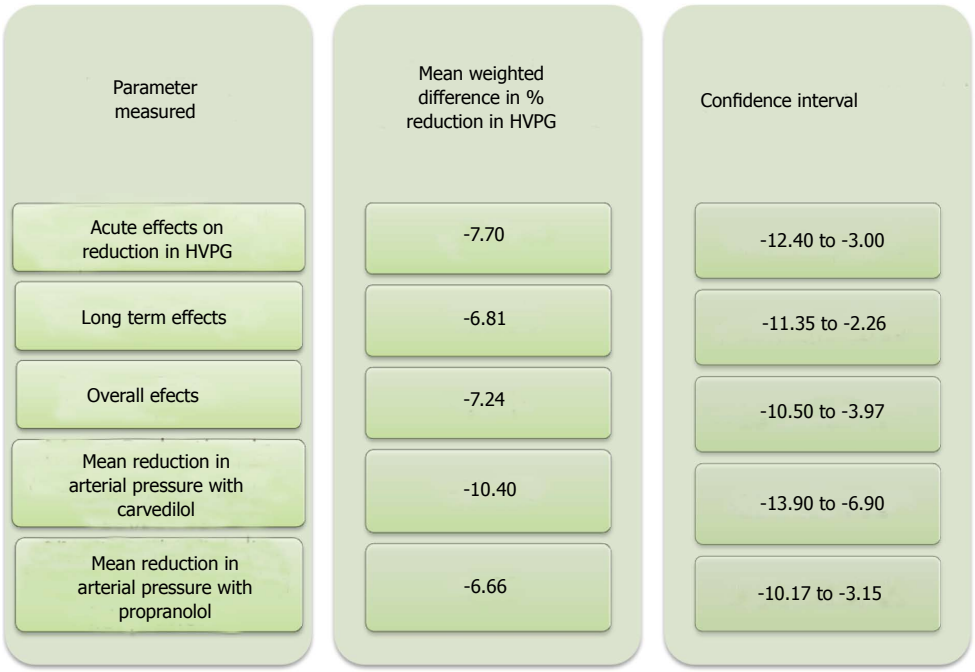

Figure 2 Hemodynamic effect of carvedilol compared to propranolol (Data from ref.[19]). HVPG: Hepatic venous pressure gradient.

and mortality reduction in patients with cirrhosis in several randomised controlled trials. A meta-analysis of sixteen randomised controlled trials found EBL causing significant reduction of the risk of first variceal bleeding compared to propranolol (relative risk difference 9.2%, 95%CI: 5.2%-13.1%, and POR 0.5, 95%CI: 0.37–0.68). However there was no statistically significant difference in Mortality between the two groups (POR 0.94, 95%CI: 0.70-1.28). On average, 3 endoscopic sessions were required to eradicate varices and at least 33 endoscopic procedures were needed to prevent one bleeding episode as compared with NSBBs[35]. However as NSBB are cheap, as haemodynamic monitoring is not required[36].

In a randomized control trial, Carvedilol has been compared with EBL and showed a significantly lower rate of first variceal bleeding (with minor adverse effects) in patients taking carvedilol 12.5 mg daily compared with EBL (10% *vs* 23%, HR = 0.41, 95%CI: 0.19-0.96)[37]. The lowest dose of carvedilol tested in this trial was 12.5 mg, which is known to cause a smaller reduction in HVPG than to actually cause prevention of first bleeding episode. So the results of this study need to be interpreted after considering its limitations[38].

Another randomised controlled trial by Shah *et al*[39] reported that both EBL and carvedilol groups had comparable variceal bleeding rates (8.5% *vs* 6.9%), bleeding related mortality (4.6% *vs* 4.9%) and overall mortality (12.8% *vs* 19.5%) respectively[39]. Although the study was underpowered, the authors suspect that carvedilol is not superior to EBL for primary prophylaxis of varices.

Use of carvedilol has been found to cause reduction of HVPG in patients failing to respond to propranolol, thus leading to lesser bleeding episodes in this group of patients. Bleeding rates followed up for 2 years were 11% with propranolol *vs* 5% with carvedilol and 25% with EBL (P = 0.0429)[23]. We did not find any studies comparing propranolol with carvedilol head-to-head for primary prevention.

Secondary prophylaxis: Secondary prophylaxis is prevention of recurrence after index variceal bleeding episode. The 1-year mortality after an episode of variceal bleeding is 40%[11]. Variceal bleeding recurs in 60% at 1-year with 6-wk mortality of 20% for every re-bleeding episode[2]. NSBBs have been widely used for prevention of re-bleeding and have been shown to decrease the rate of re-bleeding from varices to 42%, as compared to 63% in controls in several meta-analyses[32]. In addition these agents decrease overall mortality from 27% to 20%, and bleeding related mortality[40].

Carvedilol was compared with combination of nadolol and isosorbide-5-mononitrate in a randomized controlled trial in patients who previously had variceal bleeding. This study demonstrated that after a follow-up of 30 mo there was no significant difference in incidence of recurrent upper gastrointestinal bleeding between carvedilol and combination groups (62% *vs* 61%; P = 0.90). There was no significant difference between the Rate of recurrence of variceal bleeding between the carvedilol and combination groups (51% *vs* 43%; P = 0.46)[41]. Interim analysis of a multicentre randomised controlled study comparing carvedilol with endoscopic band ligation for secondary prevention of variceal bleeding, demonstrated no significant

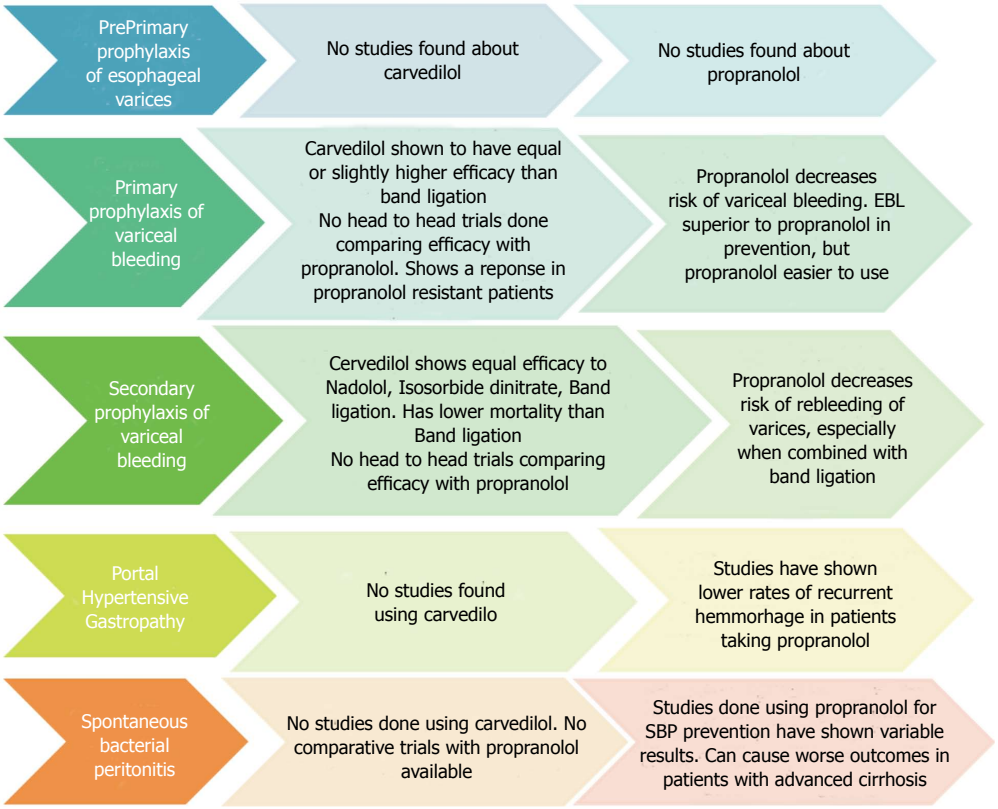

Figure 3 Current evidence about carvedilol and propranolol as prophylactic therapy.

difference between the groups in re-bleeding rates (37.5% *vs* 29%; $P = 0.72$). However the patients in carvedilol group had lower 1-year mortality rates as compared to EBL group (25% *vs* 51.6%; $P = 0.058$)[42].

The pioneer trial by Pagliaro *et al*[8] demonstrated that propranolol was effective in decreasing the incidence of variceal re-bleeding when compared to controls. A comprehensive meta-analysis of 12 randomised controlled trials for secondary prophylaxis of variceal bleeding showed that, use of β-blockers (11 using propranolol) was associated with increase in mean percentage of patients with no re-bleeding (21% mean improvement rate, 95%CI: 10%-32%, $P < 0.001$), the mean percentage of patients with no variceal re-bleeding (20% mean improvement rate, 95%CI: 11%-28%, $P < 0.001$), the mean survival rate (5.4% mean improvement rate, 95%CI: 0%-11%, $P < 0.05$, RR = 1.27), the mean percentage of patients free of bleeding death (7.4%, 95%CI: 2%-13%, $P < 0.01$, RR = 1.50)[40].

Baveno V consensus guidelines recommend a combination of β-blockers and variceal band ligation as the preferred therapy for secondary prophylaxis because it results in lower re-bleeding rates compared to either therapy alone[2]. Ahmad *et al*[43] compared combination of EBL and propranolol against propranolol for secondary prevention and found no statistical difference in re-bleeding (22% *vs* 38%) and mortality rates (23% *vs* 19%) between the groups. However the incidence of re-bleeding was higher in patients on propranolol alone[43].

Propranolol retains its place as the most widely used and studied drug for secondary prophylaxis with clear benefits as compared to placebo and combination with EBL. The evidence for carvedilol in variceal rebleeding recurrence is minimal but promising.

Portal gastropathy

Described as mosaic, snake-skin-like appearance of gastric mucosa with or without red punctuate erythema, portal hypertensive gastropathy (PHG) is estimated to be present in up to 80% of cirrhotic patients[44]. PHG can cause acute bleeding rarely with an incidence of 3% in three years, and in 2.5%-30% patients it may result in chronic insidious bleeding[45,46].

NSBBs have been shown to lower the incidence of bleeding in acute and chronic forms of haemorrhage from PHG. One of the earliest randomised controlled trials using propranolol showed lower haemorrhage rates, increase in haemoglobin level and an apparent improvement in the endoscopic appearance of the lesion when compared to placebo[47]. Pérez-Ayuso *et al*[12], in a randomised trial of used propranolol against no therapy in patients for secondary prophylaxis of bleeding from PHG. The study demonstrated higher number of patients remaining free of bleeding with propranolol in acute (85% *vs* 20%) and chronic setting (69% *vs* 30% at 30 mo). On multivariate analysis, the sole independent predictor of recurrent haemorrhage was the absence of propranolol[12].

Although the use of β-blockers for PHG is widespread, based upon current evidence strong recommendations can't be made for NSBB for this indication. We also did not find any studies using carvedilol to control bleeding from portal gastropathy.

Spontaneous bacterial peritonitis

NSBBs have been shown to have preventive effect on development of spontaneous bacterial peritonitis in a meta-analysis by Senzolo *et al*[13]. This analysis included three randomised controlled trials and two retrospective studies all using propranolol for prophylaxis of variceal bleeding, with respect to the incidence of SBP. Statistically significant difference of 12.1% ($P < 0.001$) was found in favour of propranolol in prevention of SBP.

A recently published thorough retrospective analysis of data from 607 patients with cirrhosis by Mandorfer *et al*[48] demonstrated no difference in incidence of SBP between NSBB users and patients who did not. Occurrence rates of SBP were similar between patients with and without NSBB treatment. However, NSBB use was associated with higher transplant-free survival in patients without SBP and reduced hospitalization rates[48].

In contrast, Mandorfer *et al*[48] demonstrated that in patients who have developed SBP, NSBB were associated with hemodynamic compromise and decreased blood pressures, reduced transplant free survival, increased hospitalization rates, and increased incidence of the hepatorenal syndrome and acute kidney injury. In another study, using a NSBB (propranolol) in patients with refractory ascites was found to reduce 1-year survival against those not using this drug (median survival: 5 mo *vs* 20 mo respectively)[49]. These results advocate against the use of NSBB in patients with advanced cirrhosis with ascites and SBP.

To conclude, the current evidence is variable about the role of NSBB in decreasing the incidence of SBP. However they can increase transplant-free survival in patients without SBP. In cases of advanced cirrhosis with ascites and the patients who have developed SBP, their use proves detrimental causing higher rates of hemodynamic compromise, time of hospitalization and risks of renal dysfunction. All the studies on NSBB use for SBP have used propranolol. We did not find any study about the use of carvedilol in patients with advanced cirrhosis and SBP, nor a head-to-head comparison of propranolol and carvedilol in this regard.

CONCLUSION

After reviewing the existing literature, it seems that Carvedilol has more potent desired physiological effects when compared to Propranolol. However, it is uncertain at the present juncture whether the improvement in hemodynamics also translates into a decreased rate of disease progression and complications when compared to propranolol (Figure 3).

There have been no clinical trials comparing carvedilol and propranolol for pre-primary prophylaxis. For Primary prophylaxis, the effects of Carvedilol have been compared to Endoscopic band ligation in a few trials and show some promise, but there has been no head to head comparison with propranolol. However, patients not responding to propranolol have shown clinical response to Carvedilol, opening a new window of clinical application.

For secondary prophylaxis, carvedilol has been compared to Beta blockers other than propranolol and Endoscopic Band Ligation, and seems to be equally effective. However, the most effective therapy to date remains a combination of Endoscopic Band Ligation, and no head to head trials have been conducted comparing carvedilol with propranolol. Similarly, there have been no trials exploring the role of carvedilol in portal hypertensive gastropathy and spontaneous bacterial peritonitis.

Thus, currently Carvedilol shows promise as a therapy for portal hypertension but more clinical trials need to be carried out before we can consider it as a superior option and a replacement for propranolol.

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ORIGINAL ARTICLE

Clinical Trials Study

Tripartite comparison of single-incision and conventional laparoscopy in cholecystectomy: A multicenter trial

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Data sharing: No additional data are available.

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Abstract

AIM: To compare the characteristics of two single-incision methods, and conventional laparoscopy in cholecystectomy, and demonstrate the safety and feasibility.

METHODS: Three hundred patients with gallstones or gallbladder polyps were admitted to two clinical centers from January 2013 to January 2014 and were randomized into three groups of 100: single-incision three-device group, X-Cone group, and conventional group. The operative time, intraoperative blood loss, complications, postoperative pain, cosmetic score, length of hospitalization, and hospital costs were compared, with a follow-up duration of 1 mo.

RESULTS: A total of 142 males (47%) and 158 females (53%) were enrolled in this study. The population characteristics of these three groups is no significant differences exist in terms of age, sex, body mass index and American Society of Anesthesiology (P > 0.05). In results, there were no significant differences in blood loss, length of hospitalization, postoperative complications.The operative time in X-Cone group was significantly longer than other groups.There were significant differences in postoperative pain scores and cosmetic scores at diffent times after surgery (P < 0.05).

CONCLUSION: This study shows that this two single-incision methods are safe and feasible. Both methods are superior to the conventional procedure in cosmetic and pain scores.

Key words: Cholecystectomy; Laparoscopic surgery; Single-incision laparoscopic cholecystectomy

Core tip: This is an article about single-incision laparoscopic surgery. It compares three methods in laparoscopic cholecystectomy. The study concludes that the three-device and X-Cone methods are safe and feasible for single-incision laparoscopic cholecystectomy. Compared with conventional laparoscopic cholecystectomy, single-incision laparoscopic surgery techniques have advantages in pain and cosmetic factors.

He GL, Jiang ZS, Cheng Y, Lai QB, Zhou CJ, Liu HY, Gao Y, Pan MX, Jian ZX. Tripartite comparison of single-incision and conventional laparoscopy in cholecystectomy: A multicenter trial. *World J Gastrointest Endosc* 2015; 7(5): 540-546 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/540.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.540

INTRODUCTION

Single-incision laparoscopic surgery (SILS) is an area of research interest in minimally invasive surgery. Its main advantage is a scar-free abdominal wall after surgery, as well as milder postoperative pain, faster recovery, shorter hospital stay, and better cosmetic outcomes. Since the first report of single-incision resection of gallbladder through the abdominal cavity by Navarra *et al*[1] in 1997, there has been a growing number of clinical reports on this topic[2-10]. At present, a variety of auxiliary means are used, such as the X-Cone method, triport method, Kirschner-aid exposure method, suspension sutures method, and three-device method[11-16]. However, there has been no comparative study of the various methods.

We enrolled 200 cases of laparoscopic cholecystectomy completed using the three-device and X-Cone methods in our two centers, as well as 100 cases of conventional laparoscopic cholecystectomy, to compare their technical characteristics and clinical outcomes, and demonstrate the safety and feasibility of the single-incision methods.

MATERIALS AND METHODS

Patients

Inclusion criteria were: patients with gallstones or gallbladder polyps; age 18-85 years; either sex; and body mass index (BMI) < 35 kg/m^2. Exclusion criteria were: complication by common bile duct or intrahepatic bile duct stones; acute cholecystitis; suspicion of complicated cholecystitis; BMI $\geqslant$ 35 kg/m^2; drug addiction; ASA physical classification > 3; previous upper abdominal surgery; pregnancy; presence of umbilical hernia; or previous umbilical hernia repair.

All 300 patients were admitted to the two clinical centers for laparoscopic cholecystectomy from January 2013 to January 2014. They were randomly assigned to three groups of 100. The case characteristics are shown in Table 1. All surgery was performed by three surgeons, each of whom had conducted > 1000 cholecystectomies, including $\geqslant$ 100 single-incision laparoscopic cholecystectomies.

The primary end points of this study were feasibility and safety of the three-device method and X-Cone method compared with conventional laparoscopic cholecystectomy, as indicated by intraoperative and postoperative adverse events up to 1 mo, operative time, and estimated blood loss. The secondary end points were: (1) pain as determined by a 10-point pain intensity scale performed at days 1 and 2, 1 wk, and 1 mo; (2) cosmesis evaluated *via* a body image questionnaire, photo series questionnaire, and cosmesis scale performed at 1 and 2 wk, and 1 mo; and (3) length of hospital stay and hospital costs.

Surgical methods

Umbilical disinfection was completed 1 d before surgery. Following routine anesthesia with tracheal intubation, second-generation cephalosporin was intraoperatively administered once. After pneumoperitoneum was established in patients undergoing three-device or conventional surgery, the patients were placed with their legs closed in the Trendelenburg position at approximately 30°, left tilted at approximately 20°. The surgeons stood on the left side of the patient, with the monitor on the right side. For patients undergoing X-Cone surgery, the legs were placed apart in the Trendelenburg position at approximately 30°, left tilted approximately 20°. The surgeons stood between the legs with the monitor on the patient's head side.

General anesthesia was induced with propofol (2 mg/kg) and sufentanil (0.5-2 μg/kg). Tracheal intubation facilitated by injection of Atracurium (0.5 mg/kg). Anesthesia during surgery was maintained with isoflurane 1.2% and administration of Atracurium (0.1 mg/kg) and sufentanil (0.1 μg/kg) and every 30 min. The patients were monitored by ECG, pulse oximetry, noninvasive blood pressure. Patients were recovered by administration of neostigmine (40 μg/kg) and atropine (20 μg/kg).

Three-device method: The umbilical incision was approximately 2.0 cm. Three trocars were directly placed into the incision. The locations are shown in Figure 1. The inferior 10-mm trocar was for insertion of the 30° laparoscope, while the two 5-mm trocars above were working ports for the scalpel and forceps,

Table 1 General data of the patients

	X-Cone method (n = 100) (No.1 group)	Three-device method (n = 100) (No.2 group)	Conventional method (n = 100) (No.3 group)	P value	Statistical methods and values
Sex					
Male	47	44	52		$\chi^2 = 1.31$
Female	53	56	48		
Age (yr)	39.5 ± 14.5	40.0 ± 12.5	41.7 ± 12.0	0.465	One-Way ANOVA F = 0.768
BMI (kg/m^2)	26.1 ± 5.5	28.2 ± 7.5	26.1 ± 8.4	0.06	One-Way ANOVA F = 2.847
Surgical risk grade (ASA)	1.6 ± 0.5	1.6 ± 0.4	1.6 ± 0.4	0.681	One-Way ANOVA F = 0.385
Diagnosis					
Stones	58	52	47		$\chi^2 = 2.43$
Polyps	42	48	53		

ASA: American society of anesthesiology; BMI: Body mass index.

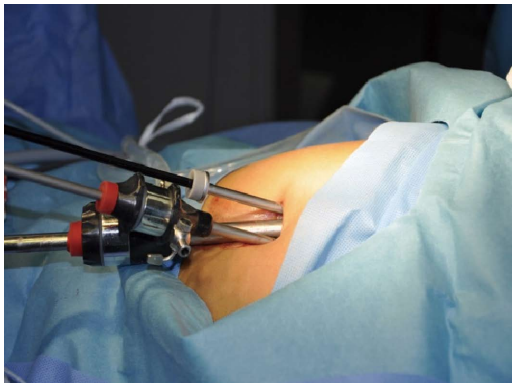

Figure 1 Diagram of the three-device method.

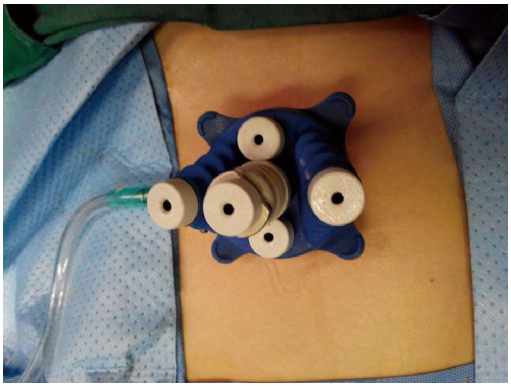

Figure 2 Device for the X-Cone method.

respectively. There was 1-2 mm of tissue between the three trocars to prevent leakage. The cystic artery was directly cut with the ultrasonic scalpel, and the cystic duct was closed with a 5-mm Hem-o-lok titanium clamp and transected with scissors. If the 5-mm Hem-o-lok was too small for the occlusion, the 5-mm trocar in the right working port was replaced with a 10-mm one for placement of a 10-mm Hem-o-lok. Once there was no abnormality of the abdomen, the gallbladder was removed. All equipment was removed first, and a pair of vessel forceps was inserted into the original 10-mm trocar to enlarge the incision in the abdominal cavity, and grasping forceps and a 10-mm trocar laparoscope were in turn placed to extract the gallbladder as a whole. The umbilicus white line was closed with a 3-0 Polysorb absorbable suture, and the umbilical skin incisions intradermally closed with absorbable sutures.

X-Cone method: A 3.0-cm curved incision was made around the upper or lower edge of the umbilicus. The subcutaneous tissue and anterior sheath were divided and the posterior sheath separated. As the middle space was pulled with hemostatic forceps, the X-Cone device (Karl Storz, Tuttlingen, Germany) was inserted (Figure 2). Pneumoperitoneum up to 12 mmHg was established through the pole of the X-Cone, and a 5-mm 30° laparoscope was inserted. The clamp and scalpel were placed into the other two ports. The surgeon pulled the gallbladder with curved traction forceps in the left hand and resected the gallbladder triangle with the ultrasonic scalpel in the right hand. The cystic artery was directly separated with the scalpel. After separation of the cystic duct, a 5 or 10-mm Hem-o-lok was used to close it and the cystic duct was then cut with scissors. The gallbladder was then removed as a whole from the gallbladder bed. The gallbladder was taken directly from the umbilical port. The umbilicus white line was closed with a 3-0 Polysorb absorbable suture, and the umbilical skin incisions intradermally closed with absorbable sutures.

Conventional method: A curved incision of 1.0 cm was made at the umbilical lower edge, an incision of 1.0-1.2 cm was made below the xiphoid, and a 0.5-cm incision was made 1-2 cm above the right clavicular line at the umbilical level. Two 10-mm trocars and one 5-mm trocar were placed into these incisions. The 10-mm umbilical trocar was for placement of the laparoscope, and the other two were working ports for placement of the ultrasonic scalpel and forceps.

Postoperative care: After completion of surgery in all three groups, the incisions were treated with a 50% dose of 75 mg ropivacaine for local anesthesia. Subsequently, the patients were extubated and closely

Table 2 Surgical data of the three groups

	X-Cone method (n = 100) (No.1 group)	Three-device method (n = 100) (No.2 group)	Conventional method (n = 100) (No.3 group)	P values	Statistical methods and values
Operative time (min)	56.3 ± 14.0	45.6 ± 12.0	42.1 ± 11.0	0.000 G1 *vs* G2 0.000 G1 *vs* G3 0.000 G2 *vs* G3 0.111	One-Way ANOVA F = 36.86
Blood loss[1] (mL)	16.4 ± 3.7	17.1 ± 4.5	15.8 ± 4.7	0.089	One-Way ANOVA F = 2.439
Conversion to multiple-incision LC	1	2	0	0.776	Fisher exact test
Complications					
Incision contusion	3	4	1	0.543	Fisher exact test
Wound infection	1	1	3	0.625	Fisher exact test
Bile duct injury	0	0	0	1.0	Fisher exact test
Bile leakage	2	2	1	1.0	Fisher exact test
Abdominal infection	0	0	0	1.0	Fisher exact test
Postoperative hospital stay (d)	1.66 ± 0.5	1.69 ± 0.5	1.68 ± 0.4	0.928	One-Way ANOVA F = 0.075
Hospital costs	11658 ± 1435	10406 ± 1246	10036 ± 1154	0.000 G1 *vs* G2 0.000 G1 *vs* G3 0.000 G2 *vs* G3 0.415	One-Way ANOVA F = 52.66

[1]Estimated intraoperative blood loss; LC: Laparoscopic cholecystectomy.

observed in the postanesthetic care unit and then transferred to the surgical ward once their Aldrete score was ⩾ 9. Postoperative electrocardiography was performed and oxygen was administered for 6 h, in combination with rehydration and bleeding control, as well as other fluid replacement. Liquid food and ambulation were allowed 6 h after surgery. In the postoperative period, Intravenous rotundine sulfate, at a dose of 1 mg/kg was administered according to patient request every 12 h until discharge home. Surgical dressings were changed on the first day after surgery. The patients were discharged on the second day after surgery. They were also asked to return for check-up at 1, 2 wk and 1 mo after surgery.

Statistical analysis

Data were analyzed using SPSS version 13 (Chicago, IL, United States). Base on Kolmogorov-Smirnov test, operative time, estimated blood loss, postoperative hospital stay, pain scores and cosmetic scores were all summarized using mean ± SD and compared among the 3 groups by using the One-Way ANOVA test (Tukey method). Intraoperative and postoperative adverse events was compared among the three procedures by Fisher exact test. χ^2 tests were performed to explore the effects of sex, and the clinical diagnosis. A value of $P < 0.05$ was considered to indicate significance.

RESULTS

A total of 300 patients were enrolled in this study and assigned to three groups of 100: three-device, X-Cone method, and conventional method. There were no significant differences in age, sex, BMI and ASA among the groups. The operation time, blood loss and complications are listed in Table 2. There were no significant differences in blood loss and postoperative hospital stay. The X-Cone method required longer operation time compared to the conventional (56.3 min *vs* 42.1 min, P = 0.000) and three-device methods (56.3 min *vs* 45.6 min, P = 0.000), while the latter two did not differ significantly in this regard (42.1 min *vs* 45.6 min, P = 0.111). Hospitalization costs were higher in the X-Cone group than the three-device group (P = 0.000) and the conventional group (P = 0.000). The conventional group was the cheapest group in the three groups.

In the X-Cone group, there were three cases of surgical incision contusion, and one case of wound hematoma. In the three-device group, two patients required additional working ports due to severe inflammatory adhesions, and there were four cases of incision contusion. In the conventional method group, all patients were successfully operated, and there were one case of incision contusion and three cases of incision wound infection under the xiphoid. No patient converted to laparotomy, and there was no serious complication such as bile duct injury or bile peritonitis. There was no postoperative bleeding or conversion to laparotomy. Percutaneous incision suture was successful without umbilical hernia.

The pain and cosmetic scores are listed in Table 3. The pain score was evaluated using a visual analog scale of 1-10 on days 1, 2 and 7, as well as 1 mo after surgery. There were differences in the pain scores on day 1 between the single-incision methods and

Table 3 Pain and cosmetic scores among the three groups

	X-Cone method (n = 100) (No.1 group)	Three-device method (n = 100) (No.2 group)	Conventional method (n = 100) (No.3 group)	P values	Statistical methods and values
Pain score[1]					One-Way ANOVA
1 d after surgery	3.4 ± 1.2	3.6 ± 1.2	4.2 ± 1.1	0	
				G1 *vs* G2 0.296	F = 11.16
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.005	
2 d after surgery	2.8 ± 0.8	3.0 ± 1.0	3.2 ± 1.0	0.002	F = 6.34
				G1 *vs* G2 0.155	
				G1 *vs* G3 0.001	
				G2 *vs* G3 0.204	
7 d after surgery	2.2 ± 0.6	2.0 ± 0.6	2.3 ± 0.7	0.014	F = 4.35
				G1 *vs* G2 0.252	
				G1 *vs* G3 0.365	
				G2 *vs* G3 0.010	
1 mo after surgery	1.6 ± 0.4	1.5 ± 0.3	1.7 ± 0.5	0	F = 9.435
				G1 *vs* G2 0.123	
				G1 *vs* G3 0.048	
				G2 *vs* G3 0.000	
Cosmetic score[2]					
1 wk after surgery	8 ± 0.7	8 ± 0.5	6 ± 0.4	0	F = 423.61
				G1 *vs* G2 0.999	
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.000	
2 wk after surgery	8 ± 0.8	8 ± 0.6	7 ± 0.3	0	F = 93.67
				G1 *vs* G2 0.966	
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.000	
1 mo after surgery	9 ± 0.2	9 ± 0.3	8 ± 0.5	0	F = 308.9
				G1 *vs* G2 0.814	
				G1 *vs* G3 0.000	
				G2 *vs* G3 0.000	

[1]Pain score 1-10; [2]Cosmetic score 1-10.

the conventional method in favor of the former (P < 0.0001), there was no difference between the two single-incision methods (P = 0.296). The X-Cone group was the most comfortable on day 2, while the three-device group on day 7 after surgery. At 1 mo, single-incision methods were better than the conventional method.

The cosmetic scores were rated on a 1–10 scale with questionnaires, with 10 being satisfied and 0 being unsatisfied. At 1 wk (P = 0.000), 2 wk (P = 0.000) and 1 mo (P = 0.000) after surgery, the single-incision methods were significantly better than the conventional group in terms of cosmetic scores. The X-Cone group and the three-device group had no differences (P > 0.05).

DISCUSSION

SILS techniques have been extensively applied both at home and abroad in recent years[7,11,17-20]. It is performed using a 1-wound laparoscopic surgical procedure or by using speciic ports[21-24].Compared with conventional laparoscopic cholecystectomy, they are associated with fewer injuries and better cosmetic outcomes, as well as many other advantages[25-29]. Some investigators believe that single-incision laparoscopic cholecystectomy will replace conventional laparoscopic cholecystectomy, and become the new gold standard[13,14].

This was an unplanned preliminary analysis of a continuing clinical trial to establish the safety of SILS as an operative approach for treatment of gallbladder disease. This article presents preliminary data of a multicenter, prospective randomized, single-blinded study comparing two single-incision cholecystectomy (three-device and X-Cone methods) with conventional standard multiport laparoscopic cholecystectomy. Primary end points included feasibility and safety, with pain, cosmesis, and costs as secondary end points.

In terms of feasibility and safety, except for the two patients who had additional working ports due to severe inflammatory adhesions in the three-device group, all patients underwent surgery successfully. None of the 200 patients converted to laparotomy or had complications such as bile duct injury, suggesting that single-incision laparoscopic cholecystectomy was feasible and safe. The low conversion rate may differ from that in other studies[18,30], which was probably due to the fact that patients with acute cholecystitis were excluded from our study. There were no significant differences in the complication rates among the three groups. There were four cases of incision contusion in

the three-device group, and three and one cases in the X-Cone and conventional groups, respectively. To avoid conflict of instruments in the abdominal cavity with the single-incision method, repeated external squeezing of the surrounding tissue is often required, which may explain the incision contusion in the three-device and X-Cone groups. In addition, there were different numbers of cases of bile leakage in all groups, which were treated with repeated rinsing with saline until the liquid turned clear. There was no case of biliary peritonitis infection afterwards.

There was no significant difference in blood loss and postoperative hospital stay. The X-Cone method required a longer operation time compared to the conventional (56.3 min *vs* 42.1 min, $P = 0.000$) and three-device methods (56.3 min *vs* 45.6 min, $P = 0.000$). Although all three surgeons had conducted > 100 cases of gallbladder SILS, the X-Cone procedure was associated with inconvenient operation across multiple ports and conflicting handling of instruments such as curved apparatus and solid textures, which might have extended the operation time. In contrast, the three-device method and conventional technique did not differ significantly in this regard (45.6 min *vs* 42.1 min, $P = 0.111$). The space between the instruments in the three-device method comprises soft subcutaneous tissue, which allows for a wider range of motion for the instruments, which is conducive to surgery.

Regarding the pain and cosmetic scores, there were differences between the single-incision methods and the conventional method in the pain score on day 1 after surgery, in favor of the single-incision methods. The main complaint was pain below the xiphoid incision in the conventional group. As the pain scores declined on days 2 and 7, as well as 1 mo after surgery, the differences became insignificant. At 1 and 2 wk and 1 mo after surgery, the single-incision methods were significantly better than the conventional group in terms of cosmetic scores. No difference was noted between the three device and X-Cone methods.

There was no difference in the hospitalization costs between the three-device and conventional methods, but there was when compared with the X-Cone method, suggesting that the latter method had an impact on the overall hospital costs. In three-device techniques, conventional equipment and devices were used, resulting in no cost difference from the conventional method, so the three-device method has a more cost-effective. Hence, the three-device approach is more suitable for community hospitals in China.

The present study had the following limitations. First, patients with acute cholecystitis were excluded, and this explains the low laparotomy conversion and low complication rates. Second, although all three surgeons had conducted > 100 operations for gallbladder SILS, the X-Cone procedure was associated with inconvenient operation across multiple ports and conflicting handling of instruments such as curved apparatus and solid textures, which might have extended the operation time. Both of these limitations are routinely seen when a new technique is evaluated. Also, long-term complications were not addressed by this study. The frequency of events still needs to be evaluated by long-term trials.

In summary, both the three-device and X-Cone methods are safe and feasible for single-incision laparoscopic cholecystectomy. Compared with conventional laparoscopic cholecystectomy, SILS techniques have advantages in pain and cosmetic factors. Due to its use of conventional instruments and cost-effective nature, the three-device method is more suitable for community hospitals in China, while the X-Cone device, which allows the placement of more surgical instruments, is more advantageous in more complicated procedures such as laparoscopic liver resection.

COMMENTS

Background

Single-incision laparoscopic cholecystectomy is a new laparoscopic procedure in laparoscopic surgery. This technique has been denominated by some authors as "scarless". The best advantage is a scar-free abdominal wall after surgery, as well as milder postoperative pain, faster recovery, shorter hospital stay, and better cosmetic outcomes.

Research frontiers

It is a lot of studies about the single-incision laparoscopic surgery (SILS). But there has been no previous reported study of the comparison of these three methods in cholecystectomy.

Innovations and breakthroughs

In this study, the three-device and X-Cone methods are safe and feasible for single-incision laparoscopic cholecystectomy. Compared with conventional laparoscopic cholecystectomy, SILS techniques have advantages in pain and cosmetic factors.

Applications

These two SILS techniques were used more and more in different hospitals. Further study is needed to confirm whether these potential advantages of the SILS techniques can change the clinical course of patients with liver surgery.

Peer-review

This is a very interesting paper about the SILS in cholecystectomy. The most important innovations of this study that was applied in the manuscript is the comparison of three methods in cholecystectomy. In addition, it demonstated that single-incision three-device and X-Cone methods are safe and feasible for laparoscopic cholecystectomy.

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ORIGINAL ARTICLE

Observational Study

Biliary leakage after urgent cholecystectomy: Optimization of endoscopic treatment

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Author contributions: Ljubičić N, Bišćanin A and Mijić A contributed to study conception and design; Ljubičić N, Bišćanin A, Pavić T, Nikolić M, Budimir I, Mijić A and Đuzel A performed the research; Ljubičić N, Bišćanin A and Đuzel A analyzed the data; Ljubičić N and Bišćanin A wrote the paper.
Ethics approval: The study was approved by the "Sestre milosrdnice" University Hospital Review Board (EP-13127/08-15).
Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.
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Abstract

AIM: To investigate the results of endoscopic treatment of postoperative biliary leakage occurring after urgent cholecystectomy with a long-term follow-up.

METHODS: This is an observational database study conducted in a tertiary care center. All consecutive patients who underwent endoscopic retrograde cholangiography (ERC) for presumed postoperative biliary leakage after urgent cholecystectomy in the period between April 2008 and April 2013 were considered for this study. Patients with bile duct transection and biliary strictures were excluded. Biliary leakage was suspected in the case of bile appearance from either percutaneous drainage of abdominal collection or abdominal drain placed at the time of cholecystectomy. Procedural and main clinical characteristics of all consecutive patients with postoperative biliary leakage after urgent cholecystectomy, such as indication for cholecystectomy, etiology and type of leakage, ERC findings and post-ERC complications, were collected from our electronic database. All patients in whom the leakage was successfully treated endoscopically were followed-up after they were discharged from the hospital and the main clinical characteristics, laboratory data and common bile duct diameter were electronically recorded.

RESULTS: During a five-year period, biliary leakage was recognized in 2.2% of patients who underwent urgent cholecystectomy. The median time from cholecystectomy to ERC was 6 d (interquartile range, 4-11 d). Endoscopic interventions to manage biliary leakage included biliary stent insertion with or without biliary sphincterotomy. In 23 (77%) patients after first endoscopic treatment bile flow through existing surgical drain ceased within 11 d following biliary therapeutic endoscopy (median, 4 d; interquartile range, 2-8 d). In those patients repeat ERC was not performed and

the biliary stent was removed on gastroscopy. In seven (23%) patients repeat ERC was done within one to fourth week after their first ERC, depending on the extent of the biliary leakage. In two of those patients common bile duct stone was recognized and removed. Three of those seven patients had more complicated clinical course and they were referred to surgery and were excluded from long-term follow-up. The median interval from endoscopic placement of biliary stent to demonstration of resolution of bile leakage for ERC treated patients was 32 d (interquartile range, 28-43 d). Among the patients included in the follow-up (median 30.5 mo, range 7-59 mo), four patients (14.8%) died of severe underlying comorbid illnesses.

CONCLUSION: Our results demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy.

Key words: Urgent cholecystectomy; Acute cholecystitis cholecystectomy complications; Biliary leakage; Endoscopic retrograde cholangiography; Endoscopic treatment

Core tip: Biliary leakage can be a serious complication of urgent cholecystectomy even in the hands of an experienced surgeon. Endoscopic interventions replaced surgery as first-line treatment for most of the biliary ducts injuries and biliary leakage after cholecystectomy. Long-term follow-up results demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy. Early cessation of bile output from the external abdominal drain strongly indicates healing of the leak and in those patients repeat cholangiography is not necessary, particularly if the presenting symptoms and/or signs of the biliary leakage disappeared.

Ljubičić N, Bišćanin A, Pavić T, Nikolić M, Budimir I, Mijić A, Đuzel A. Biliary leakage after urgent cholecystectomy: Optimization of endoscopic treatment. *World J Gastrointest Endosc* 2015; 7(5): 547-554 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/547.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.547

INTRODUCTION

Biliary leakage can be a serious complication of urgent cholecystectomy even in the hands of an experienced surgeon and can lead to considerable morbidity and prolonged hospitalization. Despite the fact that there are no properly controlled trials which could identify risk factors for bile duct injury, the risk of possible perioperative complications can be estimated based on patient characteristics (commorbidity, age, gender, body weight), intraoperative findings, and the amount of training and experience of the surgeon[1-3]. Large prospective and retrospective studies have defined the risk of biliary leakage arising from either open[4-6] or laparoscopic[6-9] cholecystectomy. The number of occurrences of biliary leaks during open cholecystectomy is not precisely known, but most large series demonstrated rates of 0.5% or less[10,11]. Despite several advantages over the open approach, laparoscopy, particularly in the cases of urgent cholecystectomy, provides a limited view of the biliary tract anatomy and can result in a higher rate of biliary leaking[7]. A two to four-fold increased incidence of biliary leakage following laparoscopic cholecystectomy was demonstrated[6,9,12].

The role of endoscopic retrograde cholangiography (ERC) in the management of biliary leakage is well established. Endoscopic treatment of biliary leakage includes biliary stent insertion with or without biliary sphincterotomy, biliary sphincterotomy alone or nasobiliary tube placement. All those methods have been demonstrated to be effective treatment for biliary leakage without need for further surgery[13-15]. However, the need for an endoscopic sphincterotomy, the choice between nasobiliary tube drainage and endoscopic biliary stenting and the preferable type of stent (short or long stent; larger or smaller diameter) are still the matter of extensive debate. Therefore, optimal endoscopic intervention is still not established and data regarding the long-term follow-up of those patients is missing.

The aim of this study was to determine the results of endoscopic treatment of postoperative biliary leakage occurring after urgent cholecystectomy with a long-term follow-up.

MATERIALS AND METHODS

This is an observational database study conducted in a tertiary care center with primary uptake area covering a population of approximately 300000 people (City of Zagreb, Republic of Croatia). The study was approved by the "Sestre milosrdnice" University Hospital Review Board. All consecutive patients who underwent ERC for presumed postoperative biliary leakage following urgent cholecystectomy between April 2008 and April 2013 were considered for this study. All the patients included in the study signed the informed consent statement. Patients with bile duct transection and biliary strictures were excluded. Biliary leakage was suspected in case of bile appearance from either percutaneous drainage of abdominal collection or abdominal drain placed at the time of cholecystectomy.

Information of all consecutive patients with postoperative biliary leakage, including cholecystectomy details such as indication for cholecystectomy, etiology and type of leakage, ERC findings and post-ERC complications, were reviewed from our electronic database. The grading of overall health and comorbidity

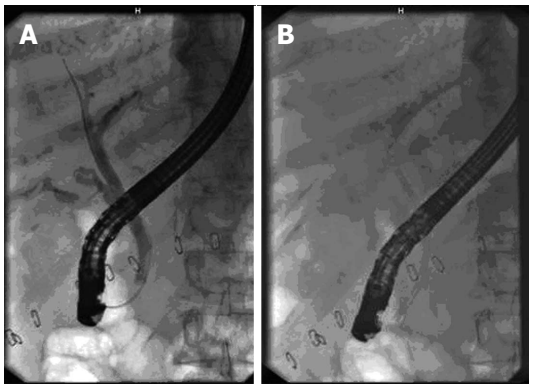

Figure 1 Radiograph at endoscopic retrograde cholangiography. A: Radiograph at endoscopic retrograde cholangiography showing biliary leakage into peritoneum from cystic duct stump; B: Radiograph showing 10 F biliary stent inserted above the level of the leak from cystic duct stump.

was performed according to the American Society of Anesthesiology classification[16]. All ERC successfully treated patients were followed-up after they were discharged from the hospital and the main clinical characteristics and laboratory data, including levels of bilirubin, alanine transaminase (ALT), aspartate aminotransferase, GGT, alkaline phosphatase, CRP and common bile duct diameter measured on transabdominal ultrasound were electronically recorded every month during first 6 mo, then every 6 mo.

ERC was performed with standard equipment (TJF 145, Olympus Optical Co., Japan), and by the well-trained endoscopists, each with at least five-year experience. Selective cannulation of the common bile duct was attempted with a standard wire-guided sphincterotome and 0.035-inch hydrophilic guidewire. If the efforts to enter the common bile duct were unsuccessful, a needle-knife papillotomy was performed. In all patients ERC was performed under intravenous sedation and analgesia (propofol and fentanyl) under direct anesthesiologist control. Pre-procedural antibiotics were administered (ciprofloxacin 400 mg *iv*).

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis was identified by characteristic abdominal pain associated with serum amylase levels at least three times the upper limits of normal. Postprocedural bleeding was defined as one or more signs of ongoing bleeding, including fresh hematemesis or melena, hematochezia, aspiration of fresh blood *via* nasogastric tube, vital signs instability, and a reduction of hemoglobin level by more than 2 g/dL over a 24-h period.

In all patients with a cholangiographic evidence of a biliary leakage the placement of a plastic 10 F biliary stent without biliary sphincterotomy was performed. The standard procedure was to place proximal end of a biliary stent above the level of the leak in patients with the cholangiographic evidence of a leakage from the common bile duct or from cystic duct stump or cholecystohepatic duct of Luschka (Figure 1). If biliary leakage from the right hepatic duct or intrahepatic duct was confirmed, and in patients in whom biliary leakage was not located, only short plastic 10F biliary stent was inserted. In patients with a cholangiographic evidence of a biliary leakage and a common bile duct stone(s), biliary sphincterotomy was performed and after the stone was removed (with balloon catheter or Dormia basket), plastic 10F biliary stent was placed.

The clinical healing of the biliary leakage was determined by the complete absence of the symptoms, cessation of the output of the bile from the drain and by the removal of the drain without any further adverse outcomes. The failure of the endoscopic treatment was determined by the need for further intervention to control the leak including surgery and/or percutaneous drainage of the biliary tree.

Statistical analysis

All analysis were performed by an expert biomedical statistician with a statistical package (Statistica 10.0 for Windows, United States). Descriptive statistics were used in this case series to describe characteristics of the patients, procedures and outcomes. Continuous variables are expressed as medians with interquartile ranges for nonparametric values. Median time to biliary leakage closure and median time were estimated using a Kaplan-Meier survival curve. Spearman correlation coefficients were calculated to assess interrelationships of certain quantitative variables. A *P* values below 0.05 were considered statistically significant.

RESULTS

Study population

Among 2472 ERCP procedures that were performed in our center between April 2008 and April 2013, there were 34 patients who underwent ERC because of postoperative biliary leakage occurring after urgent cholecystectomy: 23 patients in whom urgent cholecystectomy was performed at our institution and 11 patients referred from our collaborating institutions (Figure 2). In the same period urgent cholecystectomy was performed in 1058 patients (31 patients with gallstones and hydrops of the gallbladder, 662 patients with acute or subacute calculous cholecystitis, 365 patients with gangrenous cholecystitis and one patient with Mirizzi's syndrome) at our institution. Since endoscopic treatment is a standard practice for management of post-cholecystectomy biliary leakage at our hospital, all the patients with suspected biliary leakage were referred to the endoscopy unit. Therefore, during a 5-year period biliary leakage occurred in 2.2% of all patients who underwent urgent cholecystectomy. In all those patients indications for urgent cholecystectomy were acute or subacute calculous cholecystitis (21 patients) or gangrenous cholecystitis (13 patients).

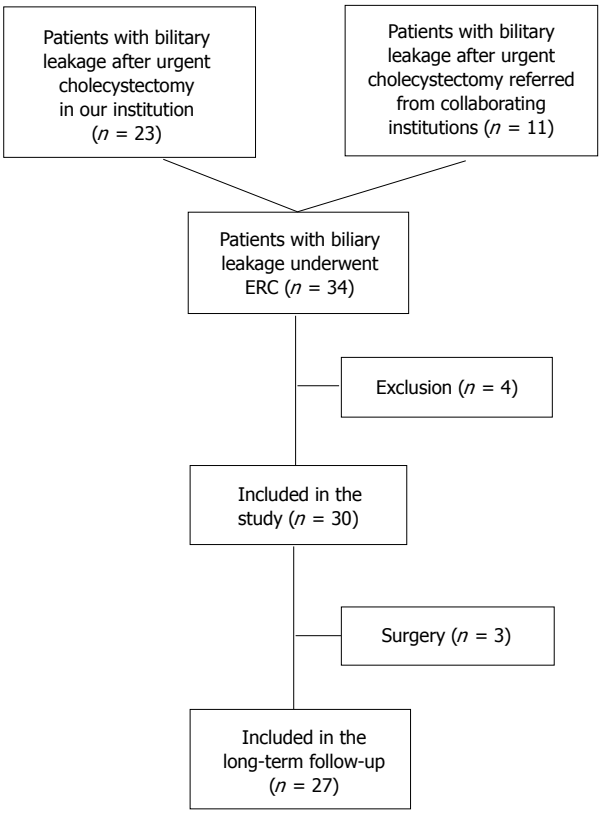

Figure 2 Schematic of subjects included in the study and long-term follow-up. ERC: Endoscopic retrograde cholangiography.

Endoscopic procedures

Initial ERC was successful in 32 out of 34 patients (94%). The reasons for failure of ERC in two patients were intradiverticular location of the papilla seen in one patient and the presence of a Billroth Ⅱ operation in a second patient. Patient with intradiverticular location of the papilla was successfully treated with the rendezvous technique[12] and this patient was included in the study. In two patients in whom ERC was successfully performed, the cholangiography demonstrated a complete transection of the common bile duct (first patients) and significant common bile duct stenosis because of multiple clips across the bile duct (second patient). Surgery was recommended for those patients as well as for the patient with the presence of a Billroth Ⅱ operation. Those three patients were excluded from the study. One patient, at the age of 79, with severe comorbidities, including heart failure with permanent atrial fibrillation, arterial hypertension, diabetes and renal insufficiency, died immediately after ERC (with stent in place) because of acute myocardial infarction and cardiac arrest. This patient was also excluded from the study.

The main clinical characteristics of 30 consecutive patients with postoperative biliary leakage included in the study are summarized in Table 1.

The median time from cholecystectomy to ERC was 6 d (interquartile range, 4-11 d) and 4 (13%) patients underwent ERC more than 2 wk after surgery.

Table 1 Clinical characteristics of 30 consecutive patients with post-cholecystectomy biliary leakage included in the study

Parameter	*n* (%)
Age (yr) (median)	62
Male/female	14 (46.7)/16 (53.3)
Cholecystectomy details	
Open	9 (30.0)
Laparoscopic	13 (43.3)
Laparoscopic to open conversion	8 (26.7)
Abdominal drain:	
Bile leak ⩽ 400 mL/d	24 (80.0)
Bile leak > 400 mL/d	6 (20.0)
Abdominal pain	20 (66.7)
Jaundice	8 (26.7)
Fever	14 (46.7)
Abdominal collection	8 (26.7)
Abdominal distension	6 (20.0)
Ascites	1 (3.3)
Comorbidity	
ASA 1-2	24 (80.0)
ASA 3-4	6 (20.0)

ASA: American Society of Anesthesiology.

Most common biliary leakage sites included leak from the cystic duct stump in 13 patients, the right hepatic duct or intrahepatic duct in 12 patients, leak from the common bile duct in three patients and from cholecystohepatic duct of Luschka in one patient (Table 2).

Endoscopic biliary sphincterotomy was performed in 17 patients: 11 patients with cholangiographic evidence of common bile duct stone(s), 3 patients with suspected but not proven common bile duct stone, and three patients in whom cannulation of the common bile duct was difficult (in two of them needle-knife papillotomy was performed). All those patients underwent plastic 10 F biliary stent placement. The proximal end of the biliary stent was placed above the site of the biliary leakage in 16 patients with leakage from the cystic duct stump, cholecystohepatic duct of Luschka and leakage from the common bile duct (based on the endoscopist's discretion, only in one patient biliary stent was placed below the site of the biliary leakage). In patients with biliary leakage from the right hepatic duct or intrahepatic duct and in patients in whom biliary leakage was not located on cholangiography, only short plastic 10 F biliary stent stranding the papilla was inserted.

After first endoscopic treatment bile flow through existing surgical drain ceased in 23 (77%) patients within 11 d following biliary therapeutic endoscopy (median, 4 d; interquartile range, 2-8 d). Those patients become asymptomatic with the normalization in laboratory data, and the biliary stent was removed on gastroscopy.

Mild post-ERC pancreatitis was observed in two patients after needle-knife papillotomy was performed. The occurrence of ERC-related pancreatitis did not affect the ultimate outcome in any of them. Post-ERC bleeding

Table 2 Endoscopic retrograde cholangiography findings in patients with post-cholecystectomy biliary leakage included in the study

1st ERC findings	*n* (%)
Number of patients	30
Bile leak characteristics	
Leak from the cystic duct stump	13 (43.3
Leak from the right hepatic duct or intrahepatic duct	12 (40.0)
Leak from the common bile duct	3 (10.0)
Leak from cholecystohepatic duct of Luschka	1 (3.3)
Could not be located	1 (3.3)
CBD stone(s)	11 (36.7)
Endoscopic management	
Biliary stent	13 (43.3)
EBS + stone extraction + biliary stent	11 (36.7)
EBS + biliary stent	6 (20.0)
Adverse effect	
Pancreatitis	2 (6.7)
Bleeding	1 (3.3)
1st ERC leakage resolution success rate	23/30 (76.7)
Repeated ERC findings	
Number of patients	7
Bile leak characteristics	
Leak from the right hepatic duct or intrahepatic duct	6 (85.7)
Could not be located	1 (14.3)
CBD stone(s)	2 (28.6)
Endoscopic management	
Biliary stent	5 (71.4)
EBS + extraction + biliary stent	2 (28.6)
Adverse effect	0
ERC leakage resolution success rate	27/30 (90)
Referred to surgery	3 (10)

ERC: Endoscopic retrograde cholangiography; EBS: Endoscopic biliary sphincterotomy; CBD: Common bile duct.

was observed in only one patient with liver cirrhosis and heart failure in which biliary sphincterotomy was performed (reduction of hemoglobin level by more than 2g/dL over a 24-h period). This patient was successfully treated conservatively and the occurrence of post-ERC bleeding did not affect the ultimate outcome of this patient. Duodenal perforation was not observed (Table 2).

Necessity for repetition of endoscopic procedure

In seven (23%) patients in whom persistent bile flow through existing surgical drain was demonstrated, suggesting the absence of the biliary leakage resolution, repeat ERC was performed within one to 4 wk, depending on the extent of the biliary leakage. In all those patients biliary stent was removed and replaced with a new one (Table 2). In two patients common bile duct stone was recognized and removed with a balloon catheter. After the repeat ERC was performed, four of those seven patients had cessation of bile flow through existing surgical drain within two to nine days (median, 5.5 d). Those four patients become asymptomatic with the normalization in laboratory data, and the biliary stent was removed on gastroscopy. There were no adverse events related to the repeat ERC.

Overall, 27 (90%) patients with biliary leakage after urgent cholecystectomy included in study were successfully treated with ERC, and all those patients were included in the long-term follow-up. ERC was repeated in 14.8% of patients, and 1.1 ERC procedure was needed for every patient with leakage resolution.

Three patients (10%) with biliary leakage after urgent cholecystectomy included in the study had more complicated clinical course. One of them had a continuous biliary leakage demonstrated as the high-output bile flow through existing surgical drain. In this patient second repeat ERC revealed large right hepatic duct biliary leakage. This patient was referred to surgery together with two patients in whom large symptomatic subphrenic abscess was confirmed along with a persistent biliary leakage through the surgical drain. Altogether eight patients had the abdominal fluid collection, and six were treated conservatively.

Table 3 Clinical characteristics of endoscopic retrograde cholangiography successfully treated patients with post-cholecystectomy biliary leakage in the long-term follow-up

Parameter	*n* (%)
Number of patients	27
Abdominal pain	0
Abdominal distension	0
Elevated bilirubin[1]	0
Elevated ALT[2]	13 (48.2)
Dilated common bile duct (> 6 mm)[3]	0
Death	4 (14.8)

[1]Bilirubin > 20 mmol/L; [2]ALT > two times above normal; [3]Measured by transabdominal or endoscopic ultrasound. ALT: Alanine transaminase.

Endoscopic treatment outcomes and long term follow-up

In all patients in whom endoscopic therapy led to the complete resolution of biliary leakage, median interval from the first endoscopic intervention and biliary stent placement to the stent extraction was 32 d (interquartile range, 28-43 d) (Figure 3). Median interval from the therapeutic ERC (first or repeated) to the stent extraction was 32 d, also (interquartile range, 28-42 d). Cessation of the bile flow through existing surgical drain occurred up to eleventh day after therapeutic ERC (first or repeated; median, 4 d, interquartile range, 2-8 d). There was no correlation between the volume of bile leak output on a surgical drain and the probability of bile leakage resolution after ERC ($r = 0.161$, $P = 0.537$).

Among 27 patients initially included in the long-term follow-up (median 30.5 mo, range 7-59 mo), four patients (14.8%) died. All of deceased patients died of severe underlying comorbid illnesses: malignancy (one patient), cerebrovascular accidents (one patient), heart failure (two patients). The main clinical characteristics and laboratory data of patients included in the long-term follow-up are demonstrated in Table 3. All those patients were asymptomatic with normal levels of bilirubin and without any signs of cholangitis and bile duct dilation. In 13 (48.2%) patients increase in ALT

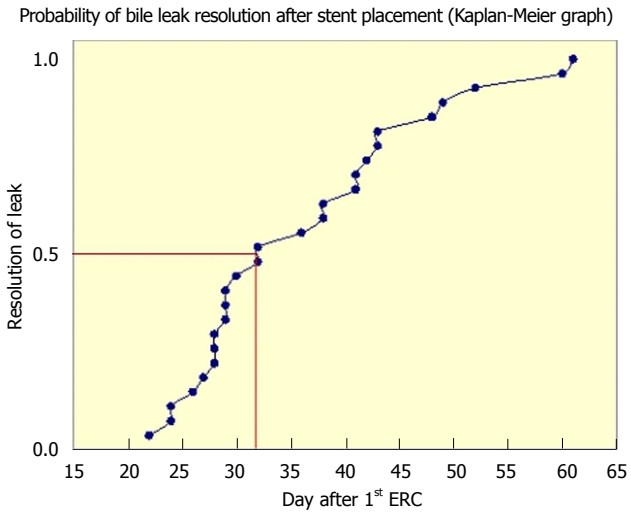

Figure 3 Kaplan-Meier graph demonstrates probability of resolution of bile leak after first endoscopic retrograde cholangiography with biliary stent placement for postcholecystectomy biliary leakage. ERC: Endoscopic retrograde cholangiography.

concentration (up to two times above the normal values) was observed. In all those patients endoscopic ultrasound revealed normal finding of common bile duct.

DISCUSSION

Postoperative biliary leakage is a serious complication that occurs in 0.2%-2.2% of all cholecystectomies[4-7,17], and even more frequently after laparoscopic cholecystectomy for acute cholecystitis[9]. In accordance with the results of our study, during 5-year period biliary leakage occurred in 2.2% of patients who underwent urgent cholecystectomy. This percentage is high with regard to the percentage of biliary leakage among patients who underwent either open or laparoscopic cholecystectomy that had been reported previously. It is possible to assume that mechanisms responsible for those findings in patients after urgent cholecystectomy include the presence of inflammation and edema (the cystic duct is indurated and shortened, lying in close contact with the common bile duct), or bleeding[6,9]. That may lead to the poor identification of anatomical structures including possible aberrant anatomy and dislodgement of suboptimally placed clips or a bile duct injury, where the experience of the surgeon is crucial[1,6,9,13].

Endoscopic interventions replaced surgery as first-line treatment for most of the biliary ducts injuries and biliary leakage following cholecystectomy. All of them are aimed towards decreasing the transpapillary pressure, allowing bile to flow through the path of decreased resistance. As a consequence, biliary leakage closes spontaneously. Recent data strongly suggest that biliary stent placement without biliary sphincterotomy is more efficient and has a lower complication rate than biliary sphincterotomy[18,19]. Since endoscopic treatment is a standard practice for management of postcholecystectomy biliary leakage at our institution, all the patients with suspected biliary leakage were referred to the endoscopy unit. Therefore, only patients with biliary leakage after urgent cholecystectomy were included in our study. To our knowledge this is the first long-term follow-up study investigating the efficiency of the endoscopic therapy in patients with biliary leakage occurring after urgent cholecystectomy. Our results clearly demonstrated the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage. Among our group of patients closure of bile leaks was achieved with endoscopic therapy in great majority of patients (90%).

There are several limitations to this study. First, the number of patients was relatively small, although the study period included five years, but the protocol narrowed the inclusion criteria. Second, our management algorithm did not include some other available imaging methods like magnetic retrograde cholangiography because technical success of the initial ERC was rather high (94%) and this could be regarded as redundant.

There are no uniform recommendations regarding the need for repeat cholangiography at the time when previously positioned biliary stent need to be removed after resolution of biliary leakage. Namely, when endoscopic biliary stents are placed, the precise time when the leak closes cannot be determined. To our results, early cessation of bile output from the external abdominal drain strongly indicates healing of the bile leak. In majority of those patients presenting clinical symptoms and/or signs disappear very fast. Contrary, the persistent bile flow through existing surgical drain, in our study more than 11 d after endoscopic stent placement, indicates the persistent biliary leakage. In those patients, repeat ERC or some other procedure seems to be necessary. Reason for the persistent biliary leakage, as we found in our study, might be the presence of a previously unrecognized common bile duct stones, inadequately drained abdominal collection with inflammation and abscess formation or magnitude of bile duct defect.

Despite the fact that there are no uniform recommendations regarding the need for cholangiography at the time of stent removal, few studies demonstrated that repeat cholangiography is not necessary in patients in whom the presenting symptoms and/or signs of the biliary leakage had been disappeared. In those clinically well patients gastroscopy with biliary stent removal is effective if performed after the median time of 33 d following biliary stent placement[20-22]. In our study we clearly demonstrated that in asymptomatic patients following urgent cholecistectomy in whom early cessation of bile output from the external abdominal drain occurred (median, 4 d, interquartile range, 2-8 d), biliary stent removal on gastroscopy is safe after the median time of 32 d after biliary stent placement

without any need for repeat cholangiography.

During hospitalization, only one 79 years old patient with severe comorbidities, including heart failure with permanent atrial fibrillation, arterial hypertension, diabetes and renal insufficiency, died immediately after ERC (with stent in place) because of acute myocardial infarction and cardiac arrest. Among 27 patients included in the long-term follow-up four of them died. The main contributory factor that considerably affects patient's prognosis seems to be the comorbidity. Namely, among deceased patients all of them died of severe underlying comorbid illnesses, unrelated with cholecystectomy or endoscopic procedure.

In conclusion, despite the fact that the major limitation of our study is relatively small number of patients, long-term follow-up results demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage following urgent cholecystectomy. Early cessation of bile output from the external abdominal drain strongly indicates healing of the leak and in those patients repeat cholangiography is not necessary, particularly if the presenting symptoms and/or signs of the biliary leakage disappeared.

COMMENTS

Background

Biliary leakage can be a serious complication of urgent cholecystectomy even in the hands of an experienced surgeon. Endoscopic interventions replaced surgery as first-line treatment for most of the biliary ducts injuries and biliary leakage. Long-term follow-up results in this study demonstrate the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy.

Research frontiers

This paper describes a novel approach to endoscopic retrograde cholangiography procedure as a treatment for resolution of biliary leakage following urgent cholecystectomy.

Innovations and breakthroughs

This paper for the first time demonstrates the great efficiency of the endoscopic therapy in the treatment of the patients with biliary leakage after urgent cholecystectomy. Early cessation of bile output from the external abdominal drain strongly indicates healing of the leak and in those patients repeat cholangiography is not necessary.

Applications

Considering the tendency of early cholecystectomy in acute cholecystitis, and an increase in the number of laparoscopic procedures in the future, it is possible to expect a lot of patients with biliary leakage, especially after the urgent cholecystectomy. These results could be also applied to all patients with biliary leakage.

Peer-review

This is an interesting and practical paper about biliary leakage after surgery for acute cholecystitis. The subject is of paramount importance because most of the series mixed leakage after planned and emergency cholecystectomies.

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ORIGINAL ARTICLE

Prospective Study

Polyp detection rates using magnification with narrow band imaging and white light

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Author contributions: Gilani N and Ramirez FC designed and performed the research study; Stipho S, Panetta JD, Petre S and Young MA helped to collect the data; Gilani N and Ramirez FC performed statistical analysis and wrote the paper.

Ethics approval: This study was approved by Institutional Review Board at Phoenix VA Medical Center, Arizona, United States.

Clinical trial registration: Not applicable as this was a non-randomized study.

Informed consent: All patients in the study gave informed consent for the colonoscopy. Informed consent for the study was waived by the Institutional Review Board per request due to non-randomization.

Conflict-of-interest: None.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at (ngilani@hotmail.com). Consent for data sharing was not obtained from the participants but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To compare the yield of adenomas between narrow band imaging and white light when using high definition/magnification.

METHODS: This prospective, non-randomized comparative study was performed at the endoscopy unit of veteran affairs medical center in Phoenix, Arizona. Consecutive patients undergoing first average risk colorectal cancer screening colonoscopy were selected. Two experienced gastroenterologists performed all the procedures that were blinded to each other's findings. Demographic details were recorded. Data are presented as mean ± SEM. Proportional data were compared using the χ^2 test and means were compared using the Student's t test. Tandem colonoscopy was performed in a sequential and segmental fashion using one of 3 strategies: white light followed by narrow band imaging [Group A: white light (WL) → narrow band imaging (NBI)]; narrow band imaging followed by white light (Group B: NBI → WL) and, white light followed by white light (Group C: WL → WL). Detection rate of missed polyps and adenomas were evaluated in all three groups.

RESULTS: Three hundred patients were studied (100 in each Group). Although the total time for the colonoscopy was similar in the 3 groups (23.8 ± 0.7, 22.2 ± 0.5 and 24.1 ± 0.7 min for Groups A, B and C, respectively), it reached statistical significance between Groups B and C ($P < 0.05$). The cecal intubation time in Groups B and C was longer than for Group A (6.5 ± 0.4 min and 6.5 ± 0.4 min *vs* 4.9 ± 0.3 min; $P < 0.05$). The withdrawal time for Groups A and C was longer than Group B (18.9 ± 0.7 min and 17.6 ± 0.6

min *vs* 15.7 ± 0.4 min; $P < 0.05$). Overall miss rate for polyps and adenomas detected in three groups during the second look was 18% and 17%, respectively (P = NS). Detection rate for polyps and adenomas after first look with white light was similar irrespective of the light used during the second look (WL → WL: 13.7% for polyps, 12.6% for adenomas; WL → NBI: 14.2% for polyps, 11.3% for adenomas). Miss rate of polyps and adenomas however was significantly higher when NBI was used first (29.3% and 30.3%, respectively; $P < 0.05$). Most missed adenomas were ⩽ 5 mm in size. There was only one advanced neoplasia (defined by size only) missed during the first look.

CONCLUSION: Our data suggest that the tandem nature of the procedure rather than the optical techniques was associated with the detection of additional polyps' and adenomas.

Key words: Colonoscopy; Narrow band imaging; High-definition; Magnification; Screening; Yield

Core tip: The role of narrow band imaging for polyp detection is controversial. We studied 3 groups of 100 patients each, undergoing tandem colonoscopy by (1) white light followed by narrow band imaging; (2) narrow band followed by white light; and (3) white light followed by white light. Detection rate for polyps with white light used first was similar irrespective of the light used afterwards. Miss rate of polyps and adenomas was higher when narrow band imaging was used first (29.3% and 30.3%, respectively; $P < 0.05$). Our study suggests that the tandem nature of colonoscopy rather than the optical techniques, detects missing pathology.

Gilani N, Stipho S, Panetta JD, Petre S, Young MA, Ramirez FC. Polyp detection rates using magnification with narrow band imaging and white light. *World J Gastrointest Endosc* 2015; 7(5): 555-562 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/555.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.555

INTRODUCTION

Colonoscopy and polypectomy is aimed at prevention or identification of early colorectal cancer[1-3]. Colonoscopy however is not infallible in the detection of polyps and adenomas with reported miss rates in the order of 14% to 32% using tandem colonoscopy[4-10] and 23.3% for lesions (polyps and cancers) in resected colonic specimens[11]. Advances in the optics of endoscopy such as high definition, magnification and narrow band imaging have been introduced in clinical practice, and amongst others, are aimed at improving the yield of polyp and adenoma detection[12-20]. Our hypothesis was that narrow band imaging (NBI) detects more polyps and adenomas than white light (WL) when used in a tandem fashion during screening colonoscopy.

MATERIALS AND METHODS

As part of a quality improvement assessment of new technology, we sought to assess the yield of polyp and tubular adenoma detection when using wide angle magnification colonoscopy either with narrow band imaging or white light in average risk patients referred for their first colorectal cancer screening colonoscopy. These procedures were performed using the Olympus 180 H series colonoscopies (Olympus America Inc., Center Valley, PA). Cecal intubation was carried out using WL and without magnification. Once the cecum was reached, the electronic magnification featured at 1.5X was turned on. All these procedures were performed by one of two experienced board certified gastroenterologists (who had performed > 2500 and > 5000 colonoscopies each and > 250 colonoscopies using narrow band imaging) using one of the following strategies: (1) Group A: white light followed by narrow band imaging (WL → NBI); (2) Group B: narrow band imaging followed by white light (NBI → WL) and; (3) Group C: white light followed by white light (WL → WL) in a sequential and segmental fashion of tandem endoscopy every 15-20 cm. Measurements included: cecal intubation, withdrawal and total procedure times; grading of bowel preparation; anatomical location, size and histological diagnosis of polyps detected with white light or NBI, when using either of the strategies. Removed polypoid lesions, were classified based on histology as neoplastic (adenomas, hyperplastic and other tumors) and non-neoplastic (normal mucosa, hyperplastic mucosa, prominent lymphoid aggregates).

Patients underwent bowel cleansing with 4 L of polyethylene glycol solution and 4 bisacodyl tablets (20 mg total dose). Patients with suboptimal preparation (as determined by the colonoscopist during the insertion portion of the examination) were not included in the study. All procedures except four were performed using moderate sedation with incremental doses of midazolam and meperidine or fentanyl. Cecal intubation was confirmed by photo documentation of appendiceal orifice and ileocecal valve. Procedure times (cecal intubation, withdrawal and total procedure times) were documented by the Olympus stopwatch built in the processors. The watch was not stopped for rinsing and cleaning or while performing polypectomy. Polyp's size was estimated using an open biopsy forceps or the snare used for polypectomy. All polyps were removed during the withdrawal portion of the procedure even if visualized during the insertion phase. Colon was anatomically divided into proximal (proximal to splenic flexure) and distal (splenic flexure or distal to it) portions. Advanced neoplasia was defined as the presence of a tubular adenoma ⩾ 10 mm, villous component, or the presence of high grade dysplasia or

Table 1 Demographics, adequacy of bowel preparation, procedure-related times and polyps/adenomas detection

	Group A (WL → NBI)	Group B (NBI → WL)	Group C (WL → WL)	$P < 0.05$
Age (mean ± SEM) in years	62.2 ± 0.7	59.3 ± 0.6	62.0 ± 0.7	
Gender				
Men	99	98	98	
Women	1	2	2	
Cecal intubation time (mean ± SEM) in minute	4.9 ± 0.3	6.5 ± 0.4	6.5 ± 0.4	A *vs* C A *vs* B
Withdrawal time (mean ± SEM) in minute	18.9 ± 0.7	15.7 ± 0.4	17.6 ± 0.6	A *vs* B C *vs* B
Total procedure time (mean ± SEM) in minute	23.8 ± 0.7	22.2 ± 0.5	24.1 ± 0.7	B *vs* C
Bowel preparation				
Excellent	36 (%)	18 (%)	22 (%)	
Good	56 (%)	74 (%)	67 (%)	
Fair adequate	8 (%)	8 (%)	11 (%)	
Patients with polyps	78	67	73	
Total polyps detected	211	147	219	
Polyps/patient with polyps	2.7	2.2	3.0	
Of patients with adenomas	47	47	57	
Total adenomas detected	97	76	111	
Adenomas/patient with adenomas	2.1	1.6	1.9	

WL: White light; NBI: Narrow band imaging.

invasive carcinoma on histology.

The study was approved by the local Institutional Review Board and exemption for informed consent was granted due to non-randomized design and the fact that all patients underwent standard white light colonoscopy. However, informed consent for colonoscopy was obtained from all patients undergoing procedures.

Statistical analysis

SPSS 16.0 was used for statistical analysis. Data are presented as mean ± SEM. Proportional data were compared using the χ^2 test and means were compared using the Student's *t* test.

RESULTS

Three-hundred patients, 100 consecutive in each Group were studied. Table 1 shows the demographics, adequacy of bowel preparation and procedure-related times in each group. Although the total time for the colonoscopy was similar in the 3 groups, it reached statistical significance between Groups B and C ($P < 0.05$). The cecal intubation time in Groups B and C was longer than for Group A. The withdrawal time for Groups A and C was longer than Group B ($P < 0.05$).

In Group A, (WL → NBI) 211 polyps were detected in 78 patients (2.7 polyps/ patient); in Group B (NBI → WL) 147 polyps were detected in 67 patients (2.2 polyps/ patient) whereas in Group C (WL → WL) 219 polyps were detected in 73 patients (3.0 polyps/ patient). Adenomas were detected in 151 patients (50% of all patients) and similar in the 3 groups (47%, 47% and 57% for Groups A, B and C, respectively).

Yield for detection of polyps

As shown in Figure 1, in Group A (WL → NBI), the withdrawal with WL detected 181 polyps (62.4% distal and 37.6% proximal). Of those detected distally, 89.4% were ⩽ 5 mm in size; 7.1%, 6-9 mm in size and, 3.5%, ⩾ 1 cm. Of those detected proximally, 72% were ⩽ 5 mm in size; 17.7%, 6-9 mm and, 10.3%, ⩾ 1 cm in size. Switching to NBI detected 30 additional polyps (14.2% of all polyps detected in Group A) of which 70% were distal and 30% proximal. Ninety-five percent and 89% of the newly detected distal and proximal polyps were ⩽ 5 mm in size, respectively.

In Group B (NBI → WL), the first withdrawal with NBI detected 103 polyps (59.2% distal and 40.8% proximal). Of those detected distally, 91.8% were ⩽ 5 mm; 6.6%, 6-9 mm and, 1.6% was ⩾ 1 cm in size. Of those polyps detected proximally, 83.3% were ⩽ 5 mm; 14.3%, 6-9 mm and, 2.4%, ⩾ 10 mm in size. Switching to WL detected 44 additional polyps (30.8% of all polyps detected in Group B) of which 48% were distal and 52% proximal. Ninety-five percent and 92% of the newly detected distal and proximal polyps were ⩽ 5 mm in size, respectively.

In Group C, (WL → WL) the first withdrawal with white light detected 189 polyps (61.9% distal and 38.1% proximal). Of the polyps detected distally, 76.9% were ⩽ 5 mm in size, 17.1% were 6-9 mm and the remaining 6% were ⩾ 10 mm in size. Of the polyps detected proximally, 65.3% were ⩽ 5 mm in size, 23.6% were 6-9 mm and 11.1% were ⩾ 10 mm. When the second look with white light again was used, 30 additional polyps (13.7% of all polyps in Group C) were detected and of which 56.7% were proximal and 43.3% distal. Eighty-five percent and 76.5% of the polyps newly found in the distal and proximal colon were ⩽ 5 mm in size, respectively.

The newly diagnosed polyps detected with NBI (Group A, 14.2%) and white light (Group C, 13.7%) during the second look were significantly fewer than the ones detected using the WL after NBI (Group B, 30.8%) ($P < 0.05$). Overall, the second look of the tandem segmental colonoscopy detected 18% new polyps (104/577 polyps).

Yield for detection of adenomas

As can be seen in Figure 2, In Group A (WL → NBI), the first withdrawal with WL detected 86 adenomas: 50 (58.1%) proximal (64%: ⩽ 5 mm in size, 20%:

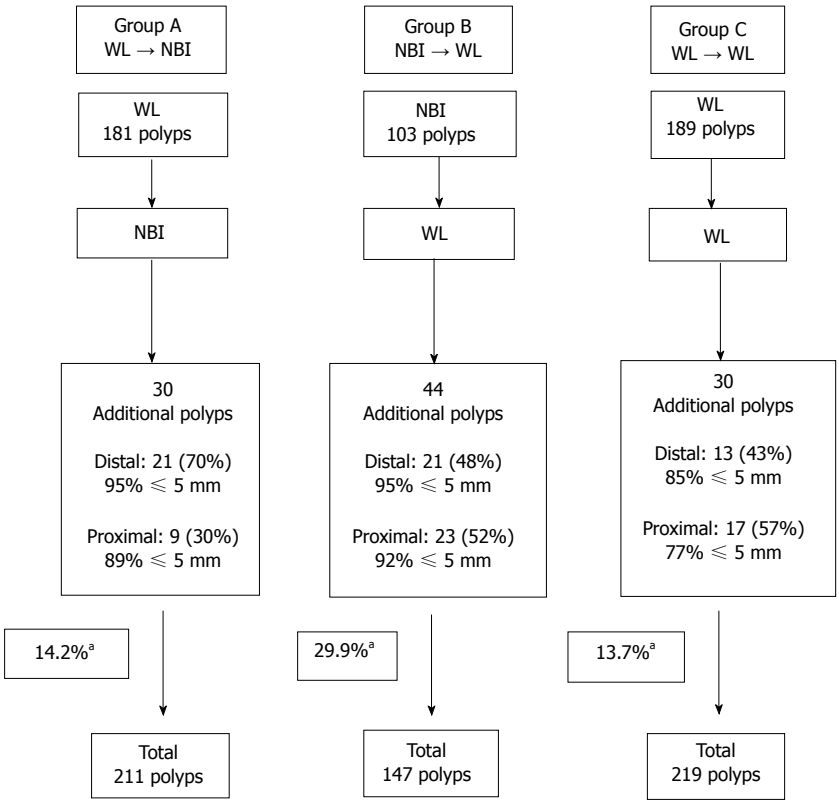

Figure 1 Yield of polyp detection. [a]*P* < 0.05, Group A and Group C *vs* Group B. WL: White light; NBI: Narrow band imaging.

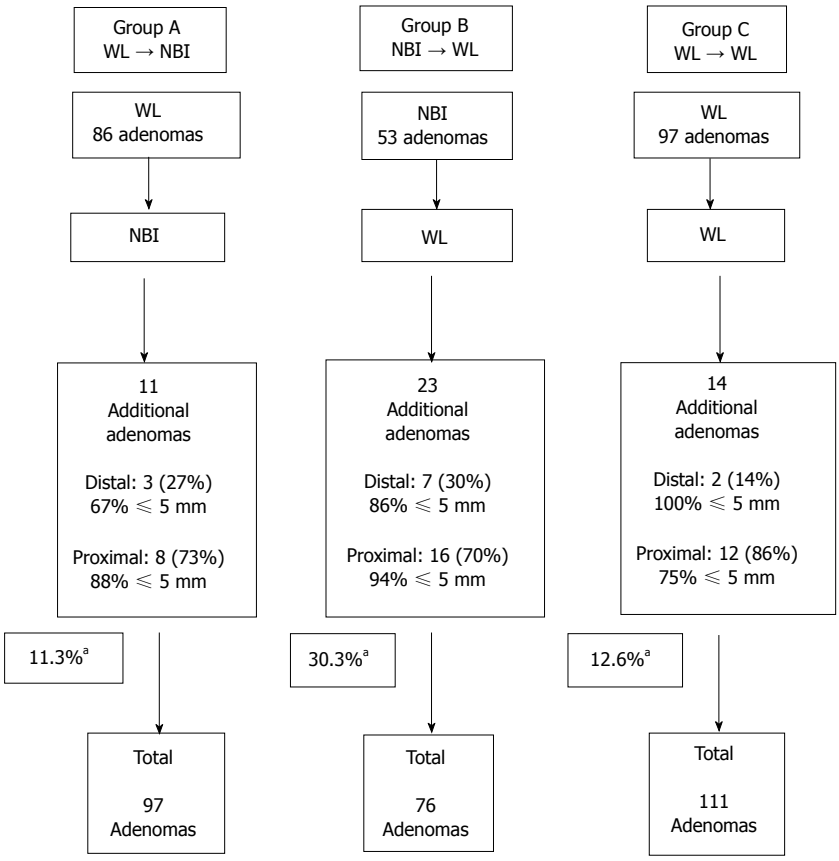

Figure 2 Yield of adenoma detection. [a]*P* < 0.05, Group A and Group C *vs* Group B. WL: White light; NBI: Narrow band imaging.

6-9 mm and, 14%: ⩾ 10 mm in size) and, 36 (41.9%) distal (77.8%: ⩽ 5 mm, 13.9%: 6-9 mm and 8.3%: ⩾ 10 mm). Switching to NBI detected 11 additional adenomas (11.3% of all adenomas detected in Group A): 8 (73%) proximal (88%: ⩽ 5 mm and 12%: 6-9 mm), and 3 (27%) distal (67%: ⩽ 5 mm and 37%: 6-9 mm).

In Group B (NBI → WL), the first withdrawal with

NBI detected 53 adenomas: 34 (64.2%) proximal (79.4%: ⩽ 5 mm, 17.6%: 6-9 mm and 2.9%: ⩾ 10 mm) and 19 (35.8%) distal (89.5%: ⩽ 5 mm, 5.3%: 6-9 mm and 5.3%: ⩾ 10 mm). Switching to WL detected 23 additional adenomas (30.3% of all adenomas detected in Group B): 16 (70%) proximal (94%: ⩽ 5 mm, 6%: ⩾ 10 mm) and 7 (30%) distal (86%: ⩽ 5 mm, 14%: 6-9 mm).

In Group C (WL → WL), there were 97 adenomas detected by white light during the first withdrawal: 61 (62.9%) proximal (70.5%: < 5 mm, 23%: 6-9 mm, 6.5%: > 10 mm) and 36 (37.1%) distal (58.3%: ⩽ 5 mm, 25%: 6-9 mm, 16.7%: ⩾ 10 mm). During the second withdrawal with white light, 14 additional adenomas were detected (12.6% of all adenomas detected in Group C): 12 (85.7%) proximal (75%: ⩽ 5 mm, 25%: 6-9 mm) and 2 (14.3%) distal (100%: ⩽ 5 mm).

The newly diagnosed adenomas detected with NBI (Group A, 11.3%) and WL (Group C, 12.6%) during the second look were significantly fewer than those detected using the WL after NBI (Group B, 30.3%) ($P < 0.05$). The second look of the tandem segmental colonoscopy thus, detected 16.9% new adenomas (48 out of 284 adenomas).

Yield for detection of advanced neoplasia

In Group A (WL → NBI), there were 8 patients (10 polyps) with advanced neoplasia (all defined by size ⩾ 10 mm only). None of these advanced neoplasias were detected during the second look performed by NBI. In Group B (NBI → WL), there were 3 patients (3 polyps) with advanced neoplasia (all defined by size ⩾ 10 mm only), and one of these (10 mm polyp in ascending colon) was detected during the second look using WL. In Group C (WL → WL), there were 9 patients (11 polyps) with advanced neoplasia including 1 villous adenoma in the sigmoid and 1 invasive carcinoma in the rectum (the remaining 9 adenomas were defined as advanced neoplasia by a size ⩾ 10 mm). None of the advanced neoplasias were detected during the second look with WL.

When NBI was used as the second look, it diagnosed 2 patients (1 adenoma each) that otherwise would have been diagnosed as having no adenomas at all and representing 4.3% (2 out of 47) of patients with adenomas. When WL was used as the second look, it identified 8 patients that otherwise would have been missed as having any adenomas (6 of these had single adenomas, and the other 2 had 2 adenomas each) and representing a pick up rate of 17% (8 out of 47 patients with adenomas). For Group C, when a second look with white light was performed, 5 patients (1 adenoma each) were detected that otherwise would have been missed as having any adenomas at all and representing 10.6% (5 out of 57) of patients with adenomas. The differences among the groups were not statistically significant. None of these patients in either group had advanced neoplasia that would have been undetected at all.

Yield for non-neoplastic polypoid lesions

Non-neoplastic polyps represented 17.8% (103/577) of all polyps and were similarly distributed among the 3 groups.

There was one case of post-polypectomy bleeding requiring admission and endoscopic intervention to secure hemostasis with endoscopic clips. There were no sedation-related complications.

DISCUSSION

The impact of new optical technologies such as high-definition, magnification and NBI on polyp detection rate is unknown. Tandem colonoscopy studies have yielded an additional detection rate up to 22% for adenomas and 27% for non-adenomas[9]. Our study showed that the detection rate of missed polyps and adenomas after a first look with white light was similar when using narrow band imaging (14.2% for polyps, 11.3% for adenomas) or white light (13.7% for polyps and 12.6% for adenomas) as the second look modality. We also found that when white light was used after narrow band imaging, the detection rate of missed polyps (29.9%) and adenomas (30.3%) was higher in comparison to where white light was used as first modality. The explanation for this unexpected finding is not completely clear. To further address this issue, we studied 100 additional consecutive patients undergoing screening colonoscopy using the following strategy (NBI → NBI → WL). Out of 198 polyps (92 adenomas) detected, the second look with NBI added 24 new polyps (7 adenomas) and the "third look" with WL added 28 additional polyps (15 adenomas) representing 12.1% polyps and 7.6% adenomas with the second NBI look and, 14.1% polyps and 16.3% adenomas with the "third look" using WL. Thus, the combined miss rate after a first look with NBI (26.2% and 23.3% for polyps and adenomas, respectively) was similar to the one reported in the present study when using the NBI → WL strategy. In our study, the bowel cleanliness was not associated with improved polyp detection. Another shortcoming of NBI appears to be relative poor visualization unless endoscope is held closer (more so than the WL) to the inspected area.

The adenoma miss rate in the tandem colonoscopy studies is inversely related to the size and directly related to the number detected during the first look[9]. In a prospective multicenter study[10] of tandem colonoscopy the miss rates for polyps, adenomas, polyps > 5 mm, adenomas > 5 mm and advanced neoplasia was 28%, 20%, 12%, 9% and 11%, respectively. The sessile or flat shape and left colonic location were associated with higher miss rates. Interestingly, in that study, not all recto-sigmoid polyps (thought to be hyperplastic) were removed. The explanation for rather significant and fairly similar miss rates reported by experienced endoscopists remains

speculative at best. Operator's-related factors that may influence the miss rate include: technique, rate of withdrawal, difference in recognition of pathology (only applicable when two different endoscopists with different levels of expertise are involved) and thus related to inter-observer variability, a more careful look performed by the second endoscopist because of the prior knowledge of the goals/objectives of the study (bias). Other factors may be polyp-related: location (*i.e.*, behind folds) that possibly becomes "more exposed" to the second look and, estimated polyp size; and/or, bowel preparation-related: a cleaner colon resultant from the cleaning performed during the first look. Optical enhancements in endoscopy are expected to reduce the miss rate of both polyps/adenomas; better predict histology and, enhance demarcation of neoplastic tissue and thus improve the rate of complete polypectomy. The development of these technologies in part, is in response to the lack of complete protection against interval cancer development[21], polyp detection and clearance such as adequacy of bowel preparation[22,23], operator's expertise and completeness (cecal intubation) of examination[24-28], adequate withdrawal times[29,30], incomplete polyp resection[31,32] and inherent limitations of the colonoscopy itself[33-35]. NBI was initially reported to increase the yield of detection of polyps and adenomas[12,15,17,19,20]. The studies investigating the role of NBI in the detection of colonic polyps have yielded controversial results. In a study[36], of 40 patients undergoing screening colonoscopy, NBI detected 51 additional polyps (41.5% of total polyps) and 29 adenomas (40.3% of total adenomas). The polyp/adenoma miss rate appeared somewhat higher than what has been reported in the literature (10%-20%), even if a potential gain provided by NBI from 5% to 15% was added. The study included WL → NBI arm but lacked NBI → WL and WL → WL) arms. In another study[15], NBI detected numerically more adenomas (23%) than conventional endoscopy (17%). However, procedures were not performed in a tandem fashion. There also appeared to be a learning effect upon adenoma recognition/detection due to involvement of multiple endoscopists, some with less experience even in conventional endoscopy. In a randomized controlled study[37], again, tandem colonoscopy was not performed, and thus the miss rate with each of the lights remained unknown. Nevertheless, in that study the authors found no difference in the detection rates of overall adenomas or adenomas of any size. To compare, detection rate for adenomas in our group of 300 patients was 50% (range: 47% to 57%) which is similar to the above mentioned study[37]. This may suggest that in the hand of experienced endoscopists with a high detection rate, NBI may not have an added benefit. In another randomized study comparing conventional *vs* pan-colonic narrow band imaging[38], NBI detected significantly more adenomas, especially diminutive (< 5 mm) in the distal colon without compromising the withdrawal time than conventional colonoscopy. The main limitation of the study again was the lack of tandem colonoscopy. Finally, a randomized tandem colonoscopy study[39] comparing NBI → WL *vs* WL → WL showed that there were no significant differences either in the miss or detection rates between two modalities (12.6% miss rate in NBI and 12.1% in WL group). Although, the miss rates in the, WL → WL group was similar to ours, the miss rate in the NBI → WL was lower than that found in our study.

The main limitations of our study are a non-randomized nature and being carried out by two experienced endoscopists at a single center, and thus the results may not be generalized.

In summary, the overall miss rate of adenomas by segmental tandem endoscopy was 17%; being highest (30%) after NBI had been used as the first modality. Most missed adenomas were in the proximal colon and were ⩽ 5 mm in size. When white light was used first, the detection rate of missed adenomas was similar with white light and NBI. In conclusion, our data suggest that the tandem nature of the procedure rather than the optical technique used was the most important factor for detecting missed pathology. We recommend taking extra time to "take a second look" at each segment during colonoscopy to increase the yield for detection of pathology.

COMMENTS

Background

Polyp detection is of paramount importance during colonoscopy. Conventional colonoscopy may miss polyps, some of which could be pre-cancerous. Narrow band imaging (NBI) is one of the several modalities that are being investigated to enhance polyp and adenoma detection rates.

Research frontiers

In narrow band imaging, light of specific blue and green wavelengths is used to enhance the details of certain aspects of the mucosa. NBI has been utilized to classify the colon polyps based on their pit patterns, to differentiate normal from dysplastic tissue in Barrett's esophagus and ulcerative colitis, and in some cases to improve the detection of colonic polyps/lesions.

Innovations and breakthroughs

The impact of new optical techniques such as high-definition, wide angle, magnification and NBI on polyp detection rate is unknown. The authors know, that a second look back-to-back colonoscopy when performed by a second endoscopist (tandem colonoscopy), may yield additional polyps. The study showed, that the additional detection of missed polyps and adenomas after a first look with white light (WL) was similar when either NBI (WL → NBI) or white light (WL → WL) were used as a second look. This suggests that NBI did not increase the rate of detection of polyps/adenomas but that the tandem nature of the procedure did.

Applications

This study suggests that white light may be a relatively better modality in comparison to narrow band imaging when routinely used for purposes of polyp detection during colonoscopy.

Terminology

NBI: Light of specific blue and green wavelengths that can be used in endoscopy to enhance the details of certain aspects of the lining of gastrointestinal tract; Adenoma: A potentially pre-cancerous polyp.

Peer-review

The authors present a well-designed study investigating the use of second look with narrow band *vs* white light endoscopy and the effect on polyp detection rates.

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CASE REPORT

Chronic abdominal pain secondary to mesenteric panniculitis treated successfully with endoscopic ultrasonography-guided celiac plexus block: A case report

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Informed consent: Patient consented to publish the case, consent attached.
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Abstract

Mesenteric panniculitis is a chronic illness that is characterized by fibrosing inflammation of the mesenteries that can lead to intractable abdominal pain. Pain control is a crucial component of the management plan. Most patients will improve with oral corticosteroids treatment, however, some patients will require a trial of other immunosuppressive agents, and a minority of patients will continue to have refractory disease. Endoscopic ultrasound guided celiac plexus block is used frequently to control abdominal pain in patients with pancreatic pathology. To our knowledge there are no case reports describing its use in mesenteric panniculitis patients with refractory abdominal pain.

Key words: Endoscopic-ultrasound; Abdominal pain; Celiac plexus; Mesenteric panniculitis

Core tip: Mesenteric panniculitis is a rare disorder that can present with refractory and disabling abdominal pain, we describe a novel intervention using endoscopic ultrasonography guided celiac plexus block to control the refractory abdominal pain in a patient with mesenteric panniculitis. This approach is based on the anatomical supply of the epigastric area where the pain is originating.

Alhazzani W, Al-Shamsi HO, Greenwald E, Radhi J, Tse F. Chronic abdominal pain secondary to mesenteric panniculitis treated successfully with endoscopic ultrasonography-guided celiac plexus block: A case report. *World J Gastrointest Endosc* 2015; 7(5): 563-566 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/563.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.563

INTRODUCTION

Mesenteric panniculitis is a rare, benign condition

characterized by acute inflammation of the mesenteric adipose tissue that can progress to chronic fibrosis[1]. The disease was first described by Jura[2] in 1924, he used the term retractile mesenteritis to describe this condition. Subsequently, the term mesenteric panniculitis was developed by Aach *et al*[3] to describe the acute inflammatory phase of the disease. Since then, this has been widely used and adopted term to describe this disease. Mesenteric panniculitis is also known as mesenteric lipodystrophy, primary liposclerosis, isolated lipodystrophy, lipogranuloma, and Weber-Christian disease[4]. The etiology of this disorder remains largely unknown; an association with inflammatory disorders, infection, malignancy (particularly lymphoma)[5], trauma, and abdominal surgery has been described[6]. The prevalence of the disease is estimated to be around 0.6%, and it is more common in Caucasians. The clinical course of mesenteric panniculitis is indolent and favorable[7].

The disease usually progresses slowly and may subside spontaneously[7], around 30%-50% of patients are asymptomatic[5]. However, 20% of patients will have more symptomatic debilitating disease[8]. The most common symptom is chronic abdominal pain, some patients may present with acute abdomen[9]. Abdominal pain can be accompanied by other non-specific symptoms including fever, nausea, vomiting, anorexia and non-intentional weight loss[10]. The diagnosis is usually suggested by high resolution computed tomography (CT) scan[11]. Histological confirmation is rarely required[1]. The majority of patients will respond to systemic corticosteroids[8]. However, some patients will require a more intense immunosuppressive therapy like azathioprine or cyclophosphamide. Only a minority of patients will continue to have refractory disease despite immunosuppressive therapy[12]. Other modalities including progesterone, colchicine, tamoxifen, antibiotics and emetine, or radiotherapy have been used in refractory disease with limited success[13,14]. Surgical resection is reserved for the treatment of complication like intestinal obstruction or ischemia[7]. Refractory abdominal pain can be a major source of morbidity in these patients[15].

CASE REPORT

We report here on a 62-year-old caucasian male who presented with right upper quadrant abdominal pain for several months prior to his first presentation to our institution in 2005. The abdominal pain was not associated with changes in bowel habits, nausea, vomiting, or constitutional symptoms. Initial investigations including complete blood count, liver and kidney function tests, and abdominal ultrasonography were normal. The patient underwent cholecystectomy in 2005 for possible biliary cause of pain, but the pain persisted after surgery. Subsequently, imaging study using CT imaging scan demonstrated thickening and irregularity of the mesentery surrounding the pancreatic head. The radiologic findings were in keeping with the diagnosis of mesenteric panniculitis (Figure 1). Extensive investigations ruled out luminal pathology, pancreatic or adrenal diseases, intermittent porphyria, vascular etiology, and other conditions.

Figure 1 Computed tomography of the abdomen. Computed tomography scan of the abdomen showing mesenteric irregularity and thickness.

Given the radiologic findings and the patient symptoms, the patient was started on prednisone 40 mg once daily for two months. This was associated with a significant improvement in the severity of abdominal pain. However, prednisone therapy was complicated by severe systemic side effects, including worsening of pre-existing depressive disorder, hypertension and cataracts. For this reason, the patient was subsequently weaned off corticosteroids. He remained symptom free for 6 mo after discontinuation of steroid therapy, and then had recurrence of abdominal pain. Because of the chronicity and severity of the symptoms, the patient underwent diagnostic laparoscopy primarily to rule out malignant process. The operative findings showed thickening of the mesentery with no discrete visible masses. Samples from the thickened mesentery were obtained. The pathology results confirmed the diagnosis of mesenteric panniculitis (Figure 2). The patient was started on a steroid-sparing agent (azathioprine) for 6-mo with no response. Further attempts using 3 to 6 mo courses of tamoxifen and subsequently thalidomide failed to improve his symptoms. Different non-opiate analgesic agents were unsuccessful in controlling his symptoms, including acetaminophen and non-steroidal anti-inflammatory drugs. Eventually the patient was started on opioids (oxycodone and morphine) and a serotonin-norepinephrine reuptake inhibitor for pain control. A follow-up CT imaging of the abdomen showed similar findings.

After discussion with the patient, the patient was referred for endoscopic ultrasonography (EUS) guided celiac plexus block in an attempt to control relief the intractable abdominal pain and minimize the use of narcotics.

After obtaining consent from the patient, the linear echoendoscope was advanced through the oral cavity

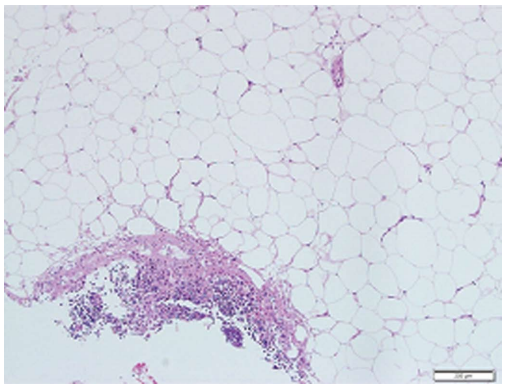

Figure 2 Mesenteric biopsy. Mesenteric biopsy showing fibrotic band of dense collagen infiltrated by mixed inflammatory cells (lymphocytes, plasma cells and neutrophils). There is fat necrosis, no vasculitis or malimgnancy seen. There is no cellular atypia or lipoblast identified in the biopsy.

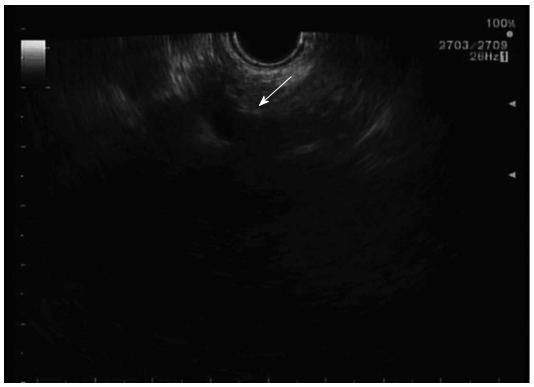

Figure 3 Ultrasonographic image of celiac plexus. This image is showing the celiac artery and celiac plexus (arrow).

into the stomach; the celiac trunk was identified using the ultrasound images (Figure 3). A 19-gauge needle (Echotip; Wilson-Cook) was used to inject 40 mg of Triamcinilone and 10 mL of 0.25% bupivicaine on both sides of the celiac trunk. This protocol is similar to that described by Gress *et al*[16]. Intravenous crystalloids were administered during the procedure to prevent hypotension caused by the procedure. The patient tolerated the procedure well and was discharged home within few hours.

Within the first week after the procedure, the patient noticed a dramatic improvement in his symptoms. Within 2 mo, he was weaned off narcotics with complete resolution of his symptoms. However, symptoms recurred 6 mo after the procedure. Given the initial response to this therapy, the procedure was repeated using identical protocol. Few days after the procedure, the patient developed a back injury that led to a surreptitious diagnosis of a 1 cm schwannoma at T12-L1 spinal levels. Surgical resection of the spinal cord tumor was done soon after celiac block, which confounded the assessment of pain. Three months after the second EUS-guided celiac plexus block, the patient was pain free and off all analgesics.

DISCUSSION

To our knowledge, there are no published reports of applying this unique intervention to control refractory abdominal pain in a patient with mesenteric panniculitis. Mesenteric panniculitis is a rare disorder that is characterized by chronic inflammation leading to fibrosis of the mesentery. Patients' presentation varies from asymptomatic incidental radiologic findings to severe abdominal pain, vomiting, changes in bowel habits, and constitutional symptoms[17,18]. Associated malignancy is not uncommon, with one report showing that 70% of included patients had radiological findings consistent with malignant disorders[19].

Due to the low incidence of this condition, the prognosis of the disease is not well defined. One report with more than 5 years of follow-up showed that mortality rate approaches 45%, majority of fatalities (50%) were related to co-existing malignancy[20]. Several case reports showed that immunosuppressive medications are effective in controlling disease activity[4,21,22]. However, there are no published reports on the utility of celiac plexus block for controlling refractory symptoms.

Celiac plexus is composed of sympathetic efferent fibres, which are derived from the greater, lesser, and least splanchnic (T5-T12) nerves[23]. The visceral afferent fibres supplying the distal esophagus down to the transverse colon pass through the celiac plexus, before ending in the spinal cord. Therefore, pain originating from pancreatic disease may respond to celiac plexus block. In fact, the most studied application of EUS-guided celiac block is in pancreas-related pain[1,24-26]. The application of this procedure in other disorders is very limited. There are few case reports on the use EUS-guided block in the management of pelvic cancer pain[27], acute intermittent porphyria[28], and pain caused by diabetic gastroparesis[29]. No published literature on the utility of this intervention in patients with mesenteric panniculitis related pain.

Theoretically, pain originating from upper abdominal organs could be alleviated by this procedure. However, this was not tested in clinical trials or observational studies. More research in this area is required in order to ascertain or dispute our observation.

COMMENTS

Case characteristics

Recurrent right upper quadrant abdominal pain.

Clinical diagnosis

Mesenteric panniculitis.

Differential diagnosis

Upper endoscopy ruled out an intraluminal pathology, computed tomography (CT) scan finding was not suggestive of neuroendocrine or pancreatic malignancy, diagnostic laparoscopy done to rule out intra-abdominal malignant process.

Laboratory diagnosis

Extensive investigations including complete blood count, Lipase, Liver enzymes, kidney function, porphyria screening, radiological imaging with CT scan, the

diagnosis was confirmed with histology.

Imaging diagnosis

Imaging study using CT scan demonstrated thickening and irregularity of the mesentery surrounding in keeping with the diagnosis of mesenteric panniculitis.

Pathological diagnosis

Mesenteric biopsy showing fibrotic band of dense collagen infiltrated by mixed inflammatory cells (lymphocytes, plasma cells and neutrophils) in keeping with the diagnosis of mesenteric panniculitis.

Treatment

The patient was treated with multiple pharmacological agents including prednisone, azathioprine, tamoxifen and thalidomide that failed control his symptoms. Subsequently, responded to endoscopic ultrasonography (EUS)-guided celiac plexus block.

Related reports

Nicholson *et al* reported that mesenteric panniculitis in merseyside: a case series and a review of the literature in 2010.

Experiences and lessons

Mesenteric panniculitis is a rare disorder that can present with refractory and disabling abdominal pain, the authors describe a novel intervention using EUS guided celiac plexus block to relieve refractory abdominal pain in a patient with mesenteric panniculitis.

Peer-review

Novel intervention for a rare disease is based on the anatomical supply of the epigastric area where the pain is originating.

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CASE REPORT

Anaemia in Waldmann's disease: A rare presentation of a rare disease

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Author contributions: All authors performed the research, designed, wrote, critically analysed the manuscript; El-Etreby SA, Altonbary AY and Bahgat MH were responsible for medical assessment and follow up of the patient; Mazroa JA was responsible of radiological assessment; Elkashef W examined the pathological specimens; El Sorogy M performed the surgical procedure; finally, El-Etreby SA and Bahgat MH analyzed the data, revised the draft and approved of the final version of the paper to be published.

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Ethics approval: The study was reviewed and approved by the Mansoura Faculty of Medicine Institutional Review Board, Mansoura University, Egypt.

Informed consent: The study participant, or her legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest: None.

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Abstract

A 32-year-old female presented with 5-year history of iron deficiency anemia, marked pallor and edema of both lower limbs. Laboratory investigations including complete blood count, blood film, iron studies, lipid profile, ascitic fluid analysis, test of stool for occult blood and alpha 1 anti-trypsin. Upper, lower gastrointestinal (GIT) endoscopies, and enteroscopy were performed. Imaging techniques as abdominal ultrasonography and computed tomography were done. Echocardiography, lymph node biopsy and bone marrow examination were normal. The case was diagnosed as Waldmann's disease with protein losing enteropathy and recurrent GIT bleeding. Management started with low fat diet with medium chain triglyceride, octreotide 200 μg twice a day, tranexamic acid and blood transfusion. Then, exploratory laparotomy with pathological examination of resected segment was done when recurrent GIT bleeding occurred and to excluded malignant transformation.

Key words: Waldmann's disease; Lymphangiectasia; Gastrointestinal bleeding; Iron deficiency anemia

Core tip: To our knowledge, this is the first "Egyptian" case of primary intestinal lymphangiectasia. In addition, its presentation is rare with blood loss anemia in contrast to the more common presentation with hypoproteinemia and edema. So, we are reporting a case with a rare clinical presentation of a rare disease. Double balloon enteroscopy was so beneficial in the diagnosis of the case superior to capsule endoscopy

because the advantage of biopsy and histopathologic examination. There is controversy about medical treatment options, surgical treatment may be preferred in localized lesions otherwise, has no role. Prognosis may be favorable.

El-Etreby SA, Altonbary AY, El Sorogy M, Elkashef W, Mazroa JA, Bahgat MH. Anaemia in Waldmann's disease: A rare presentation of a rare disease. *World J Gastrointest Endosc* 2015; 7(5): 567-572 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i5/567.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i5.567

INTRODUCTION

Waldmann's disease; also called primary intestinal lymphangiectasia (PIL) is a rare form of protein losing enteropathy caused by leakage of lymph inside the small intestinal lumen from dilated lacteals. The manifestations begin before the age of 30 years in 90% of cases, often in childhood. Whether bleeding into gastrointestinal tract a feature of PIL or not is still controversial. Here, we present a case of a young women with chronic blood loss anemia (iron deficiency and positive fecal occult blood test) caused by Waldmann's disease.

CASE REPORT

A 32-year-old female with 5 year history of iron deficiency anemia was referred to our Gastroenterology Unit for further evaluation. History was irrelevant apart from easily fatigability and repeated blood transfusions as well as iron therapy. Examination revealed marked pallor and edema of both lower limbs.

Laboratory findings of a 32 years old female with Waldmann's disease are shown in Table 1.

Upper and lower GI endoscopies were done twice within two-month period and did not reveal any gross pathology. So, Fujinon's Double Balloon Endoscopy System (with 2.8 mm forceps channel) was used to examine the small bowel through oral route down to 310 cm from the ligament of Trietz. Multiple lymphangectasias (Figure 1) were seen starting at about 100 cm, extending all through the assessed parts; some of them were actively bleeding. The most affected area (at about 100 cm) was tattooed with India Ink. Histopathological examination of the lesions revealed multiple dilated vascular and lymphatic spaces and few lymphocytes with no evidence of malignancy, picture consistent with capillary telangiectasia.

Abdominal ultrasonography, abdominal computed tomography (CT), echocardiography, inguinal lymph node biopsy, and bone marrow examination were performed to exclude secondary causes of lymphangiectasia. All tests were normal except for mild splenomegaly (due to multiple hemangiomas).

Table 1 Laboratory results for the patient

Test	Result	Normal reference
Complete blood count		
Hemoglobin	5.2 g/dL	12-18 g/dL
HCT	18.30%	37%-51%
MCV	70.2 pg	80-97 flpg
MCHC	28.4 g/dL	31-36 g/dL
Platelets	284	140-440 cell/cm^3
WBCs	3.8	4.1-10.9 cell/cm^3
Lymphocytes	500	600-1400
Blood film		
Hypercellular bone marrow with no blast cells		
Blood chemistry		
s. Albumin	2.1 g/dL	3.5-5 g/ dL
AST	30 IU/L	Up to 40 U/L
ALT	25 IU/L	Up to 45 U/L
s. cholesterol	107 mg/dL	Up to 200 mg/dL
s. triglyceride	54 mg/dL	Up to 160 mg/dL
s. iron	23 ng/dL	28-170 ng/dL
s. ferritin	12 ng/mL	40-430 ng/mL
TIBC	750 ng/dL	261-478 ng/dL
s. TSH	1.2 mIU/L	0.3-3.04 mIU/L
Stool tests		
Occult blood	Positive	
α-1 AT clearance	2 folds above normal range	

HCT: Hematocrit; MCV: Mean corpusclar volume; MCHC: Mean corpuscular hemoglobin concentration; WBCs: White blood cells; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TIBC: Total iron binding capacity; TSH: Thyroid stimulating hormone; α-1 AT: Alpha 1 antitrypsin.

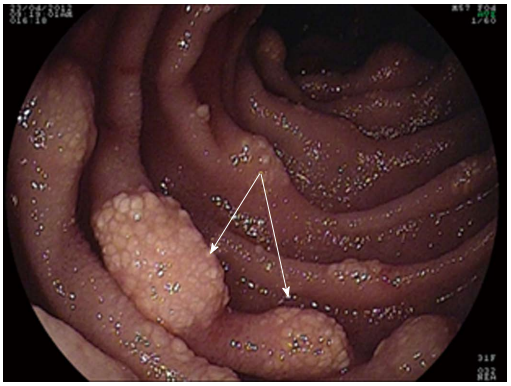

Figure 1 Multiple jejunal lymphangiectasia.

Management started with low fat diet with medium chain triglyceride, octreotide 200 μg/twice a day, tranexamic acid and blood transfusion till an acceptable level of hemoglobin was achieved (about 9 g/dL). She was discharged on diet regimen and regular follow up.

Nine months later during routine follow up, clinical examination showed marked pallor (Hb 6 g/dL) and abdominal ultrasonography revealed moderate ascites and mild right sided pleural effusion. Ascitic fluid was milky and turbid. Chemical analysis of ascitic fluid sample revealed glucose of 108 mg/dL, total protein of 1170 mg/dL, lactate dehydrogenase of 195 U/L, triglycerides of 1232 mg/dL (diagnostic of chylous ascites), WBCs of 250 cell/cm^3 mainly lymphocytes,

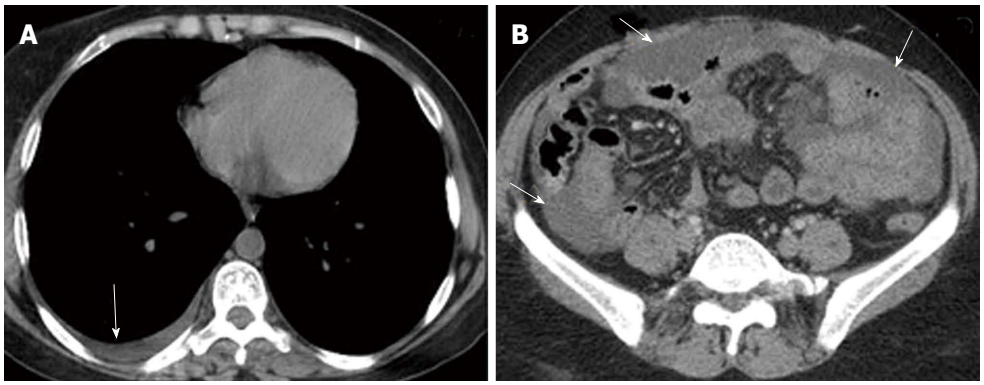

Figure 2 Pre contrast axial computed tomography scan showing (A) mild right-sided pleural effusion and (B) mild ascites.

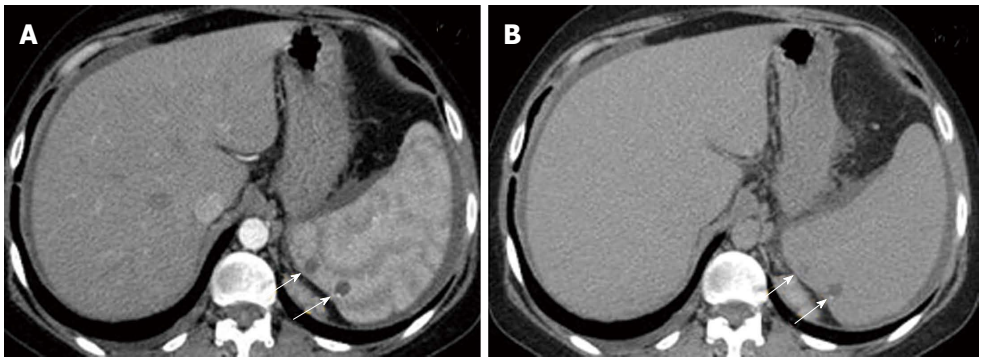

Figure 3 Triphasic post contrast axial computed tomography showing. Multiple splenic hemangiomas in portal (A) and delayed (B) phases respectively showing filling in (arrows).

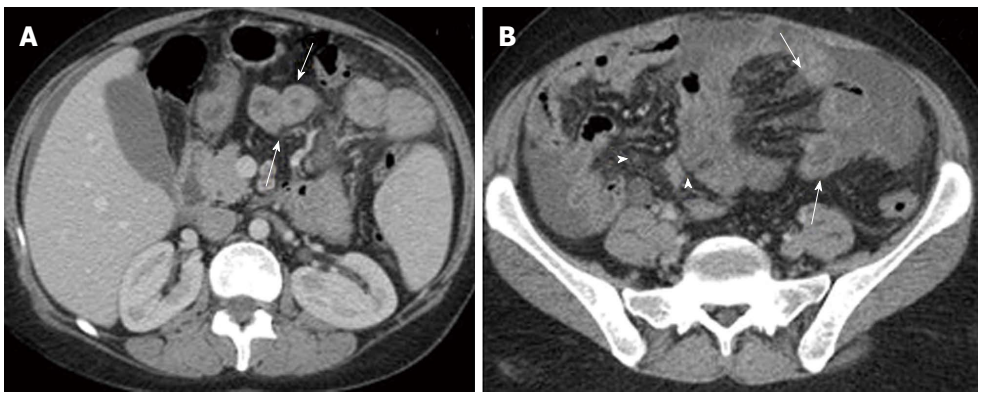

Figure 4 Triphasic post contrast axial computed tomography (portal phase) showing. A: Dilated small intestinal wall (arrows); B: Mesenteric hypodense bands indicating obstructed lymphatics (arrows), and dirty fat appearance due to mesenteric oedema (arrow heads).

and RBCs of 0.01×10^6. Cytological examination of ascitic fluid revealed no atypical or malignant cells. ZN stain and adenosine deaminase were negative. Triphasic CT scan was performed by 8 multi-slice G.E. CT scanner. It revealed right pleural effusion, mild ascites; both had uncomplicated fluid density: 0-20HU (Figure 2) and multiple splenic hemangiomas (Figure 3). Regarding small intestine, CT revealed dilated small intestinal loops with diffuse, nodular wall thickening (reaching up to 9 mm), mesenteric hypodense bands representing dilated lymphatic channels and mesenteric edema (Figure 4). Neither lymphadenopathy nor hepatomegaly was detected.

Surgical opinion was sought and malignant transformation was suspected. So, exploratory laparotomy was done through midline incision. Findings include minimal ascites, multiple cysts related to the small intestinal wall and its mesentry and a discolored segment of the proximal jejunum previously marked with India Ink by enteroscopy (Figure 5) but no masses were found. Resection anastomosis of the discolored segment was done. Histopathological examination revealed large gaping vascular spaces lined by flat endothelial cells and filled by lymph fluid, picture consistent with primary intestinal lymphangectasia (Figure 6).

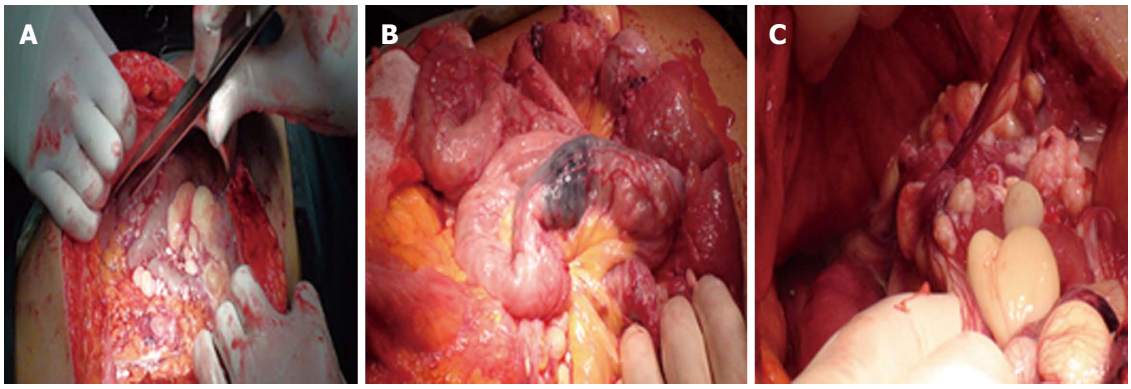

Figure 5 Exploratory laparotomy, multiple cysts was seen related to the small intestinal wall and its mesentry and a discolored segment of the proximal jejunum.

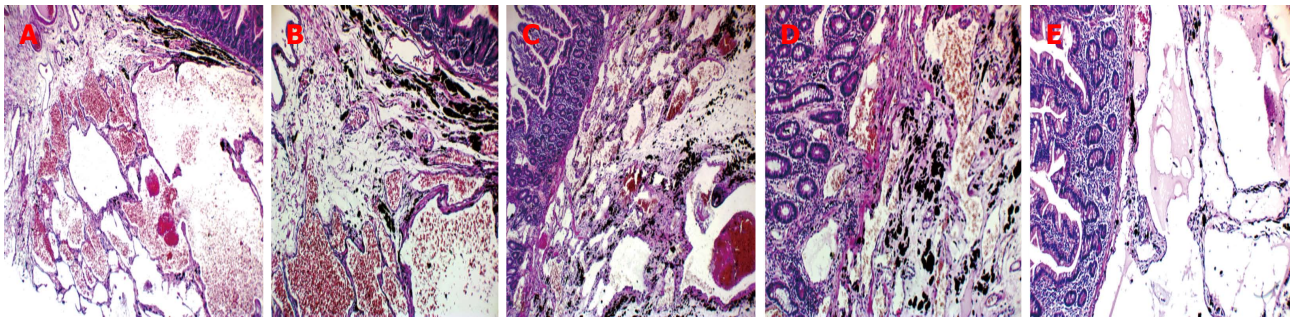

Figure 6 Histopathological examination of the resected part of small intestine. A: The sub-mucosa shows large gaping vascular filled by RBCs (HE × 40); B: The vascular spaces are lined by flat endothelial cells (HE × 100); C: Black staining is due to labeling material (India Ink) (HE × 100); D: The sub-mucosal vascular are see encroaching upon the mucosal lining (HE × 100); E: Some vascular spaces lined by flat endothelial cells and filled by lymph fluid (HE × 100).

Postoperative outcome was favorable and she was discharged home after 5 d.

On the 20th postoperative day, patient achieved marked improvement of her general condition, disappearance of edema lower limb, ascites, and pleural effusion. Laboratory investigations were; s. albumin 4.1 g/dL, HB 10.9 g/dL, platelets count 147 cell/cm^3, WBCs 4900 cell/cm^3 with normal distribution. Six months later, she remained asymptomatic with weight gain of 5 kg and rather stable hemoglobin level.

DISCUSSION

Protein losing enteropathy (PLE) is a rare cause of hypoproteinemia due to gastrointestinal (GI) loss of serum protein. This rare condition has many reported causes (Table 2) including the rare Waldmann's disease (PIL) in which GI protein loss results from leakage of lymph through the ectatic intestinal lacteals[2].

PIL predominantly affects young children although it may also be diagnosed in older age. There is slight male preponderance with 3:2 ratio. On the other hand, race is not a predictor of PIL[3,4].

Patients usually present with bilateral lower limb edema[2-7]. Other manifestations like pain, loose motion, and malnutrition are less common[8]. Rare manifestations include abdominal mass, Mechanical ileus[9-11], chylous reflux[12,13], iron deficiency with anemia[14], necrolytic migratory erythema[15], recurrent hemolytic uremic syndrome[16], and osteomalacia[17]. Recurrent gastrointestinal bleeding was even more rare being reported in only 2 cases[18,19].

Work up of diagnosis consist of laboratory, imaging studies and GIT endoscopy with confirmatory histopathological examination[20].

The most common laboratory finding is hypoproteinemia. Hypo-albuminemia is most prominent and lymphopenia. Cholesterol levels are not usually elevated. PLE can be confirmed by presence of excess fecal α1-antitrypsin[21,22].

Abdominal CT scan may show dilated thickened small intestinal loops, ascites, halo sign and edematous mesentery. It also helps rule out secondary causes[23,24].

Diagnosis can only be confirmed by finding dilated lacteals both on endoscopic and histopathologic examination[25,26]. Video capsule endoscopy imaging provides the same information and allow exploration of the whole small bowel but does not allow biopsies[27].

PIL has to be differentiated from secondary causes of intestinal lymphangiectasia such as Crohn's disease, intestinal tuberculosis, and Whipple's disease as well as from causes of PLE without lymphangiectasia such as Mentrier's disease and systemic lupus erythematosus (SLE)[20].

Medical management relies on diet modification with low fat replaced by medium-chain triglycerides

Table 2 Causes of protein losing enteropathy[1]

Erosive gastrointestinal disease
Inflammatory bowel disease
Gut malignancy
Non steroidal anti-inflammatory drug enteropathy
Erosive gastropathy
Acute graft vs host disease
Pseudomembranous enterocolitis
Ulcerative jejunoenterocolitis
Intestinal lymphoma
Sarcoidosis
Non erosive gastrointestinal disease
Celiac disease
Hypertrophic gastropathies
Eosinophilic gastroenteritis
Connective tissue disorders
Small intestinal bacterial overgrowth
Amyloidosis
Microscopic colitis
Tropical sprue
Whipple's disease
Parasitic diseases
Viral gastroenteritis
Increased interstitial pressure
Intestinal lymphangiectasia
Congestive heart failure
Constrictive pericarditis
Congenital heart diseases
Fontan procedure for single ventricle
Portal hypertensive gastroenteropathy
Hepatic venous outflow obstruction
Enteric lymphatic fistula
Mesenteric venous thrombosis
Sclerosing mesenteritis
Mesenteric tuberculosis or sarcoidosis
Neoplasia involving mesenteric lymph nodes or lymphatics
Chronic pancreatitis with pseudocysts
Congenital malformations of lymphatic
Retoperitoneal fibrosis

thus preventing fat overloading of intestinal lacteal[28,29].

Response to other medications, such as[30-31] octreotide[32-36] and steroids[37] is variable.

Small intestinal resection is indicated in localized forms of the disease[38,39].

Natural history of PIL is greatly variable; depending on involvement of intestine either generalized or localized with blockage of mesenteric lymphatic drainage. Prognosis may be favorable unless it is complicated by intestinal B-lymphoma or effusion in serous sacs[20,40].

COMMENTS

Case characteristics

A 32-year-old female presented with 5-year history of iron deficiency anemia, marked pallor and edema of both lower limbs.

Clinical diagnosis

Examination revealed marked pallor and edema of both lower limbs.

Differential diagnosis

Primary intestinal lymphangiectasia has to be differentiated from secondary causes of intestinal lymphangiectasia such as Crohn's disease, intestinal tuberculosis, and Whipple's disease as well as from causes of protein losing enteropathy without lymphangiectasia such as Mentrier's disease and systemic lupus erythematosus.

Laboratory diagnosis

Patient hemoglobin level and serum albumin were 5.2 g/dL, 2.1 g/dL respectively. α-1 AT clearance was 2 folds above normal range and stool test for occult blood yield positive result.

Imaging diagnosis

Computed tomography of the abdomen revealed dilated small intestinal loops with diffuse, nodular wall thickening, mesenteric hypodense bands representing dilated lymphatic channels and mesenteric edema.

Endoscopy diagnosis

Double balloon enteroscopy was performed, and revealed presence of multiple lymphangectasias, some of them were actively bleeding.

Pathological diagnosis

Histopathological examination of the lesions revealed multiple dilated vascular and lymphatic spaces and few lymphocytes with no evidence of malignancy, picture consistent with capillary telangiectasia.

Treatment

Management started with low fat diet with medium chain triglyceride, octreotide 200 μg/twice a day, tranexamic acid and blood transfusion till an acceptable level of hemoglobin was achieved (about 9 g/dL). But the results was unsatisfactory.

Related reports

Only two cases with primary intestinal lymphangiectasia were presented in literatures by gastrointestinal bleeding.

Term explanation

Chronic blood loss anemia (iron deficiency and positive fecal occult blood test) could be a one of manifestation of primary intestinal lymphangiectasia.

Experiences and lessons

This case report represents a case of primary intestinal lymphangiectasia with rare presentation, recurrent gastrointestinal bleeding and iron deficiency anemia. Also, it yields our experience with different treatment modalities that could be used.

Peer-review

The article highlights the clinical characteristics, diagnostic modalities and treatment options available for primary intestinal lymphangiectasia.

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Unreported complication of Bravo pH capsule dislodged into the pyriform sinus

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Abstract

We report an unexpected, previously unreported complication of Bravo pH capsule dislodgement. During Bravo pH testing of a 44-year-old man with gastroesophageal reflux disease, we were unable to endoscopically visualize the capsule attached to the esophageal wall after deployment. After multiple attempts to detect the capsule, it was visualized in the left pyriform sinus. As there was significant risk for pulmonary dislodgement, ENT and pulmonary physicians were immediately consulted to review options for safe removal. Ultimately, ENT successfully retrieved the capsule with a foreign body removal forceps. The Bravo pH test is generally a well-tolerated diagnostic tool used to confirm the presence of abnormal esophageal acid reflux. While few complications have been reported, technical difficulties can occur, including poor data reception, misplacement, and early dislodgement. Rarely, more serious complications can occur, ranging from esophageal wall trauma to capsule aspiration. Gastroenterologists performing this procedure should be aware of the low, but non-trivial, risk of complications.

Key words: Gastroesophageal reflux disease; Esophageal pH monitoring; Bravo capsule; Dislodgement; Esophagogastroduodenoscopy

Core tip: We report an unexpected, and so far unreported, complication of a Bravo pH capsule dislodgment. While Bravo probe placement is generally a well-tolerated procedure, dislodgment into the pyriform sinus in this case necessitated immediate action by an interdisciplinary team. Complications of Bravo capsule use range from technical difficulties, such as poor data reception and non-deployment, to more serious events such as esophageal wall trauma and capsule aspiration. Gastroenterologists performing this procedure should be aware of the risk of potential complications.

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LETTER TO THE EDITOR

We report an unanticipated, previously undocumented complication of Bravo capsule dislodgement. A forty-five year old patient with gastroesophageal reflux disease (GERD), non-compliant with medical therapy, presented with increasing cough, hoarseness, and other acid reflux symptoms. To verify presence of acid reflux, he underwent upper endoscopy and Bravo pH testing at our hospital. The gastroesophageal junction (Z line) was visualized at a distance of 40.0 cm from dentition. The Bravo device was deployed at 34.0 cm from dentition (6 cm above the Z line). When the capsule was not endoscopically visualized to be adherent to the esophageal wall, the endoscope was advanced beyond 34.0 cm to assess for possible device movement to the distal esophagus or stomach. When the capsule was not visualized at these locations, the endoscope was withdrawn. When the scope was withdrawn from the upper esophageal sphincter, the device was seen in the left pyriform sinus (Figure 1). The nonadherent capsule likely was either pulled up by the endoscope during withdrawal or coughed up by the patient. ENT and pulmonary physicians were immediately consulted for assistance in ensuring safe removal of the capsule from this precarious location, as there was significant risk for pulmonary dislodgement. After the anesthesiologist performed endotracheal intubation, ENT successfully retrieved the capsule with a foreign body removal forceps without further complications.

The Bravo pH test is generally a well-tolerated diagnostic tool that can verify the presence of abnormal esophageal acid reflux and determine if treatment refractory symptoms are due to persistent acid reflux in patients with GERD. As the deployment of the Bravo pH device is typically a innocuous procedure[1], very few complications have been reported. Technical difficulties most commonly include non-deployment, non-attachment, misplacement, premature dislodgement, and insufficient data reception. Infrequently, patients develop significant chest pain after capsule placement[2], necessitating removal. Rarely, more serious complications can occur in less than 2% and include esophageal wall trauma, excessive bleeding, and capsule aspiration[3]. In one reported case, the patient aspirated the capsule into the bronchus immediately after deployment, causing retching, heavy coughing, and desaturation to 74%[4]. After initial pushing into stomach with a transnasal video-endoscope, this capsule was removed with grasping forceps.

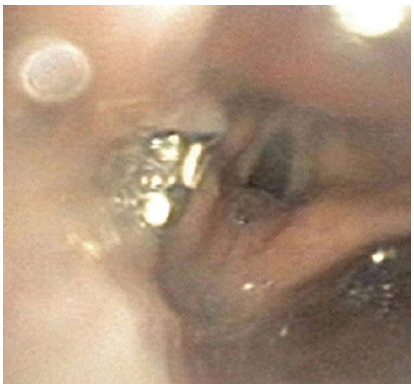

Figure 1 Bravo pH capsule in left pyriform sinus.

Gastroenterologists using the Bravo pH test should be cognizant of the low but non-trivial risk of complications, ranging from technical difficulties to aspiration of a dislodged capsule. Providers can use reports of documented complications to troubleshoot and resolve difficulties that may arise during deployment of Bravo pH capsules.

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