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EDITORIAL

Endoscopic treatment of esophageal achalasia

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Abstract

Achalasia is a motility disorder of the esophagus characterized by dysphagia, regurgitation of undigested food, chest pain, weight loss and respiratory symptoms. The most common form of achalasia is the idiopathic one. Diagnosis largely relies upon endoscopy, barium swallow study, and high resolution esophageal manometry (HRM). Barium swallow and manometry after treatment are also good predictors of success of treatment as it is the residue symptomatology. Short term improvement in the symptomatology of achalasia can be achieved with medical therapy with calcium channel blockers or endoscopic botulin toxin injection. Even though few patients can be cured with only one treatment and repeat procedure might be needed, long term relief from dysphagia can be obtained in about 90% of cases with either surgical interventions such as laparoscopic Heller myotomy or with endoscopic techniques such pneumatic dilatation or, more recently, with per-oral endoscopic myotomy. Age, sex, and manometric type by HRM are also predictors of responsiveness to treatment. Older patients, females and type Ⅱ achalasia are better after treatment compared to younger patients, males and type Ⅲ achalasia. Self-expandable metallic stents are an alternative in patients non responding to conventional therapies.

Key words: Achalasia; High resolution manometry subtypes; Eckardt score; Per-oral endoscopic myotomy; Pneumatic dilatation; Botulin toxin; Myotomy

Core tip: Achalasia is characterized by dysphagia, regurgitation, chest pain, weight loss and respiratory symptoms. Diagnosis and post-treatment assessment largely rely upon endoscopy, barium swallow study and high resolution esophageal manometry (HRM). Short term improvement in the symptomatology can be achieved with medical therapy or endoscopic botulin toxin injection. Long term relief from dysphagia can be obtained with either laparoscopic Heller myotomy, pneumatic dilatation or per-oral endoscopic myotomy. Age, sex, and manometric subtype by HRM are also predictors of responsiveness to treatment. Self-expandable metallic stents are an alternative in patients non responding to conventional therapies.

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INTRODUCTION

Achalasia is a motility disorder of the esophagus characterized by dysphagia, regurgitation of undigested food, chest pain, weight loss and respiratory symptoms[1,2].

Achalasia is a relatively rare condition with incidence ranging from 0.3 to 1.63 cases per 100000 people per year in adults[3-6]. There seems to be no difference in sex and racial distribution. Incidence rates of this pathology seems to be rising, it remains unclear if this reflects a true rise in the incidence or an improved diagnosis[3,6,7-16].

Most studies found the median age at the diagnosis to be over 50 years[3,4,17] whereas other authors have suggested a bimodal distribution of incidence by age with peaks around 30 and 60 years of age[7-9].

Although the etiology remains unknown, it has been established that achalasia results from the disappearance of the myenteric neurons leading to loss of peristalsis and failure of relaxation of the lower esophageal sphincter, particularly during swallowing[18].

Antibodies against myenteric neurons have been found in serum samples obtained from patients affected with achalasia[19-21]. Genetic[22-27], autoimmune[28,29], and viral[30-33] conditions may play a role in the development of the condition.

Since symptoms of achalasia are not specific, the diagnosis of the disease can be delayed for as long as 5 years[34,35]. Dysphagia for solids and liquids occurs in > 90% of patients affected with achalasia, other symptoms include weight loss (35%-91%), food regurgitation (76%-91%), respiratory complications such as chest pain (25%-64%) and heartburn (18%-52%) nocturnal cough (30%) and aspiration (8%)[1,36-38].

In a patient presenting with dysphagia, it is mandatory to rule out malignancies but also pseudoachalasia or any other anatomical lesions with radiology or endoscopy. Old age, weight loss and rapidly progressing dysphagia are particularly suspected for pseudo-achalasia and thus should be investigated by the mean of and endoscopic ultrasound or computer tomography (CT)-scan[39,40]. These imaging techniques will reveal thickening of the esophageal wall, mass or lesions.

However, both endoscopy and radiology only identify about half of patients with achalasia, especially in early stage. Endoscopy may reveal a dilated esophagus with retained food and a difficult access to gastric cavity due to increased resistance of the gastro-esophageal junction in advanced stages of the disease.

In addition, a timed barium swallow esophagram (TBA) can be done to assess emptying of the esophagus; the height of the barium column 5 min after the ingestion is a measure of emptying[41,42] (Figure 1). A TBA has proven itself useful also in the post-operative assessment of the disease.

Manometry is the mainstay of the assessment in achalasia both before and after treatment. Manometric features of achalasia are absence of peristalsis, incomplete relaxation of LOS on deglutition (residual pressure > 10 mmHg) with increased resting tone of LOS and, sometimes, increased intra-esophageal pressure[2].

High resolution manometry (HRM) is now regarded as the gold standard for the diagnosis of achalasia[43,44], this diagnostic technique is performed by mean of catheters incorporating 36 or more pressure sensors spaced 1 cm apart.

Thanks to the greater accuracy of HRM, three clinically relevant sub-classifications of achalasia have been distinguished on the basis of the pattern of contractility in the esophagus[45].

Type Ⅰ (classical achalasia; no pressurisation to over 30 mmHg in distal esophagus and failed relaxation on swallow), type Ⅱ (achalasia with compression or compartmentalisation in the distal esophagus > 30 mmHg), and type Ⅲ (two or more spastic contractions) (Figure 2).

TREATMENT

Since the underlying defect cannot be reversed, the treatment of achalasia remains palliative. Current therapeutic options include pharmacologic therapy, endoscopic treatment and surgery. The primary goal of all therapies is the improvement of the esophageal food passage by reducing the distal esophageal obstruction.

Pharmacological treatment

Nitrates and Calcium-channel blockers are the most widely used drugs for the treatment of achalasia[46-49]. Nifedipine is administered 15-60 min before meals in sublingual doses of 10-20 mg. It inhibits the cellular calcium uptake resulting in inhibition of LOS muscle contractions and lowering of the LOS resting pressure by 30%-60%[46-48]. Side effects are seen in up to 30% of patients and include hypotension, headache, and dizziness even if tolerance develops over time.

Only two poorly designed randomized controlled trials have been identified in a Cochrane review by Wen *et al*[50] about the use of nitrates in achalasia so no solid recommendations can be given at present about this treatment.

Botulin toxin A is a neurotoxin blocking the release of acetylcholine from the synapsis terminals. It can be

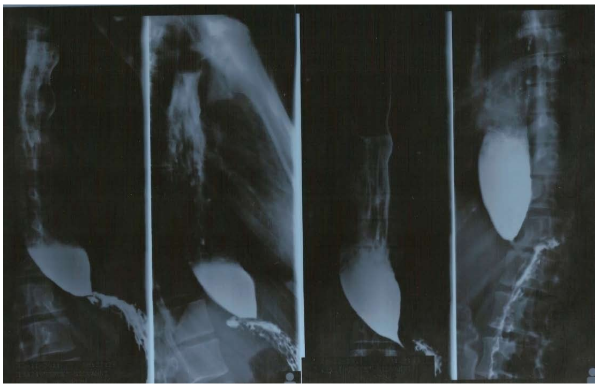

Figure 1 Barium swallow esophagrams showing typical bird-beak appearance of the distal esophagus.

injected during upper endoscopy through an injection needle directly in four or eight quadrants into the LOS at the dose of 80-100 units[51,52].

This combined endoscopic/pharmacological treatment has proven itself safe and effective. More than 80% of patients have clinical response by one month even if response fades quickly and only about 60% of patients are still in remission at 1-year follow-up[53].

Botulinum toxin compared with pneumodilatation[54-58] and laparoscopic myotomy[59] shows initial comparable relief from dysphagia but a rapid relapse of symptoms after 6-12 mo. So, botulinum toxin, as calcium-channel blockers or nitrates use, should be used as a temporary option before a more durable treatment or in high risk patients who are poor candidates for surgery or pneumodilatation.

Pneumatic dilatation

Pneumatic dilatation stretches and tears the LOS fibers with air-filled balloons, the most widely used ones are Rigiflex Balloon System (Boston Scientific, Marlborough, MA, United States). The balloons are available in three sizes (30, 35 and 40 mm) made of non-compliant polyethylene; they are placed over a guide-wire at endoscopy, positioned across the LOS and inflated under fluoroscopic guidance, a graded dilation protocol starting with a 30 mm balloon is usually preferred[60] (Figure 3).

An esophageal lavage with large-bore tubes might be needed in patients with mega-esophagus before the procedure. In patients with previous pneumdilatation failure, younger than 40 years or after a previous Heller myotomy it is possible to begin with a 35 mm balloon. The balloon positioning is checked with fluoroscopy or, sometimes, endoscopy; the waist caused by the non relaxing LOS should impinge on the middle portion of the balloon. After careful positioning, the balloon is inflated until the waist is flattened; the pressure needed in the balloon is 7-15 psi of air and is held for 15-60 s.

Patients must be on a liquid diet for several days and fast for 12 h prior to procedure. The procedure is usually performed as an outpatient surgery under conscious

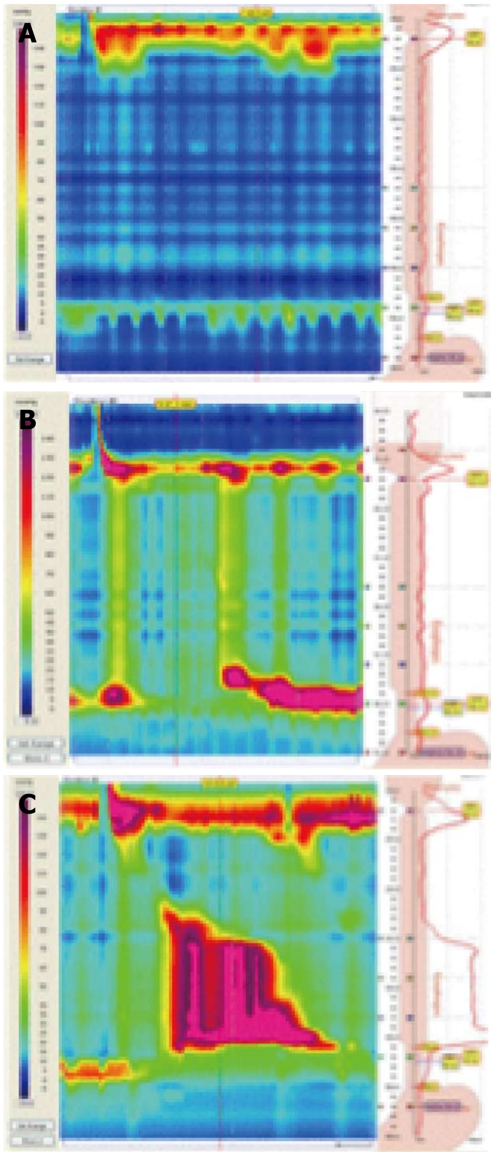

Figure 2 High-resolution manometric types of achalasia according to the Chicago Classification: Type 1, characterized by the absence of peristalsis (A); type 2, defined by the presence of esophageal compression, named panesophageal pressurization (B); type 3, characterized by the presence of peristaltic fragments or spastic waves (C).

sedation in the morning, the patient is then kept under observation for 2-6 h and can return to normal activities the subsequent day. During observation, patients should be assessed for chest pain and fever. A Gastrografin swallowing assessment should be performed in patients complaining with significant pain in order to exclude esophageal perforation.

Subsequent dilatations can be performed after a 2 to 4 wk interval if needed on the basis of symptom relief, LOS pressure measurements or improvement in esophageal emptying[36,61-63].

Pneumatic dilatation with 30, 35 and 40 mm Rigiflex Balloons results in good to excellent symptom relief in 74%, 86% and 90% of patients respectively at 3-year follow-up but nearly two thirds of patients have

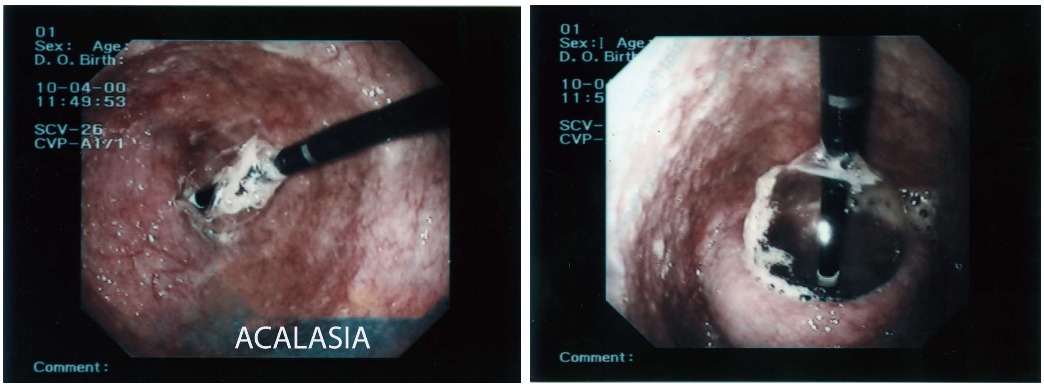

Figure 3 Pneumatic dilation with a Rigiflex balloon under endoscopic control.

symptom relapse over a 4-6 years[38,63,64].

Long term relapses can be managed to obtain long-term remission by a repeat dilatation strategy. Best outcomes are seen in patients with type Ⅱ pattern by HRM, women and in those older than 40 years[1,38,41,65,66].

Patients with type Ⅲ seem to have better results if treated with Heller myotomy compared to pneumatic dilatation, no significant differences are seen in type Ⅰ and Ⅱ. The different response in type Ⅲ patients seems to be due to the fact that Heller myotomy results in a more extensive and proximal disruption of oesophageal muscle fibers[67].

At present, pneumatic dilatation has proven itself to be the most cost-effective treatment for achalasia over a 5-10 year period[68,69]. Up to one third of patients have complications after pneumatic dilatation, most of them are minor such as bleeding, fever, chest pain, mucosal esophageal hematoma and mucosal tear without perforation. Even though severe gastro-esophageal reflux disease is rare after pneumatic dilatation, 15-35 of patients experiences heartburn which can be treated with proton pump-inhibitors[70]. Perforation is, by far, the most serious complication occurring in about 2.0% of patients[71] (reported rate of 0%-16%), about 50% of perforated patients require surgery thus, poor surgical candidates are poor candidates to pneumatic dilatation as well. In a recent series, 16 consecutive transmural perforations were managed conservatively[72]. Small perforations are usually treated with total parenteral nutrition and antibiotics for days to weeks. Large perforations will require surgical repair by thoracotomy. Difficulty in keeping the balloon in place is a reported risk factor for perforation[73]. Also, performing the initial dilatation with a 35 mm balloon seems to put the patient at risk for perforation, compared to an initial dilatation performed with a 30 mm balloon[66].

Per-oral endoscopic myotomy

Ortega first described a series of 17 patients affected with achalasia and treated with a direct trans-mucosal lower esophageal sphincter myotomy and good clinical, radiologic and manometric results in 1981. No confirmatory work was published, perhaps due to complications such as perforation and mediastinitis[74]. Natural orifice transluminal endoscopic surgery made its appearance in 2004 and there has been a tendency towards the development of less invasive alternative to transcutaneous surgical interventions since then. To obtain an access to the mediastinum or the peritoneum, a technique consisting in the creation of a submucosal tunnel closed by a mucosal flap was developed[75].

Per-oral endoscopic myotomy (POEM) was developed from this technique and features the creation of a submucosal tunnel enabling the LES myotomy to be performed away from the mucosal entry site which is closed at the end of the procedure.

In 2007, the first LES myotomy was performed in a porcine survival model[76] and in 2008, Inoue *et al*[77] used the technique of submucosal tunneling to perform the first endoscopic LES myotomy on humans and coined the term POEM for *per oral endoscopic myotomy*. Even though, POEM is mainly performed for achalasia, it can be successfully applied in diffuse esophageal spasm, nutcracker and jackhammer esophagus[78,79]. POEM can be also used in patients with prior Heller myotomy and previous endoscopic pneumatic dilatation[80,81].

POEM contraindications include severe pulmonary disease, bleeding disorders esophageal irradiation or esophageal malignancy and endoscopic intervention including endoscopic mucosal resection and[82] endoscopic submucosal dissection (ESD). POEM requires general anesthesia with the patient in supine position. It is recommended to use anesthesia with positive pressure ventilation to prevent severe mediastinal emphysema[83]. A traditional forward-viewing endoscope and equipment employed in ESD are used. Carbon dioxide is used for insufflation. The esophageal submucosal space is expanded with injection of indigo carmine-saline mixture (typically, 0.3% indigo carmine). The submucosal tunnel is initiated 10-15 cm above the gastroesophageal junction (GEJ). The recommended mucosal entry site is, generally, on the anterior wall between 11 and 2 o'clock[83,84]. In case POEM is performed in patients in which a balloon dilatation has been performed with poor results, since the anterior route can be seriously scarred, the incision is usually performed at the 7 o'clock position[85]. After a

2 cm mucosal incision is made, the submucosal tunnel is extended downward by using a technique similar to ESD to reach the gastric cardia 2-3 cm distal to the GEJ.

Accurate identification of EGJ is essential. Delineation of the GEJ is done in a variety of ways like monitoring the endoscope insertion length, identification of the longitudinal palisade vessels in the submucosal layer, change in the submucosal vascular pattern (from palisade to reticular) at EGJ, stenotic segment of the submucosal tunnel, tattooing at the gastric cardia using indocyanine green (ICG) and even transillumination viewed by a second endoscope[86]. The myotomy is performed starting at 2-3 cm distal to the mucosal entry, thus, more than 10 cm above the GEJ and carried up to, at least, 2 cm distally to the GEJ.

At the beginning of the procedure, the circular muscle is dissected and the longitudinal muscle layer is identified; the inter-muscular space is the correct dissection plane. Some authors favor the dissection of the sole circular muscle fiber, since these are regarded as having the major function in muscle contraction and the risk of surrounding structures injury is reduced by keeping the outer muscle intact[87]. The outer longitudinal muscle layer can be extremely thin, the injury to this muscle fibers and the exposure of the mediastinal structures does not cause any sequelae if the mucosa is still intact, thus an inadvertent mucosal flap injury must always be repaired promptly with clip placement, endoscopic suturing or fibrin spray glue[88].

The incision at 2 o'clock position leads to the lesser curvature of the stomach, in contrast, the hiss angle is located at 8 o'clock. Anterior myotomy potentially avoids damage to the sling muscle, and especially His angle so that no anti-reflux procedure is needed. The 2 o'clock approach might be less efficacious at the LES disruption which is the main goal of the achalasia surgery leading to less relieve of dysphagia but may be useful in avoiding symptomatic GERD after the procedure. In contrast, the 5 o'clock position for the myotomy may lead to less dysphagia but could theoretically have more GERD which can be treated with PPI[83].

Using CO_2 for insufflation and positive-pressure ventilation prevents severe pneumomediastinum should a perforation occur. The muscle layer cutting is continued for at least 2 cm distal to the GEJ; closure of the mucosal entry site can be performed with either hemostatic clips or endoscopic suturing (OverStitchTM Endoscopic Suturing System; Apollo Endosurgery Austin, Texas), no statistically significant difference in mean closure time, complications or mean cost have been noted[83].

Closure might also be performed with over-the-scope clip and fibrin glue[89,90]. Whatever closure technique is used, Gentamicin infusion within the submucosal tunnel is reported. After the procedure, patients should have a radiographic study (either plain or contrast enhanced chest and abdominal X-ray) to exclude perforations leading to pneumomediastinum or pneumoperitoneum. Antibiotics are usually given during the procedure and for several days after the discharge[83,87].

Some authors perform an EGDS and a timed barium esophagogram (TBE) on the 1st post-operative day to confirm mucosal integrity. If mucosal integrity is confirmed by these studies, the patient may be allowed to drink on day 1, soft diet is started on day 2 and normal diet can be restarted on day 3[87]. Post-operative TBE can also be used to confront the Vaezi score before and after the procedure. Reported results of POEM are excellent with dysphagia efficacy using Eckardt score in > 90% of subjects, no mortality is reported this far[82,91-100]. On the subject of POEM complications, pneumoperitoneum and pneumomediastinum are usually managed with either paracentesis and by inserting a small caliber of intercostal drainage for a couple of days[87].

Acute intraoperative bleeding can be managed, if the bleeding point can be identified, by mean of normal coagulation techniques used in ESD (Coaggrasper, APC, *etc.*). In case of an unidentified bleeding point, applying pressure with the tip of the endoscope in the submucosal space or from the natural lumen is suggested. A post-operative hematoma may occur; conservative treatment, keeping the patient fasting with intravenous antibiotics is suggested. The hematoma, usually, resolves spontaneously within 1 to 2 wk.

Post-operative hematemesis, melena, hypotension, retrosternal pain may be the hallmark of a delayed bleeding. CT-scan and emergency upper GI endoscopy are mandatory to confirm the diagnosis. The bleeding point is usually located at the edge of the sectioned muscle; in case the bleeding point cannot be identified, placing a Sengstaken-Blakemore tube is an adequate treatment[101].

GERD is the most frequent adverse event after POEM, prevalence varies considerably[82,90-92,95,96,100,101] and can be as high as 40%.

Self-expanding metallic stent

Early reports regarding the use of self-expanding metallic stent (SEMS) in the treatment of achalasia unresponsive to conventional treatments were published in 1998[102]. SEMS permanently disrupt the muscular fibers of the cardia and represents a safe and effective measure for patients not fit for more invasive therapeutic options; Nitinol coil (InStent Inc., Eden, Praire, United States), Ultraflex (Microvasive, Boston Scientific, Natick, MA, United States) or specially designed (Z-stent, Sigma, Huaian, China) stents have been tested, keeping them in place for 3-7 d[103,104] or 30 d[105].

All the trials regarding the use of metal stents in achalasia reported a technical success of 100% and early clinical success of 87%-100%[102,104-107].

Success rates largely depend on the stent diameter, being higher for 30 mm stents compared with either 25 and 20 mm (87% *vs* 73% *vs* 43% clinical remission rate respectively)[107].

Complications reported were migration (5.3% to 37.5%) and chest pain (17% to 40%)[102,104-107], one single case series of 4 patients reported the occurrence of dysphagia recurrence secondary to food bolus impaction or inflammatory stricture (100%)[108], one patient died secondary to aorto-enteric fistula. Even complication rate depends on the diameter, the wider the stent, the lower the migration rate (6.6% *vs* 13.3% *vs* 26.7%) and the higher the chest pain rate (40% *vs* 33% *vs* 17%, respectively)[107]. All the authors concluded that temporary stent placement is an effective treatment for achalasia and could be used for treating carefully selected cases.

DECISION MAKING IN THE TREATMENT OF ACHALASIA

About 90% of patients treated for achalasia can return to good quality of life and normal swallowing function[109]. On the other hand, few can be cured with only one treatment, repeat procedure might be needed as many patients relapse over time.

Success rates for Heller myotomy and dilatation defined as relieve from dysphagia or regurgitation are quite similar as shown in a study from the Cleveland Clinic[63]. Moreover, a large retrospective longitudinal study from Canada shows that the cumulative risk for any subsequent treatment (dilatation, myotomy, or oesophagectomy) after 1, 5, and 10 years was slightly higher for pneumatic dilatation compared to HLM (36.8%, 56.2%, and 63.5% after initial pneumatic dilatation *vs* 16.4%, 30.3%, and 37.5% after initial myotomy (HR 2.37; 95%CI: 1.86-3.02) but this risk difference only occurred when repeat was recorded as an adverse event[110].

Physiological studies can predict long-term success of therapeutic maneuvers. Eckardt *et al*[61] reported that remission rates at 2-year follow-up largely depended on post-procedural LOS pressure being 100% for LOS pressure less than 10 mmHg, 71% for post-procedural LOS pressure between 10 and 20 mmHg and 23% for pressure over 20 mmHg.

The timed barium oesophagram is also a better predictor of success than LOS pressure is; patients with complete symptom relief and improvement in oesophageal emptying were likely to fare better than those with symptom relief but poor oesophageal emptying (82% *vs* 10%) at 3-year follow-up as Vaezi *et al*[41] reported.

Age, sex, and manometric type by HRM are also predictors of responsiveness to treatment. Success rates for pneumatic dilatation are higher for type Ⅱ achalasia than for type Ⅰ and type Ⅲ (96% *vs* 56% *vs* 29% respectively) as Pandolfino *et al*[45] reported. Type Ⅲ achalasia might be best treated by laparoscopic Heller myotomy (LHM). It is still unclear whether the fact that a patient had been previously treated endoscopically may hamper the results of a LHM.

Some studies suggest that previous treatments could negatively impact the results of the laparoscopic operation[111-114] whereas other authors reported that only patients who had been previously treated with both botulin toxin injection and pneumatic dilatation had worst results.

With reference to the age factor, patients younger than 40 years need repeat pneumatic dilatations more often than those older than 40 years usually do; also, male respond less well than women do to pneumatic dilatation[1,61,63,66,115]. Similarly, women younger than 35 years do not respond well to pneumatic dilatation[63]. These finding are probably dues to stronger LOS tone in younger patients. Myotomy is, then, the best treatment for adolescents and young adults. Also, pseudoachalasia is best treated by LHM.

Botulinum toxin injection should be considered as a first line therapy for elderly patients or those in which severe comorbidities make them poor surgical candidates since it is safe, effective and might need to be repeated no more than once a year.

The role of POEM as a substitute for myotomy will have to be defined over time with longer follow-up studies, at present, Inoue highlights it's usefulness as a re-do procedure in case of LHM failure.

Due to the difficulty to resect adhesions in redo surgery and high morbidity of esophagectomy, POEM is a better choice for treatment recurrence achalasia. Also, a POEM can be useful in these cases as it allows to perform another myotomy in a different location from the prior surgery[87].

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THERAPEUTICS ADVANCES

Colorectal endoscopic submucosal dissection from a Western perspective: Today's promises and future challenges

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Abstract

Over the last few years, endoscopic submucosal dissection (ESD) has shown to be effective in the management of early colorectal neoplasms, particularly in Asian countries where the technique was born. In the Western world, its implementation has been slow and laborious. In this paper, the indications for ESD, its learning model, the available methods to predict the presence of deep submucosal invasion before the procedure and the published outcomes from Asia and Europe will be reviewed. Since ESD has several limitations in terms of learning achievement in the West, and completion of the procedure for the first cases is difficult in our part of the world, a short review on colorectal assisted ESD has been included. Finally, other endoscopic and surgical treatment modalities that are in competition with colorectal ESD will be summarized.

Key words: Endoscopic submucosal dissection; Endoscopic full-thickness resection; Endoscopic mucosal resection; Hybrid endoscopic submucosal dissection; Early colorectal cancer; Assisted endoscopic submucosal dissection; Magnification chromoendoscopy; Colorectal surgery; Colorectal neoplasm; Submucosal invasion; Predictive factors; Training; Learning curve

Core tip: In the Western world, endoscopic submucosal dissection (ESD) implementation is slow and laborious. In this paper, the indications for ESD, its learning model, the available methods to predict the presence of deep submucosal invasion before the procedure and the published outcomes from Asia and Europe will be reviewed. Additionally, a short review on colorectal assisted

ESD has been included. Finally, other endoscopic and surgical treatment modalities that are in competition with colorectal ESD will be summarized.

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INTRODUCTION

Current colorectal cancer (CRC) screening population-based programs[1,2] will increase the detection of early neoplastic lesions suitable for endoscopic resection[3]. Although endoscopic mucosal resection (EMR) is appropriate to resect large flat or sessile colorectal lesions[4-8], recurrence after piecemeal resection is still a limitation[9,10]. In recent years, endoscopic submucosal dissection (ESD) has been endorsed as an ideal technique for *en bloc* resection of large colorectal neoplasms with high risk of focal adenocarcinoma or submucosal fibrosis[11]. Nevertheless, the optimal outcomes of colorectal ESD (CR-ESD) achieved in Japanese series[12,13] are constrained by the long learning curve and high complication rate when trying to introduce it in Western countries[14-16]. Thus, there is some controversy regarding the best approach to the management of large early neoplastic lesions in the colon[17]. Some authors advocate for the refinement of piecemeal EMR or a hybrid method of combined submucosal incision and EMR as a more realistic option for Western endoscopists[7,10,18], whereas others support progressive embracement of CR-ESD through a well-defined training strategy[19-21]. Different topics related to CR-ESD, including training, indications, outcomes, adjunctive devices to simplify the procedure and results when ESD is compared to alternative techniques, will be reviewed.

TRAINING: JAPANESE *VS* WESTERN MODEL

ESD is a complex procedure and the mastery of technical skills by new trainees has been based on a traditional mentor-pupil close teaching relationship in Japan since the introduction of the technique[22,23]. However, recent expansion of ESD in Western countries has been led by a small group of experienced endoscopists that have usually performed a self-learning process based on observation and animal model training[24-27]. Obvious reasons for this different approach are the lack of ESD experts in Western countries and the low detection rate of early gastric cancer as the ideal setting for beginners.

Japanese training model for ESD

In Japan, the traditional model of teaching ESD has consisted of senior experts in large referral centers directly supervising new trainees in a step-by-step scheme[28-30]. Firstly, there is a selection of potential candidates based on prior achievement of good skills on endoscopic diagnosis of early gastrointestinal cancer and therapeutic maneuvers[28]. Secondly, the apprentice has to observe a certain number of ESD procedures performed by the mentor, occasionally participating as an assistant to become familiar with the special devices used. If possible, the trainee should complete this initial training period with some hands-on exposure to animal models[31]. The trainee is then invited to perform some partial phase of the ESD (marking, initial circumferential cutting, final dissection, preventive coagulation…) under close supervision by the mentor[32]. The ideal setting that has been suggested to begin with is performing ESD in selected lesions at an easily accessible gastric location[30]. When considered ready, the trainee is finally encouraged to perform a complete gastric ESD. Increasing number of cases completed eventually grant enough skills to move on to more difficult locations in the stomach. Several Japanese authors have suggested a number ranging from 20 to 80 cases to be considered proficient in gastric ESD[29,30,32]. Afterwards, the trainee may continue with other areas of the GI tract: esophagus, rectum and colon. Difficult colonic cases are generally restricted to experts with outstanding skills and extensive experience[33].

CR-ESD training in Japan

CR-ESD represents the last step in the natural evolution of ESD training. Colonic lesions are commonly located in difficult areas, where positioning of the endoscope may be extremely challenging, and there is general agreement that prior experience with gastric ESD is needed[34,35]. Several studies have investigated the appropriate number of CR-ESD to achieve proficiency. Some authors have proposed a minimum number of 20-30 cases under close supervision to achieve a certain level of competence[36], and it is advisable to begin with rectal and smaller lesions[37]. Nevertheless, the numbers needed to secure a high profile of successful R0 resection with few complications are closer to 80-100, according to some reports[38].

Western training model for ESD

Small groups of endoscopists with particular interest in the technique have commonly promoted initiation of ESD in Western countries. The typical profile is that of an experienced attending gastroenterologist with extensive background in interventional endoscopy (EUS, ERCP, EMR…)[39]. Preliminaries could be either self-study based on articles and videos of procedures, attending ESD courses with hands-on training in animal models, *etc.* It is of particular interest to complete a visit to Japanese centers, where the trainee can benefit from first-hand experience observing experts performing ESD cases[25,26]. This is a good opportunity to learn the basics of chromoendoscopy and magnification for lesion assessment, different knives and ancillary devices used, steps of the ESD procedure including management of early and late complications, as well as specimen fixation and pathological assessment[27]. Additional extensive hands-on training using animal models is essential for the next steps in skills acquirement, up to the point when main outcomes are good enough to encourage completion of the first human ESD cases[19,24,25]. The fulfillment of the first human ESD cases should be based on a careful selection with preference for small gastric or rectal lesions. All these steps have been recommended in a European Society of Gastrointestinal Endoscopy position statement[40], and a training algorithm comprising most of them has been recently proposed[19].

Unfortunately, in many centers this training pathway must be self-teaching and is limited by the unfeasibility to obtain access to animal laboratory resources. Frustration from technical struggle or frequent complications may lead the process to a premature dead end. In addition, the bulk of potential candidates for ESD according to current recommendations are colorectal lesions[11,39], which makes it ever more arduous and disheartening. There are some approaches to overcome these limitations: proposing a Japanese expert to come to your institution for direct supervision during the first ESD cases[24,27,41] or attending hands-on courses in animal models in Japan to practice ESD under expert supervision have been suggested[42].

Colorectal ESD training in Western countries

There are several studies in Europe focused on CR-ESD training. Initial reports showed suboptimal *en bloc* and R0 resection rates at the beginning[15,43], but rapid progression was observed within a relatively a short time[14,20,21,41]. The majority of endoscopists begin with selected small rectal lesions, to later move on to other colonic locations.

Some authors have proposed that a minimal intensive training may be sufficient for expert Western endoscopists to complete a sequential learning curve in rectal and colonic ESD, with a minimum of 20 untutored cases each after a short initial animal hands-on period (< 10 cases)[41]. Nevertheless, such an approach should be carefully considered since reports from high volume Japanese centers recommend a minimum of 80 cases to obtain adequate skills, both in terms of speed (< 15 min/cm^2), perforation (< 6%), *en bloc* (> 95%) and R0 (> 90%) resection rates[38]. These numbers must be considered in light of the well-established scenario of close expert supervision in Japanese centers, which is frequently not the case in Europe[16]. Some experts have recommended for inexperienced Western endoscopists to complete at least 40 cases before attempting large or fibrotic CR lesions[44], two characteristics commonly present in the eligible population for CR-ESD[11].

In summary, it has been shown that the ESD training process in Europe in a prevalence-based approach will be undoubtedly shaped by a significant number of colonic and rectal cases[39]. Untutored ESD training can achieve good outcomes in CR-ESD, but it is encouraged that initial cases are early neoplastic lesions with a low risk of invasion due to the fact that R1 resection is common in inexperienced endoscopists[39]. Western reports have generally considered a resection rate > 80% acceptable; however, if Western endoscopists wish to pursue excellence in ESD, target outcome standards should probably not be less than those established in Japan, *i.e.*, *en bloc* and R0 resection rate > 90%.

HISTOLOGICAL PREDICTION AND INDICATIONS IN THE WEST

Intramucosal lesions and those well or moderately differentiated T1 adenocarcinomas with submucosal invasion less than 1000 μm and no lymphovascular infiltration, have little or no risk of metastasis[45] and therefore constitute a typical indication for endoscopic treatment and especially for ESD. In a retrospective series of patients treated at the National Cancer Center Hospital (NCCH) in Tokyo, it was noted that the mucosal morphological pattern accurately predicted the risk of submucosal invasion. In this study, the laterally spreading tumor non granular (LST-NG) type lesions showed a higher risk of submucosal invasion compared with granular (LST-G) type lesions with a statistically significant difference (14% *vs* 7%; $P < 0.01$)[46]. On the other hand, the presence of large nodules in LST-G type lesions, the finding of an invasive pit-pattern, "sclerotic" changes in the colorectal wall and a larger size in LST-NG type neoplasms, were also predictors of submucosal invasion. In this series, whereas submucosal invasion in LST-G most often occurs beneath the largest nodules and less frequently under depressed areas, 28% of LST-NG showed multifocal submucosal invasion in areas where there was no endoscopic warning signs. These findings were recognized as evidence of a different biological behaviour and drew attention to the need for an *en bloc* resection of these neoplasms.

The development of magnification chromoendoscopy (MCE) allowed Japanese endoscopists to describe different pit-patterns[47] as well as microvascular structures[48] in early CRC, increasing the accuracy of the histopathological prediction and improving the therapeutic decision-making process. When performed by Japanese expert endoscopists, MCE achieved a diagnostic accuracy of 98.8% in differentiating intramucosal or submucosal sm1 superficial invasion from sm2-sm3 deep submucosal invasion[49]. In another seminal study, the identification of a type ⅢA microvascular pattern by Narrow Band Imaging was predictive of intramucosal or sm1 neoplasia in 94.5% of cases, while a type ⅢB pattern was associated with sm2-3 carcinomas in 72% of cases[50].

We have fewer data from European or American centers, but a major Australian series of colorectal tumors treated by EMR[7] found that LST-NG type with a Paris 0-Ⅱa +

Table 1 Indications for colorectal endoscopic submucosal dissection (Japan Gastroenterological Endoscopy Society)

Lesions for which endoscopic *en bloc* resection is required
(1) Lesions for which *en bloc* resection with snare EMR is difficult to apply
LST-NG, particularly LST-NG pseudo-depressed type
Lesions showing a Vi-type pit pattern
Carcinoma with shallow T1 submucosal invasion
Large depressed-type tumors
Large protruded-type lesions suspected to be carcinoma. Including LST- G, nodular mixed type
(2) Mucosal tumors with submucosal fibrosis as a result of a previous biopsy or prolapse caused by intestinal peristalsis
(3) Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis
(4) Local residual or recurrent early carcinomas after endoscopic resection

EMR: Endoscopic mucosal resection; LST-NG: Laterally spreading tumor non granular; LST-G: Laterally spreading tumor granular.

Ⅱc morphology and a Kudo crypt pattern V had a risk of submucosal invasion of 55.5%. On the other hand, LST-G homogeneous type tumors presented submucosal invasion in only 1.5% of cases. These figures reflect that superficial colorectal neoplasms behave similarly to those described in Japanese series and therefore morphological pattern and epithelial crypt analysis can be used for histological prediction and treatment decision-making in Western patients.

Many studies confirm the accuracy of Western endoscopists in differentiating between neoplastic and non-neoplastic polyps, but few reports have focused specifically on their ability to predict the presence of deep submucosal invasion prior to an endoscopic resection attempt. A study from the United Kingdom[51] showed that Western endoscopists achieved a diagnostic accuracy of 78% in predicting deep submucosal invasion in Paris 0-Ⅱ lesions by analyzing epithelial crypts and vascular patterns with MCE. In this study, high frequency miniprobe ultrasound examination improved the accuracy up to 94%.

Nevertheless, the limited data available from surgical series, including lesions deemed as endoscopically non-resectable, have demonstrated that between 10% and 20% of the specimens showed deep colonic wall invasion (stages T2-T4) or lymph node metastases that had not been suspected in the endoscopic assessment[52-55], indicating a lower than expected accuracy in real life conditions.

The role of endoscopic ultrasonography (EUS) in the diagnosis of submucosal invasion or nodal involvement has been controversial. In one small study from Western Europe, endoscopic ultrasound with a 20 MHz probe was better than MCE in determining the depth of invasion and nodal staging[56], but these results have not been consistently observed in other series of patients. In a study including more than 430 neoplasms treated in a single center in Japan, no significant differences were noted in the diagnostic accuracy between MCE and EUS[57].

In general terms, ESD is indicated for the treatment of colorectal neoplasms that show no suspicion of deep submucosal invasion assessed by MCE and that cannot be resected *en bloc* by EMR. Given the technical characteristics of ESD, the size of the lesion is not a limitation, although circumferential lesions are generally considered a contraindication given the high risk of stenosis.

In the absence of local evidence, most Western endoscopists performing ESD have traditionally followed Japanese guidelines. Table 1 shows ESD indications of the Japan Gastroenterological Endoscopy Society[11]. In Europe, the Spanish Society of Digestive Endoscopy[58] and the European Association of Endoscopic Surgery[59] have adopted most of the Japanese indications for ESD as a standard treatment for superficial neoplasms larger than 20 mm in which *en bloc* EMR is difficult. These statements include mixed type LST-G, LST-NG, especially the pseudo-depressed type (Figure 1), large depressed lesions with a noninvasive pattern as assessed by MCE and neoplasia with fibrosis in the context of prior biopsy, attempts of resection or chronic inflammation.

Despite the gradual incorporation of Japanese knowledge about diagnosis and prediction of histological findings into European and American practices, major differences exist between Eastern and Western viewpoints on the endoscopic treatment of colorectal neoplasms. While ESD is widely accepted in Japan, and Japanese National Health Insurance has been covering its cost since 2012, in most Western hospitals a significant number of patients with endoscopically treatable lesions are still referred for surgery. In our part of the world, EMR is the preferred technique for the treatment of superficial neoplasms. As an alternative modality, ESD is still in the early steps of development, with a lack of a clear definition of its place in the treatment algorithms and significant uncertainties about the coverage of its costs.

These differences are clearly due to the greater experience of Japanese endoscopists, but also and significantly, because in Japan there has been little controversy about the importance of *en bloc* resection of tumors in which a risk of submucosal invasion is foreseeable. On the contrary, many Western endoscopists would contend that since most T1 adenocarcinomas with deep submucosal invasion can be identified in the histopathological study of piecemeal EMR, the benefits of *en bloc* resections are limited to a relatively small number

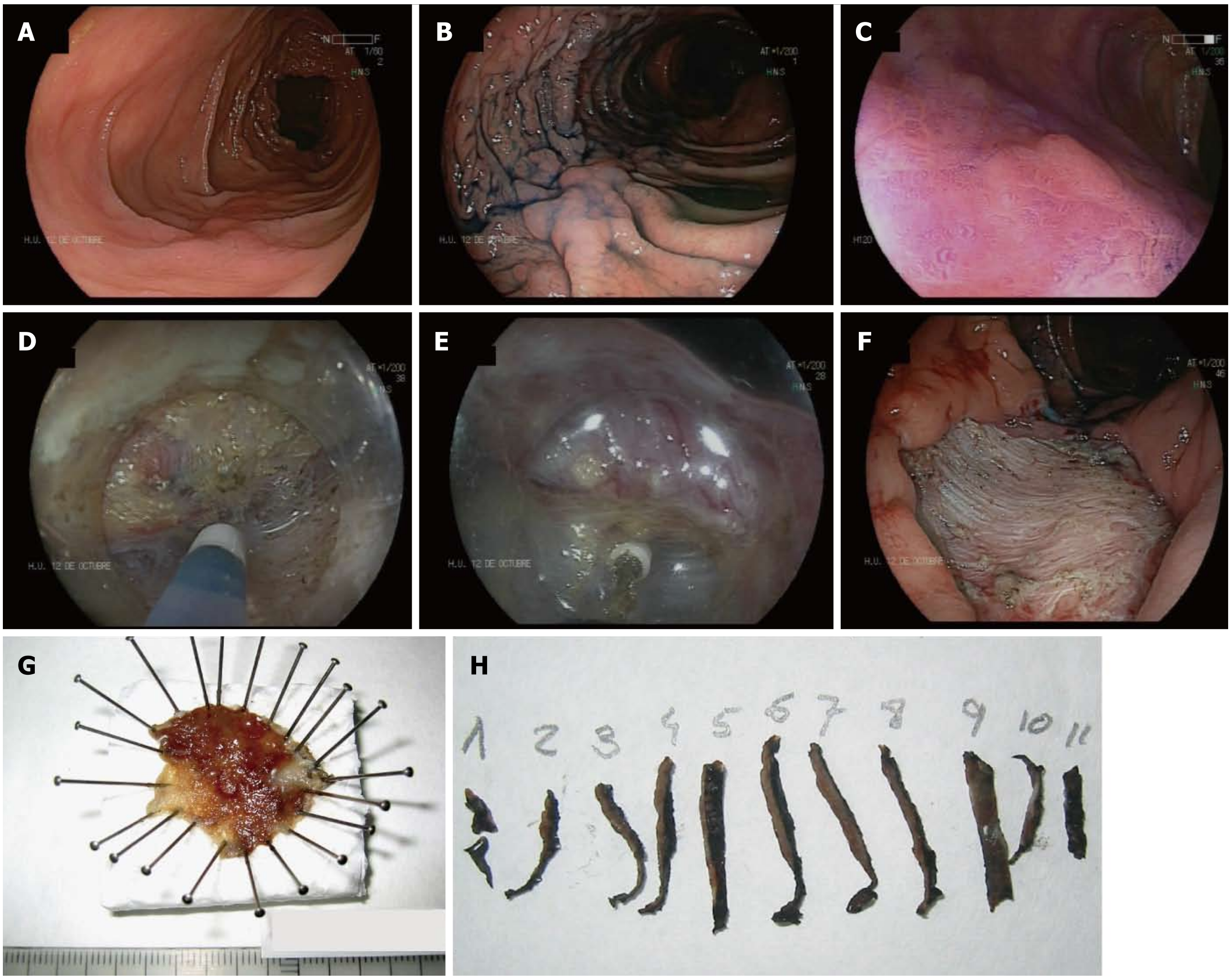

Figure 1 Endoscopic assessment and endoscopic submucosal dissection for a laterally spreading tumor non granular pseudodepressed type in the transverse colon. A: High resolution white light endoscopy; B: Targeted chromoendoscopy with indigo carmine (0.4%) highlights the border and characteristics of the lesion; C: Magnification chromoendoscopy with crystal violet (0.05%) shows a Kudo's Vi pit-pattern; D: Performing ESD with a 1.5 mm Flush-knife BT (Fujinon, Tokyo, Japan); E: Submucosal dissection of the lesion with an IT nano (Olympus, Tokyo, Japan); F: Residual scar after completion of the procedure; G: Resected specimen of CR-ESD stretched with pins on foam. Maximum diameter of the lesion was 32 mm; H: Specimen sectioned into pieces for histological assessment in the Department of Pathology. ESD: Endoscopic submucosal dissection; CR-ESD: Colorectal endoscopic submucosal dissection.

of lesions with sm1 infiltration which, in the case of R0 resections, could avoid surgery. Others would however argue that even intramucosal large LST-NG that can be difficult to resect by EMR because of partial non-lifting, could itself justify the implementation of the procedure.

OUTCOMES IN ASIAN AND IN EUROPEAN COUNTRIES

The tortuous morphology of the large intestine, a thinner wall when compared with the stomach, and the strong peristaltic motion of the colon, leads to a higher likelihood of complications during the procedure. It is very likely that the ESD learning curve is slower in the colon than in the stomach, and it has been overcome for many years in the experienced Asian centers.

As mentioned before, the experience with colorectal ESD out of the Asian countries is scarce. In European countries, our limited experience has shown less favourable results than those coming from the East, with lower *en bloc* and R0 resection rates and higher perforation rates.

Tables 2 and 3 summarize the most relevant data of the published series. Many of them have methodological limitations and an intention-to-treat analysis is lacking. Although it is commonly reported that the cases are consecutively enrolled, other information is often not provided. In most cases, they are cross-sectional studies and when follow-up is included, this is usually for a period less than 3 years. More importantly, considering that we are talking about oncological outcomes, the 5-year survival rate has been assessed in only one study[60].

The percentage of non-curative resections oscillates between 3.6%[61] and 22.7%[62]. Furthermore, it is noteworthy that the percentage of aborted procedures is scarcely reported. This is particularly striking when a complex procedure, with a prolonged learning curve, comes into focus. Reviewing the published series,

Table 2 Colorectal endoscopic submucosal dissection outcomes for epithelial neoplasms in Asian studies

Ref.	Patients, *n* (% rectal)	Study design	Enrollment period	Size (mm)	Time (min)	*En bloc* (%)	R0 (%)	Perforation rate (%)	Delayed bleeding (%)	Hospital stay (d)	Follow-up
Fujishiro et *al*[63], 2006	35 (100)	Prospective	Feb 2001 Feb 2005	32.8	NS	88.6	62.9	5.7	28.6	-	Missing rate: *n* = 0; 0% Mean: 36 mo (12-60) Recurrence rate at 2 mo: 2.8% 31/32 (96.8%) recurrence-free at 3 yr
Tamegai *et al*[64], 2007	71 (23.9)	NS	Jan 2003 Dec 2005	32.7	61.1	98.6	95.6	NS	1.4	-	Missing rate: *n* = 7; 9.86% Mean: 12.2 mo (range 3-34) Recurrences: 0%
Hurlstone *et al*[70], 2007	42 (33.3)	Prospective	Mar 2004 Aug 2006	31	48	78.6	73.8	2.4	2.4	22	Missing rate: *n* = 6; 14.3% Median: 6 mo (range: 3-18) Recurrences 4/36 (11%) Curative resections at 6 mo: 34/42 (81%)
Fujishiro *et al*[112], 2007	200 (26)	NS	Jul 2000 Mar 2006	29.9	-	91.5	70.5	6	0.5	-	Median: 18 mo (range 12-60) Recurrences: 1.8%
Saito *et al*[65], 2007	200 (30.5)	NS	Oct 2003 Jul 2006	35	90	84	70	5	2	5	Median: 7 mo Missing rate: 10% Recurrences: 0.5%
Tanaka *et al*[68], 2007	70 (48.6)	NS	< Dec 2005	28	70.5	80	-	10	1.4	-	In curative resections, 0% recurrence rate Other information not provided
Zhou *et al*[113], 2009	74 (56.7)	NS	Jul 2006 Dec 2007	32.6	110	93.2	89.2	8.1	1.4	-	Missing rate: *n* = 0; 0% Median: 14.3 mo (range 3-22) Recurrences: 0%
Isomoto *et al*[114], 2009	292 (26.7)	NS	May 2001 Dec 2008	26.8	-	90.1	79.8	7.9	0.7	-	Missing rate: 24.6% Median: 33 mo in R0 36 mo in non-R0 resections R0: 0% recurrences 1 recurrence in non-R0 resections
Saito *et al*[115], 2009	405 (27.4)	NS	NS	40	90	86.9	-	3.5	1	-	Mean ± SD: 20 ± 13 mo 2% recurrences
Iizuka *et al*[62], 2009	44 (59)	Retrospective	Jan 2000 Dec 2004	39	110	61	58	8	-	-	-
Niimi *et al*[60], 2010	310 (26.1)	Retrospective Monocentric	Jul 2000 Dec 2008	28.9	-	90.3	74.5	4.8	1.3	-	Median: 38.7 mo (12.8-104.2) 2% recurrences 3-yr overall/disease-specific survivals: 97.1%/100% 5-yr overall/disease-specific survivals: 95.3%/100% 8 died of other coexisting diseases 0 died of CRC
Yoshida *et al*[116], 2010	250 (31.6)	NS	Apr 2005 Mar 2010	29.6	106	86.8	81.2	6	2.4	-	-
Saito *et al*[81], 2010	145 (50.3)	Retrospective	Jan 2003 Dec 2006	37	108	84	-	6.2	1.4	-	Median: 20 mo 2.1% recurrences
Hotta *et al*[38], 2010	120 (27.5)	NS	Jun 2003 Sep 2008	> 30	141	93.3	85	7.5	-	-	-
Saito *et al*[12], 2010	1111 (30.3)	Multicentric Prospective	Jun 1998 Feb 2008	35	116	88	89	5.3	1.5	-	-
Toyonaga *et al*[117], 2010	268 (25.7)	Retrospective	May 2002 May 2007	40.3	64.5	99.2	98.1	2.2	0.37	-	Median: 32.2 mo (6.5-85.2) Follow-up: 227 out of the 241 curative resections (94.2%) Missing rate: 5.8% Recurrences: 0%
Matsumoto *et al*[118], 2010	203 (NS)	NS	Nov 2002 Jun 2009	33	-	85.7	-	6.9	-	-	-
Uraoka *et al*[119], 2011	202 (32.7)	NS	Apr 2006 Mar 2010	40	-	91.6	87.1	2.4	0.5	-	Median: 11.4 mo Missing rate: 14% 0% disease specific mortality 1.5% overall mortality

Shono *et al*[61], 2011	137 (26.2)	NS	Apr 2007 Oct 2010	29.2	79.2	89.1	85.4	3.6	3.6	-	0% recurrences No other information provided
Kim *et al*[120], 2011	108 (44)	Retrospective	Mar 2007 Feb 2009	27.6	61.9	-	78.7	20.4	-	-	-
Lee *et al*[84], 2012	314 (19.1)	Retrospective	Jan 2004 Nov 2009	28.9	54.7	92.7	87.6	8	0.64	3.6	-
Lee *et al*[121], 2012	499 (18.1)	Retrospective	Oct 2006 Nov 2010	28.9	61.3	95	-	7.4	-	3.6	-
Hisabe *et al*[122], 2012	200 (30)	NS	Jun 2003 Jun 2011	32.7	108.9	86	-	7	1	-	-
Saito *et al*[123], 2012	1321 (25.6)	Multicentric	-	34.2	90	95.4	87.2	2.9	2.5	-	-
Okamoto *et al*[71], 2013	30 (50)	NS	Dec 2010 Aug 2012	36	61	-	100	0	0	-	-
Lee *et al*[72], 2013	874 (20.7)	Retrospective	> Oct 2006	26.5	53.8	97.1	90.5	6.1	0.5	3.5	-
Nakajima *et al*[80], 2013	816 (36.3)	Prospective Multicentric	Oct 2007 Dec 2010	39.4	96	94.5	90.6	2	2.2	-	-
Nawata *et al*[124], 2014	150 (20.6)	Retrospective 2 groups: A < 50 mm/B ≥ 50 mm	Apr 2010 Jul 2013	26/59	38/86	98.7	97.3	0	0	-	-
Sakamoto *et al*[66], 2014	164 (38)	Retrospective	Apr 2005 Mar 2012	30	95	95	92	4	3	-	-
Saito *et al*[109], 2014	900 (NS)	NS	NS	40	100	91	87	2.7	1.7	-	-
Lee *et al*[125], 2015	173 (24.3)	Retrospective	Jan 2010 Dec 2013	25.95	-	88.4	81.5	11	3.4	-	-
Rahmi *et al*[67], 2015	28 (25)	Retrospective 100% recurrences	Dec 2008 Jul 2013	17.5	63	96.4	92.9	3.5	0	7	Median: 22 mo Missing rate: 35.7% Recurrences: 0%

The given values for the size of the lesion and time spent on the procedure are shown as the measure of central tendency reported in the study (mean or median as appropriate). NS: Not specified. -: Information is not mentioned in the original paper.

aborted ESD procedures of between 3.6% and 15.9% have been described[14,61,62].

Additionally, regarding complications, the perforation rate requiring surgery is seldom described, within a range of between 0%[61-67] and 2.8%[68]. Similarly, the need for transfusion or urgent endoscopic therapy due to severe gastrointestinal bleeding are, fortunately, rare, between 0%[12,64,65,69-71] and 2.2%[72].

Since ESD is accompanied by risk of delayed perforation and bleeding the postoperative course needs to be monitored carefully. However, no recommendations have been established for patient discharge after the procedure. Some Japanese authors have suggested a 5-d hospital stay for ESD[73]. In South Korea and some European countries, duration of the hospital stay is 2-3 d unless complications develop[16,72]. Recently, a Japanese group has published a clinical pathway to shorten hospital stays after the procedure. The authors concluded in the study that a three-day stay may be sufficient when no abnormalities occurred during ESD or on the first day after the endoscopic resection[74]. In our center, a stay that lasts 3 d is typically the case when no complications are observed. No delayed perforations have been identified after those 3 d in our experience; indeed, this complication is more likely to happen during the first 24 h after the procedure.

COLORECTAL ASSISTED ESD

A good visualization of the submucosal layer is one of the key factors for performing an effective and safe CR-ESD, and this can only be achieved by proper traction of the tissue.

Benefits of applying traction during ESD are the following: (1) It can provide better submucosal exposure and consequently decreases the risk of perforation; and (2) Traction decreases the contact area between the tissue and the endoknife, enabling a more effective cut[75].

However, achieving good traction using only one knife through the scope is not easy. Unlike surgeons, who maintain tension and visibility by the hands of assistants, or by more than one device, the endoscopist who performs ESD can be considered as a one-armed person. In order to improve this disadvantage, a number of adjunctive devices have been designed.

Sinker-assisted ESD

A sinker-assisted ESD for colorectal neoplasms was reported by Saito *et al*[76]. A 1 g sinker is attached to a metallic clip by a nylon thread. After the initial dissection of the submucosa, the clip is deployed to the edge of the mucosa. The sinker will then pull down the partly resected tumor. Finally, changing the position of the patient, will allow gravity to expose the submucosal layer in order to enhance visibility for the remaining dissection.

The Sakamoto and Osada clip

The S-O clip (Sakamoto and Osada clip) consists of

Table 3 Colorectal endoscopic submucosal dissection outcomes for epithelial neoplasms in European studies

Ref.	Patients, *n* (% rectal)	Study design	Enrollment period	Size (mm)	Time (min)	*En bloc* (%)	R0 (%)	Perforation rate (%)	Delayed bleeding (%)	Hospital stay (d)	Follow-up
Farhat *et al*[16], 2011	85 (84.7)	Prospective	Jan 2008 Aug 2010	-	-	67	62.3	-	-	-	-
Probst *et al*[14], 2012	76 (86.6)	NS	Oct 2004 Sep 2011	45.8	176	81.6	69.7	6.6	10.5	-	Median: 23.6 mo (2-83) Included in follow-up: *n* = 65 9.2% residual neoplasms (5 piecemeal and 1 en bloc R1 lateral)
Repici *et al*[20], 2013	40 (100)	Prospective	Apr 2010 Jan 2011	46.8	86.1	90	80	5	2.5	-	Recurrences: 2.5%
Thorlacius *et al*[126], 2013	29 (59)	NS	Jan 2012 Mar 2013	28	142	72	69	6.9	0	-	Recurrences: 0% at 3-6 mo Missing rate: 82.7%
Spychalski *et al*[127], 2015	70 (56)	NS	Jun 2013 Jun 2014	30	110	66	-	8	6	-	Missing rate: 14.6% Recurrences: 4.9% Follow-up < 12 mo
Rahmi *et al*[128], 2014	45 (100)	NS	Feb 2010 Jun 2012	35	110	64	53	18	13	3.4	For curative resections at 12 mo: 88%
Bialek *et al*[129], 2014	37 (67.6)	Prospective	2007 2013	37	70	86.5	81.1	0	5.7	-	At 1-yr follow-up: 1.7% recurrences

The given values for the size of the lesion and the time spent on the procedure are shown as the measure of central tendency reported in the study (mean or median as appropriate). NS: Not specified. -: Information is not mentioned in the original paper.

a metal clip attached to the end of a spring. A double nylon loop is connected at its other end. This system passes easily through the working channel of the endoscope. The device is attached to the mucosal flap and a second clip grasps the distal nylon loop to insert this end of the S-O clip to the wall opposite the lesion[77].

Thin endoscope-assisted ESD

A double-scope method for large LSTs in the distal sigmoid colon or rectum has been reported by Uraoka *et al*[78]. When partial dissection of the submucosa has been performed, a clip is attached to the edge of the mucosal flap. A thinner endoscope is then passed through the anus and the primary endoscope is removed. At that point, a snare grasps the clip and pulls the lesion away from the muscle layer. This maneuver allows retraction of the submucosa and improves visualization. The primary scope is inserted again to resume the dissection. A limitation of this method is that the thin endoscope is not stiff enough to achieve deep intubation and using it for proximal lesions is not possible.

"Clip-flap" method

Yamamoto *et al*[79] reported recently a simple procedure requiring only common clips. After the mucosal flap has been created and the submucosal layer partially dissected, the edge of the mucosa is grasped with an endoclip. The cap attached to the tip of the endoscope is slipped under the clip and the dissection can be resumed as normal. One endoclip can be used for one region and other endoclips can be deployed in additional regions as needed. It is also possible to use two clips crossing one another. However, this method has several limitations. When the colonic lumen narrows or the position of the endoscope becomes unstable, it may be difficult to grasp the mucosa with the clip and slip the cap under the device.

COLORECTAL ESD *VS* OTHER THERAPEUTIC STRATEGIES

EMR

Currently, ESD is the only technique that allows *en bloc* resection of colorectal mucosal or submucosal neoplasms of any size except for the full-thickness resection procedures. In the Western world, however, most lesions larger than 20 mm are still treated by piecemeal EMR.

In a prospective study of a large series of patients treated in 18 Japanese reference centers, it was observed that the rate of *en bloc* EMR was significantly reduced as the diameter of the lesion increased, reaching 66.5% in lesions of 20-29 mm, but was only 12.3% in lesions larger than 40 mm. Conversely, ESD *en bloc* resection rates remained above 90% regardless of the size of the lesion[80].

The first study comparing retrospectively the results of colorectal EMR and ESD included 373 (145 ESD/228 EMR) resected tumors between 2003 and 2006 by expert endoscopists at the NCCH in Tokyo[81]. As a result of differences in the indications of both procedures, the ESD group included larger lesions (37 ± 14 mm *vs* 28 ± 8 mm; P = 0.0006). However, the *en bloc* resection rate was significantly higher when performing ESD (84% *vs* 33%; P < 0.0001). An increased risk of tumor recurrence at follow-up colonoscopies was observed after EMR when compared with ESD (2% *vs* 14%;

P < 0.0001). It is worth noting that, in this study, all recurrences detected in the ESD group occurred after treatment of lesions previously treated by piecemeal EMR. The mean procedure time was nevertheless more than three times longer in patients treated with ESD (108 min *vs* 29 min; *P* < 0.0001) and perforations were almost five times higher (6.2% *vs* 1.3%), although differences were not statistically significant.

Some Japanese and South Korean studies[73,82-85] have shown better outcomes for ESD in terms of *en bloc* and R0 resections and lower recurrence rates. In addition, higher perforation rates and an increased length of the procedure time have been also observed. Some of these studies, however, excluded patients who underwent surgery because of submucosal invasion, which could represent an overestimation of the clinical effectiveness of this procedure[73,82]. Furthermore, it has been shown in both Eastern and Western series of ESD that its benefits on a lower rate of local recurrence rely on the ability of the procedure to achieve *en bloc* resections and only become evident in those procedures performed by endoscopists with a high proportion of R0 resections[14].

The endoscopic resection of recurrent adenomas is another matter of concern. Although ESD may be used in endoscopic salvage procedures for recurrent lesions, performing this procedure is extremely difficult because of the presence of submucosal fibrosis attributable to previous resection. For this reason, in the Western world, the most commonly endoscopic procedure for treating recurrent adenomas after EMR is one additional EMR, although fibrosis after a previous resection often prevents lifting of the lesion after submucosal injection and causes the snare to slip off the tumor. There are very limited published data on the results for this strategy, with more than 10% of the patients needing surgery in this scenario[7].

In a retrospective case series that included 67 cases of a second endoscopic resection for recurrent neoplasias, ESD achieved a 56% *en bloc* resection rate compared with 39% in the EMR group. Both of these results are lower than expected for primary colorectal tumors[86]. In contrast, another study observed that 27 out of 28 patients were successfully treated using ESD for residual or recurrent colorectal of tumors[67].

More recently, underwater EMR (UEMR) has been evaluated for the treatment of these recurrences. When colon water distension is used instead of gas, the mucosa and submucosa involute, keeping the muscle layer in place, and there is no need for submucosal injection. Thus, the tumor can be snared easier than with conventional EMR. In a retrospective study, the *en bloc* resection and endoscopic complete removal rates were higher in the UEMR group when compared with the EMR group, and these differences were statistically significant. In addition, argon plasma coagulation ablation of residual tumor was lower in the UEMR group[87]. Although the study had several limitations, UEMR appears to be useful for salvage endoscopic management of recurrent lesions after a previous EMR.

Finally, some aspects remain to be clarified concerning the use of these endoscopic procedures for the treatment of defiant colorectal polyps. Thus, isolated cases of submucosal recurrences after piecemeal resection for intraepithelial or intramucosal neoplasms have been reported[73,81]. This complication has been attributed to staging errors derived from the histopathological study of a piecemeal resection. Additionally, there is no data concerning the impact of perforations that occur during ESD on oncological prognosis.

ESD vs surgical procedures

The two main surgical options at present are laparoscopic-assisted colorectal surgery (LACS) and transanal endoscopic microsurgery (TEM). Several non-randomized controlled studies have compared ESD and surgical modalities for management of colorectal lesions, but good quality evidence is lacking to allow substantial recommendations. ESD has been shown to be a good option for early colorectal neoplastic lesion with absent or shallow submucosal invasion[12,20,72], but diverse results have been reported when compared with alternative surgical modalities. Recent European guidelines for early rectal cancer do recommend either ESD or TEM, both with optimal curative resection rate, and discourage against conventional transanal excision unless both ESD and TEM are not feasible[59].

LACS

LACS has widely succeeded as a less invasive technique compared with conventional open surgery[88,89]. One retrospective study performed at the NCCH in Tokyo compared ESD with LACS for colorectal early carcinoma[90]. The study population comprised T1m/T1sm1 in the ESD group and T1sm2 in the LACS group. Lesions were located from cecum to rectum, with double the proportion of rectal lesions in the ESD group (38% *vs* 17%). Results showed that ESD was associated with a shorter procedure time (106 min *vs* 206 min), shorter hospital stay (5 d *vs* 13 d) and lower complication rates (6.4% *vs* 13.6%). Nevertheless, *en bloc* and curative resection rates were lower in the ESD group (87.2% and 80.4%, respectively), compared to 100% for surgical patients. Similarly, a recent retrospective study comparing a series of 300 colorectal ESD to 190 LACS revealed high *en bloc* and curative resection rates for ESD (> 90%), with a shorter procedure time and hospital stay, and a lower complication rate compared with LACS (90 min *vs* 185 min; 5 d *vs* 10 d; 7% *vs* 15%, respectively)[91]. It should be noted, however, that this report might be shaped by selection bias since a significant proportion of cases in the LACS group (35%) were post-EMR "lesions/scars" *vs* no cases in the ESD group, and apparently different from what was defined as local recurrence on ESD. Additionally, the ESD group included more than 75% of the lesions as LSTs *vs* only 10% in the LAC group.

In terms of hospital stay, five days or longer in LACS groups are common in Japanese studies. However, other studies have reported shorter periods when an elective surgery has been performed, ranging from 3[52] to 6 d[92-94].

TEM

TEM is a technique for *en bloc* full-thickness rectal wall excision up to the level of the perirectal fat that can be applied for lesions located as far as 18-20 cm from the anal verge. The minimal distance from the anal verge is 5 cm due to the rigid structure of the rectoscope, making it troublesome to approach a lesion next to the anal verge[95]. Developed more than 25 years ago as an alternative to standard transanal surgery[96], TEM has become one of the gold standards for early rectal cancers, whenever available[59]. There is increasing evidence that TEM is superior to conventional transanal resection (TAR) in terms of *en bloc* and R0 resection rates, and thus, lower recurrence, together with lower complication rates[97-99]. Some of the limitations of TEM include the long learning curve[100], similar to ESD, and the need for quite expensive special equipment.

Contradictory results have been obtained when comparing TEM with ESD. Whereas a recent meta-analysis showed better outcomes for TEM[101], single center-based studies, either head-to-head between both techniques, or only limited to rectal location, showed better outcomes for ESD, with fewer complications or a shorter length of the hospital stay. In the aforementioned meta-analysis, TEM appeared more effective than ESD in terms of *en bloc* and R0 resection rates (98.7% *vs* 87.8% and 88.5% *vs* 74.6%, respectively), with a shorter procedure time (67 min *vs* 96 min) and with no significant differences in the complication rate or the need for additional surgery due to adverse events. Adenoma recurrence rate was, however, higher in the TEM group (5.2% *vs* 2.6%). Nevertheless, this study included small ESD series, most of them with less than 50 cases and published before 2010[101]. A report with a small study population in both groups of ESD and TEM (< 20) showed comparable *en bloc* (91%-84%) and R0 (81%-84%) resection rates, with no differences in complications or length of hospital stay[102]. A South Korean single center retrospective study included patients with flat lesions with suspected high grade dysplasia or submucosal invasive carcinoma who underwent ESD or TEM[103]. *En bloc* and R0 resection rates were similar in both groups (ESD *vs* TEM: 96.7% *vs* 100% and 96.7% *vs* 97.0%, respectively), with no statistically significant differences in complication rate (3.3% *vs* 6.1%, respectively). Hospital stay was significantly lower after ESD (3.6 d *vs* 6.6 d). It should be noted that over 20% of patients in both groups required additional treatment, mostly due to histological risk factors for lymph node metastasis.

Regarding hospital stay with TEM, this outcome may vary significantly across centers. Thus, some authors have reported a median hospital stay of 2-3 d[104-107], while other studies suggest even shorter stays and have reported a 24 h discharging policy[108]. To our knowledge, prospective direct comparisons between TEM and ESD that address the question of superiority in terms of length of hospital stay have yet to be published.

In summary, in an ideal scenario of a well-trained endoscopist, ESD might be the best option for early colorectal neoplasia as it combines a high rate of curative resection, similar to surgical procedures, while maintaining a low profile of invasiveness and less need for general anesthesia[109]. But frequently this is not the case in most institutions in Western countries, and standard surgical techniques are commonly more accessible to physicians. Favorable results for ESD compared to surgical procedures published recently were only based in retrospective analysis studies, with significant risk of selection bias. There is a lack of randomized controlled trials to establish good quality evidence regarding both techniques. Nevertheless, it seems that if colorectal ESD expansion backed with encouraging outcomes continues, it might be difficult to complete such ideal head-to-head randomized studies since less invasive procedures with good results frequently gain spontaneous acceptance by patients and physicians.

Endoscopic full thickness resection

Since CR-ESD is a technically demanding procedure, with a long learning curve and requires more time for its completion when compared with other resection techniques, simpler and more standardized methods are required for the treatment of colorectal neoplasms. Furthermore, performing CR-ESD is challenging in the presence of technically difficult lesions with severe fibrosis, recurrent lesions, or difficult locations (at the bottom of the cecum, near the terminal ileum, and in the appendix). The advantage of the full thickness resection is the ability to easily and quickly resect the main lesion and quickly close the colon wall defect. However, large-sized lesions are difficult to resect when using only a device that depends on a snare to achieve the resection[110]. To date, endoscopic treatment for this type of lesion requires additional devices to support closure and suturing. Unfortunately, most of them are not commercially available for widespread use.

Recently, a novel over-the-scope (OTSC) device has been developed for colorectal endoscopic full-thickness resection (eFTR). Although, colonic eFTR is not widely available in clinical practice, the initial results of this procedure have been published recently[111].

The full-thickness resection device (FTRD) consists of an OTSC System cap with a preloaded clip and a snare integrated into cap's distal end. The lesion that has been previously marked with a marking probe included in the kit is then identified with the colonoscope. The tumor is then pulled into the cap using a grasping forceps. After ensuring that all the marked tissue is completely included into the cap, the OTSC is deployed. Finally, the lesion is resected after closing the snare, applying electrosurgical current, and retrieved from the colon with the endoscope.

In the study mentioned above the main indication for eFTR was the presence of residual or recurrent neoplasm after a previous endoscopic resection. The median time to complete the procedure was 50 min. The mean diameter of the resection specimen was 24 mm within a range of 12 to 40 mm. The *en bloc* resection rate, R0 resection rate and the percentage of histologically confirmed full-thickness resection were 83.3%, 75.0% and 87.5%, respectively. There were no perforations or severe bleeding episodes. A postpolypectomy electrocoagulation syndrome was observed in 8% of the patients that was successfully treated with antibiotics.

The FTRD has, however, several limitations. The diameter of the outer cap does not allow the system to pass through the oral route. Consequently, it cannot be used for resection in the upper gastrointestinal tract. In the colon, the main limiting factors are the size of the lesion and the presence of submucosal fibrosis. Tumors over 25 millimeters in diameter might not easily fit into the cap and lack of elasticity of the colonic wall because of severe fibrosis often makes the resection difficult. Additionally, in the rectum, the perirectal tissue that fixes it prevents the achievement of a full-thickness resection.

CONCLUSION

CR-ESD is a major advance for the treatment of colorectal neoplasms: it has well-established indications, achieves higher *en bloc* resection rates when compared with EMR and is less invasive and costly than surgery.

Nevertheless, ESD also has several disadvantages: It has a long learning curve and the training process is not well established outside of Asian countries. These problems still have to be resolved in Europe. Additionally, complications in terms of bleeding and perforation rates are higher than those associated with EMR, a more established endoscopic procedure in Western countries.

Despite the many devices commercially available to perform the technique, standardization of CR-ESD still needs to be defined. Indeed, to date, the skill of the endoscopist seems to be the determining factor to achieve excellent outcomes.

Finally, simpler and more time-efficient methods for the treatment of colorectal tumors are required and new developments in this area are very likely to appear in the next few years. Probably, in the near future, methods such as FTRD will be competing treatments for CR-ESD in selected patients. More importantly, innovative methods and new devices for eFTR and suturing are evolving and may change the way the colorectal neoplasms are managed, blurring the boundaries between advanced endoscopy and surgery.

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TOPIC HIGHLIGHT

2016 Laparoscopic Surgery: Global view

Laparoscopic esophagomyotomy for achalasia in children: A review

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Abstract

Esophageal achalasia in children is rare but ultimately requires endoscopic or surgical treatment. Historically, Heller esophagomyotomy has been recommended as the treatment of choice. The refinement of minimally invasive techniques has shifted the trend of treatment toward laparoscopic Heller myotomy (LHM) in adults and children with achalasia. A review of the available literature on LHM performed in patients < 18 years of age was conducted. The pediatric LHM experience is limited to one multi-institutional and several single-institutional retrospective studies. Available data suggest that LHM is safe and effective. There is a paucity of evidence on the need for and superiority of concurrent antireflux procedures. In addition, a more complete portrayal of complications and long-term (> 5 years) outcomes is needed. Due to the infrequency of achalasia in children, these characteristics are unlikely to be defined without collaboration between multiple pediatric surgery centers. The introduction of peroral endoscopic myotomy and single-incision techniques, continue the trend of innovative approaches that may eventually become the standard of care.

Key words: Achalasia; Esophagomyotomy; Laparoscopy; Heller myotomy; Outcomes

Core tip: Laparoscopic Heller myotomy (LHM) is safe and effective in the pediatric achalasia population. Published studies are limited by their retrospective nature and small

sample sizes. Further information regarding the need for and type of concurrent fundoplication, a more complete description of complications, and long-term (> 5 years) outcomes is needed. Peroral endoscopic myotomy and the single-incision approach are innovative techniques that may eventually prove to be the standard of care. Herein, we review the available literature on LHM in children with achalasia.

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INTRODUCTION

Achalasia overview and diagnosis

Achalasia is a motility disorder characterized by abnormal esophageal peristalsis and partial or complete failure of the lower esophageal sphincter (LES) to relax during deglutition. The condition was first described in 1674 by physician and neuroanatomist Sir Thomas Willis of England[1,2]. It is an uncommon diagnosis with an overall incidence of 1.6 per 100000 individuals[3]. Less than 5% of patients present under the age of 15[4,5]; the childhood incidence is only 0.11 per 100000[6]. The etiology of achalasia is not fully understood but it may result from degeneration of neurons in the esophageal wall[1,7]. Associations with Down syndrome and Chagas disease have been described[8]. Between 0.5% and 7% of children with Down syndrome have been found to have achalasia[8,9]. Children with the autosomal recessive Allgrove syndrome (triple A syndrome) suffer from alacrima, achalasia, ACTH-insufficiency, autonomic dysfunction, and neurodegeneration[10]. These patients initially present with alacrima but achalasia is generally the first symptom which prompts pursuit of medical attention and diagnosis[11].

Clinical suspicion for achalasia should be raised in children with dysphagia to solids and liquids and regurgitation of undigested food or saliva[12]. Symptoms may progress to chest pain, emesis, aspiration, weight loss, and failure to thrive[8]. Table 1 summarizes common symptoms and associated conditions of achalasia in children. Manometry is the most sensitive diagnostic tool[13] characterizing incomplete or complete absence of LES relaxation with concurrent distal esophageal aperistalsis. For patients with equivocal motility testing, a barium esophagram will reveal a proximally dilated esophagus with distal tapering (Figure 1), the classic "bird-beak" appearance[14]. An abnormal esophagram should be followed by upper endoscopy, to rule out a structural abnormality such as a Schatzki ring or congenital cartilaginous stricture[15]. Newer methodologies for diagnosis include high-resolution manometry (HRM) and multichannel intraluminal impedance pH monitoring (MII-pH); both of which can offer additional physiological details in diagnostic dilemmas[16]. Specifically, HRM can plot the pressure generated by the esophagus, creating a topographical map which allows classification of achalasia into additional subtypes (Ⅰ-Ⅲ)[16]. This information can then be used to provide tailored treatment. Using a series of electrodes, MII-pH can measure the intraluminal impedance of a food bolus[16]. In general, HRM and MII-pH are not necessary if manometry is diagnostic.

Achalasia treatment overview

Treatment options for achalasia include pharmacological, endoscopic, or surgical methods. The primary goal is to decrease the pressure gradient across the LES. Calcium channel blockers are the most common pharmacological agents but their use in children is discouraged due to short-term effectiveness and concerning side effects[16-19].

Few reports focus on the endoscopic injection of botulinum toxin for achalasia in the pediatric population; however available data suggest the duration of therapeutic effect is short-lived and may be beneficial as a bridge to more definitive treatment modalities[16,20-22]. Randomized controlled trials (RCT) in adults confirm that laparoscopic surgical esophagomyotomy (Heller myotomy, LHM) is as safe, more durable[23], and similar in cost long-term[24], than injection of botulinum toxin.

Endoscopic pneumatic dilation (EPD) for achalasia in children has been described for many decades. Older reports identified favorable efficacy and durability[4,25-29] as the reason for EPD as the initial procedure of choice[4,27-30]. More recent literature with longer follow-up is mixed; some data suggest high rates of symptom recurrence necessitating repeat EPD[17,31], while one study found an 87% overall 6-year success rate[32] in children. In adults, a 2011 RCT reported equivalent therapeutic success of LHM and EPD at 2 years[33]. Recent meta-analyses however, established that LHM results in few adverse events and higher rates of response compared to EPD[34] and all other treatments[35].

Based on the aforementioned literature, it is clear that randomized trials are needed to differentiate the effectiveness and resilience of EPD and LHM in children. Despite the lack of conclusive evidence, refinement of laparoscopic techniques in pediatrics, low complication rates associated with LHM, and high rates of success have shifted treatment preferences toward LHM[17]. Herein, we aim to provide an overview of laparoscopic esophagomyotomy for achalasia in children and examine the current literature on this procedure.

PROCEDURE DETAILS

Evolution from open to laparoscopic esophagomyotomy

Heller *et al*[36] performed the first esophagomyotomy in 1913 *via* an open transabdominal approach and completed anterior and posterior myotomies on the distal esophagus (Figure 2A). The operation has undergone gradual modification including restriction to only an anterior

Table 1 Achalasia symptoms and associated conditions in children

Symptoms	
	Progressive dysphagia
	Vomiting
	Weight loss
	Regurgitation
	Aspiration
	Chest pain
	Failure to thrive
Associated conditions	
	Allgrove syndrome (triple A syndrome)
	Down syndrome
	Chagas disease

Figure 1 "Bird-beak" esophagram. Barium esophagram of a 16-year-old male demonstrating a dilated proximal esophagus with smooth tapering distally; findings consistent with achalasia.

myotomy[37], either a transthoracic or transabdominal approach[38], and the addition of antireflux procedures to the transabdominal method[39]. However, the past three decades have witnessed the development of minimally invasive (MIS) approaches that have led to significant change in the management of achalasia in adult and pediatric patients. The first minimally invasive Heller myotomy (MIS-HM) was performed by Shimi *et al*[40] *via* laparoscopy in 1991 on a 30-year-old female. This patient was discharged on postoperative day (POD) #3 and was symptom-free at 3 mo. Pellegrini *et al*[41], then adapted the procedure for a thoracoscopic approach (THM) and this was well tolerated in 17 patients, with two conversions to open for mucosal lacerations. Dysphagia did not improve in the initial 3 patients however follow-up surgery extended the myotomies distally with favorable results. Originally, THM was the MIS procedure of choice and only patients with previous myotomies or thoracotomies underwent a laparoscopic operation[42]. However, in the mid-1990s, groups began comparing THM and LHM and indicated that LHM with partial fundoplication led to reduced perioperative pain, shorter length of stays (LOS), less conversions to open procedures, improved relief of dysphagia and lower incidence of postoperative reflux[43]. The risk of an incomplete myotomy with THM[44], as well as the addition of an antireflux fundoplication by laparoscopy[45,46] were

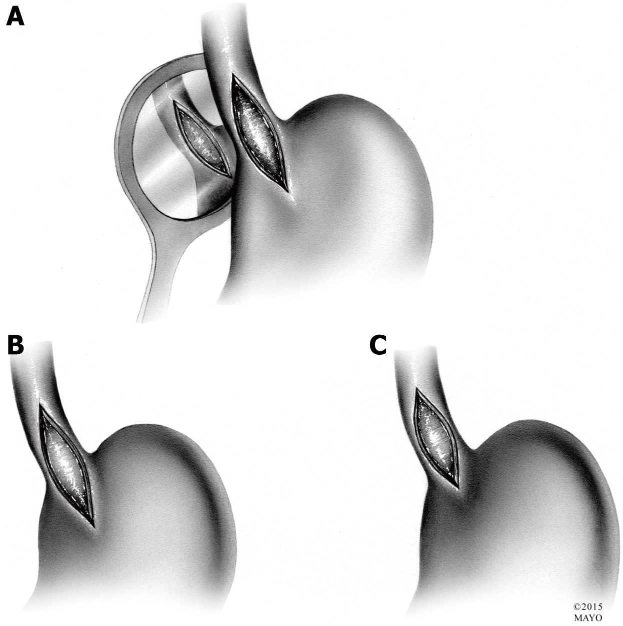

Figure 2 Esophageal myotomies. A: The original Heller myotomy, consisting of both anterior and posterior disruption of esophageal fibers; B: The most commonly performed Heller myotomy, with extension onto the stomach for 2-3 cm; C: Heller myotomy with minimal extension onto the stomach.

two key features that led to LHM gradually becoming the standard of care[47].

Operative steps for esophagomyotomy

Some surgeons prefer that patients are limited to a liquid diet for 1-2 d preoperatively to minimize the amount of debris in the esophagus[48]. After induction of general anesthesia, we perform esophageal suctioning prior to intubation to prevent the risk of aspiration. Patients are positioned in a modified lithotomy position and secured to the operating table such that there is low risk of slippage when placed in steep reverse Trendelenburg. An orogastric tube is placed and the surgeon stands between the legs of the patient (Figure 3). A total of 4-5 trocars are placed and similarly positioned as in an antireflux procedure (Figure 4). In adults, the port immediately cephalad to the umbilicus is typically used for the camera (30° laparoscope), whereas a transumbilical location is preferred in children. The remaining ports are utilized for retraction, dissection, and laparoscopic suturing. The size, location and role of each port is based on the child's size and body habitus as well as surgeon preference[16,48-52].

Once pneumoperitoneum is established and all ports are placed, the operation is begun by cephalad retraction of the liver and incision of the gastro-hepatic ligament to identify the right crus of the diaphragm (Figure 5). The peritoneum and phrenoesophageal membrane are divided and dissection is carried across the anterior midline to identify the left diaphragmatic crus. Dissection is continued cephalad, staying anterior and lateral to expose 6-7 cm of the lower thoracic and abdominal esophagus. Care must be taken to identify and preserve the anterior and posterior vagus nerves.

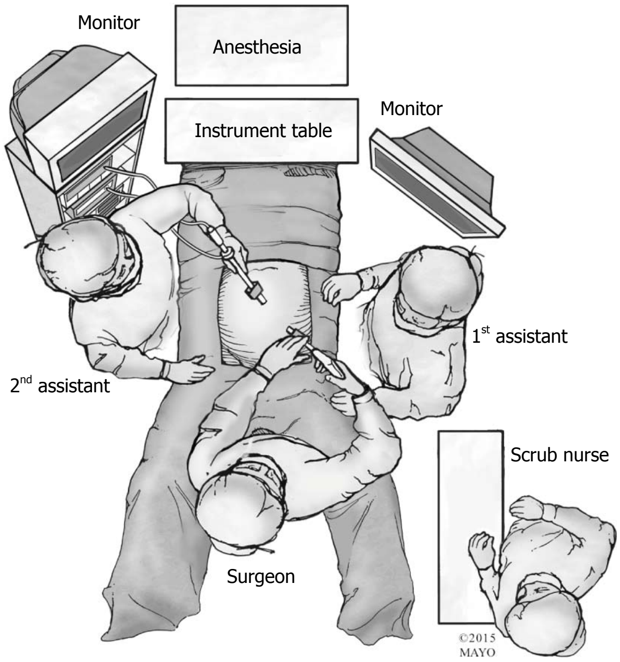

Figure 3 Patient positioning and operating room setup. The patient is placed in the modified lithotomy position and the surgeon stands between the patient's legs. First and second assistants are to the right and left of the patient.

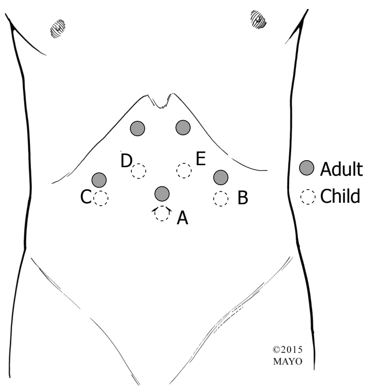

Figure 4 Trocar placement. Example trocar arrangements. A: Laparoscope; B: Babcock clamp or instrument to divide short gastrics; C: Liver retractor; D and E: Ports for dissecting and suturing; E: Electrocautery or ultrasonic shears for myotomy. The laparoscope is generally placed through a transumbilical port in children. The remaining ports are usually placed more caudad than in adults, with variable size (3 mm or 5 mm, rarely 10 mm), location, and function depending on patient body size/habitus and surgeon preference.

If an anterior (Dor) fundoplication is planned, further posterior dissection is not necessary. If a hiatal hernia is present, the crura are re-approximated posterior to the esophagus using interrupted sutures. For children undergoing fundoplication, the stomach is mobilized by dividing the short gastric vessels along the greater curvature from its midpoint to the angle of His.

To begin the myotomy, the esophageal fat pad is removed and the gastroesophageal junction (GEJ) is exposed. An esophageal dilator or bougie is placed transorally, to assist in splaying of the muscle fibers and to provide support during the myotomy. Traction is applied caudad and to the patient's left, to expose

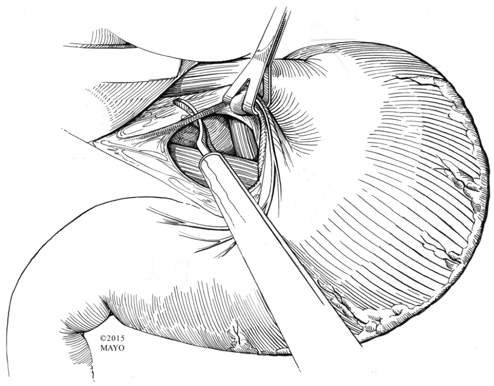

Figure 5 Incision of the gastrohepatic ligament. After retraction of the liver cephalad, the gastrohepatic ligament is incised and the lesser sac is entered. Blunt dissection is used to first identify the right crus of the diaphragm.

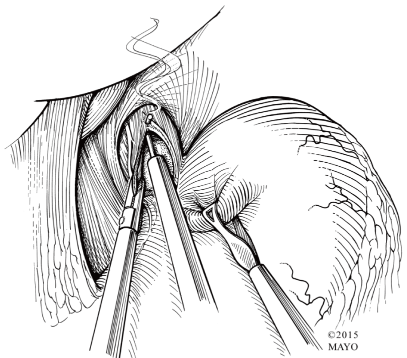

Figure 6 Myotomy with hook cautery. Electrocautery is used to begin the myotomy. It is performed at the 11 o'clock position on the anterior surface of the esophagus, taking care to avoid injury to the overlying vagus nerve. Once the submucosa is visible, blunt dissection is then typically employed to fully expose the mucosa.

the anterior surface of the esophagus. The myotomy is performed at the 11 o'clock position, typically using hook electrocautery (Figure 6). Many surgeons prefer to separate the longitudinal and circular muscle fibers of the esophagus bluntly after initial scoring sharply with electrocautery (Figure 7) or with other energy devices such as ultrasonic shears. The myotomy is then extended approximately 6 cm cephalad onto the esophagus, across the GEJ, and 2-3 cm onto the stomach (Figure 2B). Disruption and appropriate separation of muscle at the GEJ is often difficult due to decussation of the esophageal and gastric muscle fibers. The relationship between recurrence of dysphagia and length of myotomy extension onto the stomach is discussed in subsequent sections. While completing the myotomy, great care should be taken to avoid injury to the newly exposed mucosa. Previous Botox injections or EPD, prior to LHM may lead to scarring near the GEJ and portend a higher theoretical risk of perforation[48,53,54]. Post-surgical data is mixed about this increased risk; at least one study suggests the risk is higher[55] but others have shown there is no difference[56,57]. If a perforation is suspected, it can be confirmed with endoscopy or esophageal water submersion and orogastric air insufflation. Mucosal

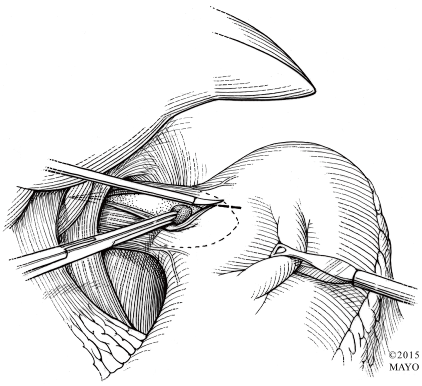

Figure 7 Myotomy with sharp and blunt dissection. Sharp and blunt dissection avoid the risk of thermal injury to the mucosa during myotomy.

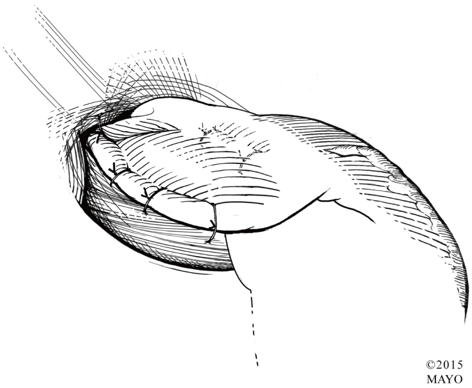

Figure 8 Anterior (Dor) fundoplication. The anterior (Dor) fundoplication is the most common fundoplication performed in children undergoing laparoscopic Heller myotomy. The fundus of the stomach is rolled over the myotomy and secured to the right and left edges of the cut esophageal muscle and crura. The myotomy is concealed. Additional stitches are placed from the anterior gastric fundus to the rim of the esophageal hiatus to relieve tension from the right sided sutures.

disruptions are typically repaired in a primary fashion with interrupted absorbable suture.

Operative steps for partial fundoplication

The options for an antireflux procedure include a partial or complete fundoplication. Most surgeons favor a partial fundoplication due to the risk for high LES pressures and progression of esophageal dilation when a full 360° wrap is performed[16,48-51,56-59].

If a 180° anterior (Dor) fundoplication (Figure 8) is planned, the short gastrics are divided and the gastric fundus is completely mobilized. In total, 2 rows of sutures between stomach and esophagus are used. The first row of 3 sutures is placed along the left esophageal wall. The cephalad-most stitch is triangular and incorporates the left diaphragmatic crus, the left side of the esophageal wall and the gastric fundus. The 2nd and 3rd stitches incorporate the fundus and left esophageal wall only. The more lateral portion of the fundus is then placed over the myotomy and is secured to the right esophageal wall in a similar fashion, utilizing a triangular stitch in the most cephalad position. The

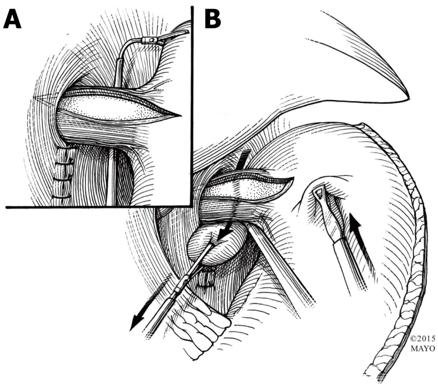

Figure 9 Passing gastric fundus posteriorly for Toupet fundoplication. A: Once the fundus is fully mobilized, it is handled by passing a grasper from right to left, posterior to the esophagus and gastroesophageal junction; B: The fundus is then pulled to the right and toward the right cut edge of the myotomy.

2nd and 3rd stitches incorporate the fundus and right esophageal wall only. An additional 2-3 stitches are then placed from the anterior gastric fundus to the rim of the esophageal hiatus to relieve tension from the right-sided sutures.

To complete a 270° posterior (Toupet) fundoplication, the gastric fundus is mobilized as above. The fundus is then passed posterior to the GEJ junction (Figure 9) to be secured to the right crus of the diaphragm (1-3 stitches) and the right edge of the myotomy (3 stitches). This is then repeated on the left esophageal wall (Figure 10).

Operative time, postoperative care, and cost

Published mean operative times for LHM with an antireflux procedure in children range from 120-190 min[17,52,54,60-65]. Although there is some variation in hospital and surgeon postoperative LHM protocols, patients are often allowed to have sips of water or clear liquids on the day of surgery[51,64,66] and an advancing diet beginning on POD #1[48-51,66] or #3[52,63,64]. Discharge often occurs on POD #3 or #4 (range POD 1.5-8)[52,61-64,67]. At our institution, we begin an oral diet on the day of surgery and discharge children between POD #1-3 contingent on pain and dietary tolerance. Differences in institutional and surgeon experience with LHM likely explain the wide ranges reported in operative time and LOS.

To date, there is no description of associated hospital charges or cost of LHM for children in the literature. At our institution, the estimated average charge for LHM alone (without consideration of fundoplication or hospital stay) is $5277. In the adult literature, a study by Shaligram *et al*[68] reported an average hospital cost of $7441 for LHM with an antireflux procedure (exclusive of hospital stay) and that this cost was significantly lower than the open or robotic approach.

OUTCOMES

Overview

In general, outcomes of pediatric laparoscopic esophag-

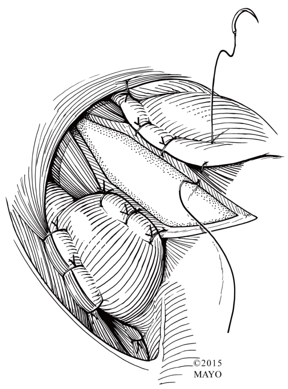

Figure 10 Posterior (Toupet) fundoplication. The stomach is secured to the right and left crura as well as the right and left cut edges of esophageal muscle, completing the posterior fundoplication. The myotomy remains exposed.

omyotomy to relieve dysphagia have been favorable. The majority of data is based on small, single-center experiences with published success rates ranging from 43%-100%[6,17,52-54,60,62-64,66,67,69-72]. The adult literature suggests success rates in the 80% range[16,73-75]. It is important to note however, that the definition of "success" has not been fully delineated. Some reports classify treatment as effective only if patients did not have any dysphagia recurrence at the longest available follow-up. Others believe success was achieved if reoperation was not necessary, even if other adjunctive treatments such as EPD were required postoperatively. Unfortunately, long-term outcome data (> 5 years) is sparse.

The two main postoperative complications available in the pediatric LHM literature are recurrence of dysphagia and symptoms of gastroesophageal reflux (GER). A summary of these and all intraoperative complications reported is provided in Table 2.

Effectiveness of LHM and adequate myotomy

The three largest pediatric LHM studies in the literature consist of 26[67], 28[53], and 31[62] patients. We published our experience with this procedure in 2009. Seven (27%) of the 26 children who underwent LHM at our institution had symptom recurrence within 5 years[67]. Among these 7 patients, 3 underwent a second LHM, 3 received EPD and/or injection of botulinum toxin[67], and 1 patient had an unspecified procedure at a different institution. The 3 patients who underwent reoperation had extension of the myotomy proximally and/or distally. Similarly, in a United Kingdom based study by Pachl *et al*[53], 8 of 28 children required additional intervention within 3 years; 7 underwent EPD, of which 4 ultimately had a reoperation. The 8th patient proceeded directly to reoperation without EPD. Reoperative patients had revisions or extensions of the original myotomy[53]. Esposito *et al*[62] published a 3-center experience in 2013 and found 5 of 31 children experienced recurrent dysphagia after LHM. Among these 5 patients, 2 had spontaneous resolution, 2 underwent EDP, and 1 underwent reoperation.

These results highlight the importance of performing an adequate myotomy. In a study by Tannuri *et al*[65], 15 children underwent LHM with a myotomy that extended 3-4 cm onto the stomach in contrast to the generally recommended 2-3 cm. Among these patients, 3 developed dysphagia; 2 cases resolved spontaneously and 1 patient required a single botulinum toxin injection. Traditionally, a longer myotomy in adults was thought to portend higher rates of GER (especially if done without an antireflux procedure)[30,65,76] or formation of epiphrenic pseudodiverticula[77]. This has not been definitively proven and continues to be debated with some authors claiming the contrary[44,78]. What is known however, is that the esophageal muscular fibers need to be fully disrupted and the underlying mucosa exposed to prevent recurrence of dysphagia[41]. The development of GER after LHM and data relating to an antireflux procedure are presented in subsequent sections.

Complications

Intraoperative complications during LHM in children include mucosal injury or perforation, aspiration, conversion to an open procedure, and hemorrhage. Mucosal injury and perforation appear to be the most common, with rates ranging from 0%-15% with the majority of studies reporting numbers < 10%[6,17,52-54,62-67,69,71]. Almost all injuries were noted at the time of surgery, however a study by Rothenberg *et al*[72] did reveal a perforation that was discovered as late as POD #5. If discovered at the time of operation, a perforation should be closed primarily with interrupted absorbable suture[48-50]. Children found to have perforation beyond the initial operative day, all underwent reoperation[52,62,72]. Adult studies reveal similar rates of perforation and conversion to an open procedure[73,74].

In general, rates of adverse events are low when children undergo laparoscopic esophagomyotomy. However, the available studies are nearly all single-center experiences and the largest experience consists of only 31 patients. Heterogeneity between and within studies makes it difficult to draw causal relationships and define etiologies for complications. As evidenced by Table 2, there is a significant amount of missing complication data. Only 2 of the 15 studies included in this review discuss other postoperative events and none report rates of infection. This may represent the relative safety of LHM or may be a reflection of the low numbers of patients. Due to the rarity of achalasia in children, prospective, multi-institutional studies are needed to provide a more comprehensive picture of LHM safety.

COMPARISONS

Laparoscopic vs thoracoscopic Heller myotomy

The available literature reveals a larger experience with LHM than THM as a form of MIS-HM in children. There are few studies which directly compare these two approaches in the pediatric population. Mehra *et al*[70] reported their experience with MIS-HM in 2001. In this study, 18 of 22 patients underwent LHM compared to 4 patients with THM. Mean duration of hospitalization

Table 2 Complications

Year	Ref.	LHM children (*n*)	Fundoplication (*n*)	Intraoperative complication (*n*)				Postoperative complication (*n*)		
				Mucosal injury or perforation	Aspiration Event	Conversion to open	Hemorrhage event	Recurrence of dysphagia	Symptoms of gastroesophageal reflux	Other
1996	Holcomb *et al*[69]	2	None	0	-/-	-/-	-/-	0	-/-	-/-
2001	Mehra *et al*[70]	18	8 Dor, 8 Toupet, 2 Nissen	2	-/-	2	-/-	a	a	-/-
2001	Patti *et al*[54]	13	12 Dor, 1 none	0	0	0	0	0	1	-/-
2001	Rothenberg *et al*[72]	5	4 Dor, 1 Toupet	1 (identified POD #5)	0	0	0	b	b	-/-
2003	Mattioli *et al*[64]	20	20 Dor	1	-/-	-/-	1	4	0	-/-
2007	Garzi *et al*[63]	12	6 Thal, 6 Dor	1	-/-	-/-	-/-	0	-/-	3 pts w/ odynophagia
2007	Paidas *et al*[71]	14	14 Dor	1	-/-	-/-	-/-	a	a	-/-
2009	Pastor *et al*[17]	14	11 Nissen, 3 unknown	2 (1 identified on unspecified POD)	-/-	2	-/-	b	b	-/-
2009	Askegard-Giesmann *et al*[67]	26	2 Dor, 23 Toupet, 1 none	2	1	0	0	7	1	-/-
2010	Corda *et al*[66]	20	None	3	-/-	4	1	5	0	-/-
2010	Lee *et al*[6]	7	4 Dor, 1 Nissen, 2 none	-/-	-/-	-/-	-/-	-/-	-/-	1 pt w/DVT
2010	Tannuri *et al*[65]	15	15 Dor	0	0	1	0	3	0	-/-
2000	Esposito *et al*[60]	31	31 Dor	3 (1 identified POD #2)	-/-	-/-	-/-	5	-/-	-/-
2014	Pachl *et al*[53]	28	9 Dor, 1 Nissen, 18 none	1	-/-	-/-	-/-	8	4	-/-
2015	Caldaro *et al*[52]	9	9 Dor	1 (identified POD #1)	-/-	-/-	-/-	2	1	-/-

-/-: Not explicitly stated in the study; a: Complication reported as average score or unclear description of number; b: Multiple myotomy approaches (laparoscopic, thoracoscopic, *etc.*) utilized in study cohort with unclear delineation of complications between groups; LHM: Laparoscopic Heller myotomy; DVT: Deep venous thrombosis.

and mean time to resumption of soft feeds were lower for those undergoing LHM[70]. Similarly, Rothenberg *et al*[72] found that THM resulted in slightly longer operative times and hospital stay in a study of 9 patients (4 THM, 5 LHM). In a 2011 review article assessing available adult meta-analyses, the authors conclude that LHM results in shorter hospital stays and reduced operative time, but that overall outcomes are similar to THM[79].

The pediatric evidence comparing LHM and THM is not robust but extrapolation from adult studies suggests LHM is superior. Although not explicitly considered in the literature, postoperative pain and the necessity for tube thoracostomy are likely lower in children undergoing LHM.

The evidence for fundoplication

The need for a concomitant fundoplication during LHM to prevent postoperative GER continues to be debated both in the pediatric and adult populations[17,53]. Among reported pediatric experiences, the study by Corda *et al*[66] in 2010 included 20 patients, none of whom underwent an antireflux procedure. In this series, no patients suffered from postoperative GER[66]. The authors believe there is a higher chance for recurrent dysphagia when a fundoplication is performed and that it is easier to treat postoperative GER than dysphagia[66]. Interestingly, another study by Pachl *et al*[53] found that only 1 of 18 patients without an antireflux procedure had postoperative GER compared to 4 of 10 who suffered from symptoms in the fundoplication group. Of the remaining pediatric LHM studies which explicitly discuss this complication, most performed a Dor fundoplication with low rates of postoperative GER[52,54,63-65,67].

The adult literature has higher level evidence and appears to favor performance of a partial fundoplication. In a 2004 RCT, Richards *et al*[59] showed that the incidence of postoperative GER was significantly lower in patients who underwent a Dor fundoplication (9.1% *vs* 47.6%, $P < 0.05$). In addition, a recent review article assessing multiple prospective studies, meta-analyses, and RCTs in adults concluded that a partial fundoplication is indicated after Heller myotomy to reduce incidence of GER[80].

Based on the available results, it is not clear whether all children should undergo a concomitant antireflux procedure during LHM. Multi-institutional randomized trials are needed to better answer this question. In the interim, surgeons should treat each patient individually and base the decision to proceed with a fundoplication on preoperative existence of GER or presence of predisposing risk factors for GER.

Type of fundoplication

If the decision to proceed with an antireflux procedure is made, the surgeon must decide what type of fundoplication to perform. The main advantage of a fundoplication is to prevent reflux and disadvantages include possible postoperative dysphagia or formation of diverticula. As evidenced in Table 2, the majority of LHM procedures performed in children are anterior or Dor fundoplications and most have favorable results. There are no pediatric studies comparing the various types of fundoplications directly. In the Mayo Clinic experience published in 2009, we found that only 1 out of 23 patients undergoing Toupet fundoplication experienced postoperative GER[67]. In other studies with multiple types of fundoplications[17,63,70], it is not clear if patients suffered from postoperative GER and if they did, which fundoplication group performed better.

Katada *et al*[81] reported on 30 adults who underwent a Toupet fundoplication with concurrent LHM. The authors found that this combination helped to straighten the esophagus, reduced LES pressure, and relieved dysphagia[81]. They did find however, that 2 patients developed esophageal diverticula postoperatively. A recent review article assessing multiple prospective studies and RCTs comparing LHM with various types of concomitant fundoplication in adults concluded that a partial fundoplication (Dor or Toupet) were superior based on higher rates of dysphagia and slightly lower rates of GER when a full (360° Nissen) fundoplication was performed[80].

There is an obvious paucity of data to definitively recommend one type of antireflux procedure over another when performing LHM in children. Due to low rates of GER and complications found with various types of fundoplication, a multi-institutional RCT would be a valuable and feasible method to better understand this component of the LHM operation.

FUTURE DIRECTIONS

Peroral endoscopic myotomy

In the last decade, a new approach to performing esophageal myotomy has been gaining interest and attention. Peroral endoscopic myotomy (POEM) was developed as a multi-institutional endeavor and initially described in 2007 after performance on pigs[82]. It is performed entirely endoscopically. A small incision is made in the esophageal mucosa and a balloon dilator is passed into the submucosal space and inflated[82]. Following this, the esophageal muscular fibers are separated with electrocautery and once the myotomy is complete, the small incision in the mucosa is closed with endoscopic clips or suturing[82]. The major advantage of this technique is that it is incision-free and performed through a natural orifice. Since 2007, a number of small studies have been published on the human experience. A recent "white paper summary" found that therapeutic success was achieved in greater than 80% of these patients, self-limited adverse events occurred in < 10% of cases, and rates of post-procedure GER ranged from 20%-46%[83].

To date, 3 studies have assessed peroral endoscopic myotomy in pediatric achalasia patients[52,84,85]. The first published report was in a 3-year-old female with severe developmental issues in which total operative time was 198 min[85]. There were no intraoperative or postoperative complications and the patient remained symptom-free at 1-year follow-up[85]. A 2013 study completed the procedure on 3 patients with a mean age of 9.6 years in an average of 60 min[84]. One patient had a small perforation of the mucosal flap and all 3 were discharged 4-7 d post-procedurally[84]. One-year follow-up on 2 patients revealed that they remained symptom-free; the third patient was 1 mo post-procedure at the time of publication and also had no symptoms. The most recent and largest POEM study in children included a total of 9 patients and compared their outcomes directly with 9 patients undergoing LHM[52]. The authors found that mean operative time was significantly lower (62 min *vs* 149 min, $P < 0.01$), myotomy length was longer (11 cm *vs* 7 cm, $P = 0.26$), postoperative oral intake occurred sooner (POD #2 *vs* POD #3, $P < 0.01$), and hospital stay was shorter (4.1 d *vs* 6 d, $P < 0.01$) in patients undergoing POEM[52]. Operative and postoperative complications (mucosal perforation, GER) were similar, however, 2 patients in the LHM group had recurrence of dysphagia and 1 POEM patient required evacuation of a pneumoperitoneum during the procedure[52].

Although the POEM experience for children with achalasia is limited, preliminary data suggests that it may be a viable and safe option when performed under experienced hands. Further studies are needed and ongoing.

Single incision LHM

Single-incision laparoscopic surgery for children has been gaining attention over the last 20 years[86]. A number of procedures have been performed *via* 1 incision including appendectomy, cholecystectomy, colonic resections, pyloromyotomy, nephrectomy, and many others[86]. In 2011, Kobayashi *et al*[87] reported their experience with single incision LHM (SI-LHM) in a 9-year-old boy. Operative time was 273 min, LOS was 8 d, and the patient had complete resolution of dysphagia with no symptoms of GER[87]. Although further studies are necessary, this may be an additional operative approach to consider for children with achalasia.

CONCLUSION

Laparoscopic Heller myotomy has become the preferred treatment for pediatric patients with achalasia. Existing literature is limited to small retrospective studies. Available data suggest that LHM is safe and effective in children. A number of related issues are yet to be definitively proven. The need for and type of concurrent fundoplication, a more comprehensive description of complications, and long-term (> 5 years) outcomes information are poorly defined and require additional evaluation. Due to the rarity of achalasia in children, these characteristics will require collaboration between multiple pediatric surgery centers and should be performed in a prospective randomized fashion when appropriate. Finally, the advent of POEM and SI-LHM techniques could ultimately change the approach chosen for esophagomyotomy and may become the standard of care in the future.

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TOPIC HIGHLIGHT

2016 Pancreatic Cancer: : Global view

Endoscopic ultrasound in the diagnosis and management of carcinoma pancreas

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Abstract

Endoscopic ultrasound (EUS) has become an important component in the diagnosis and treatment of carcinoma pancreas. With the advent of advanced imaging techniques and tissue acquisition methods the role of EUS is becoming increasingly important. Small pancreatic tumors can be reliably diagnosed with EUS. EUS guided fine needle aspiration establishes diagnosis in some cases. EUS plays an important role in staging of carcinoma pancreas and in some important therapeutic methods that include celiac plexus neurolysis, EUS guided biliary drainage and drug delivery. In this review we attempt to review the role of EUS in diagnosis and management of carcinoma pancreas.

Key words: Carcinoma pancreas; Endoscopic ultrasound; Treatment

Core tip: Endoscopic ultrasound (EUS) is becoming increasingly important in the diagnosis and management of carcinoma pancreas. It helps in identification of small tumors, histological diagnosis by fine needle aspiration, staging of the disease and its treatment. Palliation of pain with celiac plexus neurolysis and palliation of jaundice by biliary drainage can be achieved with EUS guided techniques. In this review we attempt to review the role of EUS in different aspects of diagnosis and treatment of carcinoma pancreas.

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INTRODUCTION

Pancreatic cancer, according to SEER database in the United States, constitutes 3% of all new cancer cases. The number of new cases of pancreas cancer was 12.4 per 100000 men and women per year and the number of deaths were 10.9 per 100000 men and women per year based on 2008-2012 cases. It is more common with increasing age and slightly more common in men than women. The median age of diagnosis was 71 years, the median age of death being 73 years. It is estimated that there will be 48960 new cases of pancreas cancer and an estimated 40560 people will die of this disease in 2015. Using statistical models for analysis, rates for new pancreas cancer cases have been rising on average 0.8% each year over the last 10 years but the death rates have been stable, the 5 year survival being a dismal 5%-7.2%[1,2]. This spells out the magnitude of the problem with this disease.

The role of endoscopic ultrasound (EUS) evaluation of pancreatic cancer was suggested as an independent predictor of survival and improvement in patients with loco regional pancreatic cancer in a recent study[3]. We will highlight the various aspects of the role of EUS in the setting of pancreatic cancer.

EUS FEATURES OF NORMAL PANCREAS AND PANCREATIC MALIGNANCY

Nattermann *et al*[4] and Catalano *et al*[5] described the pancreatic parenchyma as a homogeneous fine granular, reticulated pancreas with smooth margins without evidence of side-branch ectasia. The pancreatic duct diameter in the body was 1.7 to 1.9 mm on average (range, 1-3 mm), a ventral anlage (echogenic difference between the ventral and dorsal pancreas) was seen in up to 68% of controls. These data from control populations and healthy volunteers provide important standards for the normal endosonographic appearance of the pancreas but are limited by their small numbers and potential biases in control populations.

On the other hand, neoplastic masses may obscure the normal parenchymal and ductal features. They are generally more homogeneous; hypoechoic compared to surrounding tissue and are rarely calcified. In a calcified pancreas, neoplastic lesions frequently push the calcified parenchyma towards the periphery. In addition signs of vascular invasion are highly suggestive of malignancy[6].

DIAGNOSTIC ROLE OF EUS IN PANCREATIC CANCER

EUS has high sensitivity for detecting pancreatic neoplasms and further provides the ability to obtain samples from suspected lesions by fine needle aspiration (FNA) contributing to its accuracy in the diagnosis of pancreatic cancer. It has been considered one of the most precise methods for the detection of pancreatic focal lesions, especially in patients with small tumors of 3 cm or less[7,8] (Figure 1). The reported sensitivity and accuracy of combined EUS-FNA for detecting pancreatic malignancy usually exceeds 90%[9-14]. A recent meta-analysis mentioned the pooled sensitivity and specificity of EUS FNA ranging between 87% and 96%, respectively, for diagnosing a solid pancreatic mass lesion[15]. The sensitivity and accuracy of EUS are slightly higher than the sensitivity and accuracy of computed tomography (CT) and Magnetic resonance imaging (MRI) in detecting small pancreatic lesions[16-19].

EUS can be used to assess TNM staging of pancreatic tumors. T1 lesions are smaller than 2 cm, T2 are lesions larger than 2 cm, tumor extending beyond the pancreas is either a T3 (portal vein, duodenum, or ampulla of Vater) or T4 lesions (extending to the celiac artery or superior mesenteric artery; being unresectable). Malignant nodes around the pancreas are N1 lesions and rarely distant metastasis may be seen (M1 lesion). The accuracy of CT, MRI, and EUS in assessing TNM staging of pancreatic cancer was compared by Soriano *et al*[20] wherein EUS had the highest accuracy for N-staging (65%) although CT was more accurate in assessing vascular invasion and T-staging. However in a retrospective study from Russia by Egorov *et al*[21], arterial encasement on CT did not necessarily indicate arterial invasion and in unresectable pancreatic cancers (on CT), EUS data for peripancreatic involvement might suggest possible radical resection, providing survival benefits. It has also been used as a screening tool for individuals at a high risk for pancreatic cancer with incidence of clinically relevant findings at first screening being 7% with asymptomatic cancer and 16% premalignant IPMN-like lesions in a study by Poley *et al*[22].

The diagnostic reliability of EUS-FNA in the evaluation of pancreatic lesions is predictably affected by operator expertise, cytopathologic interpretation, and other variables including the presence of inflammatory changes[9,23]. A definite diagnosis cannot be ascertained in a significant minority of EUS-FNA samples alone, resulting in a cytological diagnosis of suspicious or indeterminate for neoplasm which is seen in approximately 8% to 10% of EUS-FNA samples, representing a challenging diagnostic dilemma[12,23,24]. In addition, presence of chronic pancreatitis may decrease the sensitivity of EUS-FNA as noted by Varadarajulu *et al*[25] where in the sensitivity was ranging from 73% to 91%, being lower in patients with chronic pancreatitis; and the No Endosonographic Detection of Tumor study[26] had revealed 60% patients with co-existing chronic pancreatitis and 15% patients with a diffuse malignancy which was not detected earlier. Furthermore Siddiqui *et al*[27] in their retrospective cohort trial found a false positive rate for EUS-FNA of solid pancreatic lesions of 1.1% as a result of cytologic misinterpretation in the setting of chronic pancreatitis.

Few basic remedial factors to improve the yield of EUS FNA were the use of 25 gauge needle as less blood is aspirated instead of conventional 22 gauge needle[28-30], combining cytologic and histologic analyses of the specimen to decrease the number of passes to 2[31] from 4 to 7

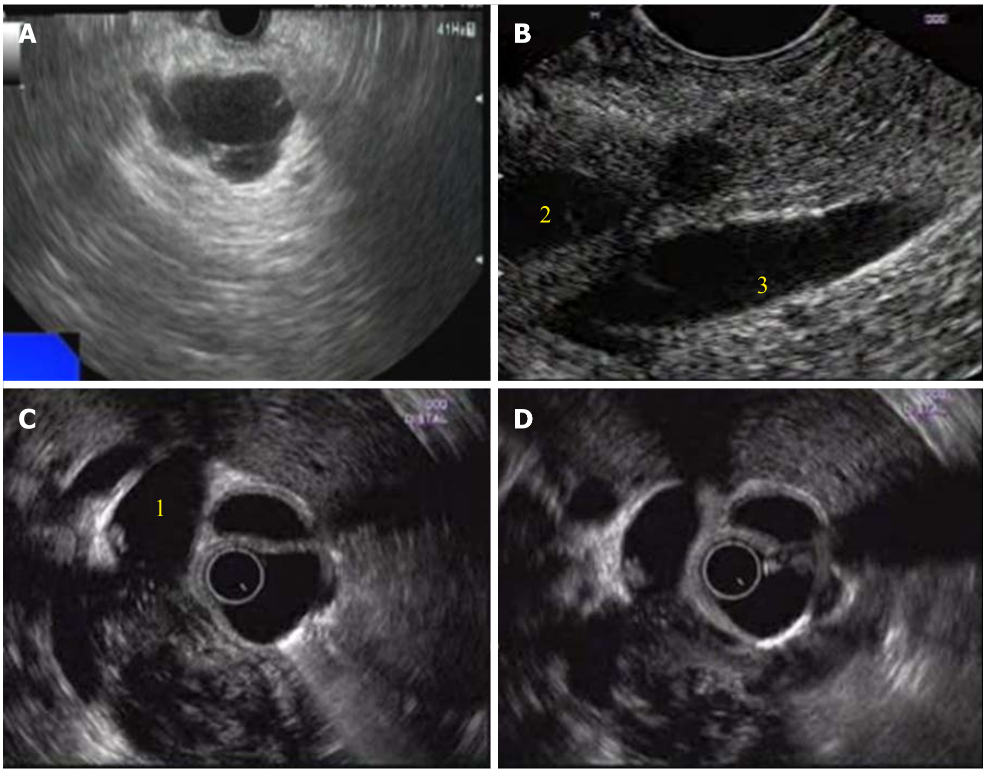

Figure 1 Endoscopic ultrasound appearance of mass lesions in pancreas. A: Serous cystic neoplasm of head of pancreas (HOP); B: Neuroendocrine tumor of head of pancreas with dilated pancreatic duct (2) and adjacent portal vein (3); C: Carcinoma HOP with loss of fat planes with confluence of superior mesenteric vein (SMV) and portal vein and dilated common bile duct (1); D: Carcinoma HOP with common bile duct and SMV infiltration..

passes[32] (higher in pancreatic cancer than in other lesions), to cater for rapid on-site cytological evaluation[33-35], the use of serum CA19-9[36] and fluid CEA and CA19-9 for increasing the ability to diagnose malignancy especially in suspicious cases[37].

WHAT IS NEW FOR DETECTION OF PANCREATIC MALIGNANCY?

Developments have taken place to further refine the ability to differentiate a malignant lesion from a benign one with a reasonable certainty and overcome other limitations. There have been improvements in the imaging techniques with EUS as well as advances in cytopathology analysis. Among the newer technologies there are EUS elastography, contrast enhanced EUS and use of chromosomal detection techniques in FNA specimen.

EUS elastography is a noninvasive technique that measures elasticity in real time by registration of differences in distortion of the EUS image after application of slight pressure by the EUS probe (Figures 2 and 3). Tissue elasticity may be altered by inflammation, fibrosis and cancer resulting in distinct elastographic appearance. Initial studies were based on qualitative elastography evaluation, using a hue-color scale representing different degrees of tissue elasticity. Giovannini *et al*[38] had sensitivity and a specificity of 100% and 67% respectively while analyzing pancreatic masses using a scoring system based on different color patterns to differentiate between benign and malignant pancreatic masses. In a subsequent multicenter study[39], the sensitivity and specificity of EUS elastography to differentiate benign from malignant pancreatic lesions were 92% and 80.0%, respectively, compared to 92% and 69%, respectively, for the conventional B-mode images. In another paper by Iglesias-Garcia *et al*[40], malignancy could be diagnosed by qualitative EUS-elastography using color patterns with a sensitivity, specificity and overall accuracy of 100%, 85.5% and 94%, respectively. Recently quantitative EUS elastography has been developed in an attempt to make the elastography interpretation less subjective. Quantitative elastography gives a numeric result, either as mean value of hues in a selected area (mean hue histogram) or as a ratio of elasticity in the target area over soft reference tissue (strain ratio). Iglesias-Garcia *et al*[41], have evaluated strain ratio in 86 consecutive patients with solid pancreatic masses and found the strain ratio was significantly higher among patients with malignant pancreatic tumors compared to those with inflammatory masses (Normal pancreatic tissue: 1.68; inflammatory masses: 3.28; pancreatic adenocarcinoma: 18.12; and the highest strain ratio was found among endocrine tumors). The sensitivity and specificity of the strain ratio for detecting pancreatic malignancies using a cutoff value of 6.04 were 100% and 92.9%, respectively, exceeding the accuracy obtained with qualitative elastography. Săftoiu *et al*[42] evaluated the usefulness of the hue-

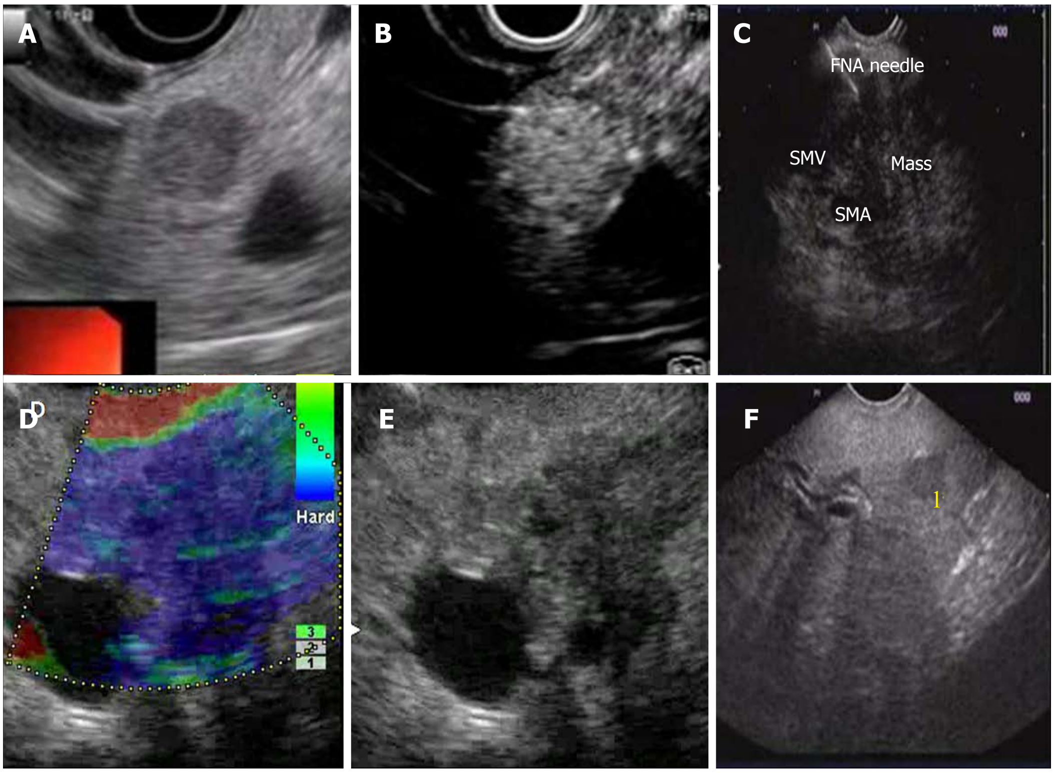

Figure 2 Contrast enhanced endoscopic ultrasound and endoscopic ultrasound elastography. A and B: Neuroendocrine tumor in the head of pancreas (HOP) before (A) and after (B) contrast administration; C: Fine needle aspiration (FNA) of mass in the HOP; D and E: Carcinoma HOP, EUS elastographic (D) appearance and B mode EUS appearance (E); F: Carcinoma HOP with metastasis (1) in the left lobe of liver..

histograms in a multicenter study wherein a sensitivity of 93.4%, a specificity of 66.0%, a positive predictive value of 92.5% and an overall accuracy of 85.4% for the mean hue-histogram in the detection of malignancy were observed. In a further development, Schrader *et al*[43] had 100% sensitivity and specificity in differentiating benign from malignant lesions in tissues with blue color (hard tissue), on histogram with less discrimination on evaluating areas with red or green colors representing softer tissue. The role of this modality is still evolving to reduce the various biases of calculation of strain.

Contrast-enhanced (CE)-EUS consists of administration of contrast agents through the blood stream. The contrast agent contains microbubbles that can be detected by EUS in the small, low-velocity vasculature of pancreatic tumors on real-time evaluation. Initial studies using Levovist®, Albunex and FS 069 Optison as contrast agents demonstrated that the hyper vascular aspect of neuroendocrine tumors and the hypo vascular aspect of pancreatic adenocarcinoma[44-48]. Modern contrast enhanced EUS relies on a dedicated contrast harmonic echo-EUS (CHE-EUS) technique that detects signals from micro bubbles delivered by new contrast agents like Sonovue® in vessels with very slow flow as they have longer perfusion time and stronger backscatter without the burden of Doppler-related artifacts. Fusaroli *et al*[49] investigated 90 patients with solid pancreatic lesions by CEH-EUS, using Sonovue® as contrast agent. The finding of a hypo-enhancing mass with an inhomogeneous pattern diagnosed pancreatic adenocarcinoma with a sensitivity of 96% and an accuracy of 82%. The study also indicated that this CEH-EUS pattern diagnosed malignancy more accurately than the finding of a hypoechoic mass on standard EUS. Hyper-enhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%). In a study by Napoleon *et al*[50], the finding of a hypo-enhanced lesion was able to detect malignancy with a sensitivity, specificity and accuracy of 89%, 88%, and 88.5%, respectively. Seicean *et al*[51] investigated the possibility to use quantitative CEH-EUS data in the differential diagnosis between pancreatic cancer and chronic pancreatitis. A hypo-enhanced pattern was the most common finding both in pancreatic adenocarcinoma and in mass forming chronic pancreatitis. However, an index of contrast uptake ratio was calculated and this was significantly lower in adenocarcinoma compared to cases with mass-forming chronic with a sensitivity of 80% and a specificity of 91.7%. A recent prospective study by Kitano *et al*[52] showed that when CH-EUS was combined with EUS-FNA, the sensitivity of EUS-FNA increased from 92.2% to 100%. Data from South Korea showed a sensitivity and diagnostic accuracy of 93% and 92%, respectively for the diagnosis of pancreatic cancer[53]. In a recent retrospective study by Park *et al*[54] pancreatic adenocarcinomas showed a hypoenhanced pattern on CH-EUS with a sensitivity of 92%, the specificity of 68% and the accuracy approximately 82%.

In a recent review, Kitano *et al*[55] have mentioned that CH-EUS identifies pancreatic adenocarcinomas

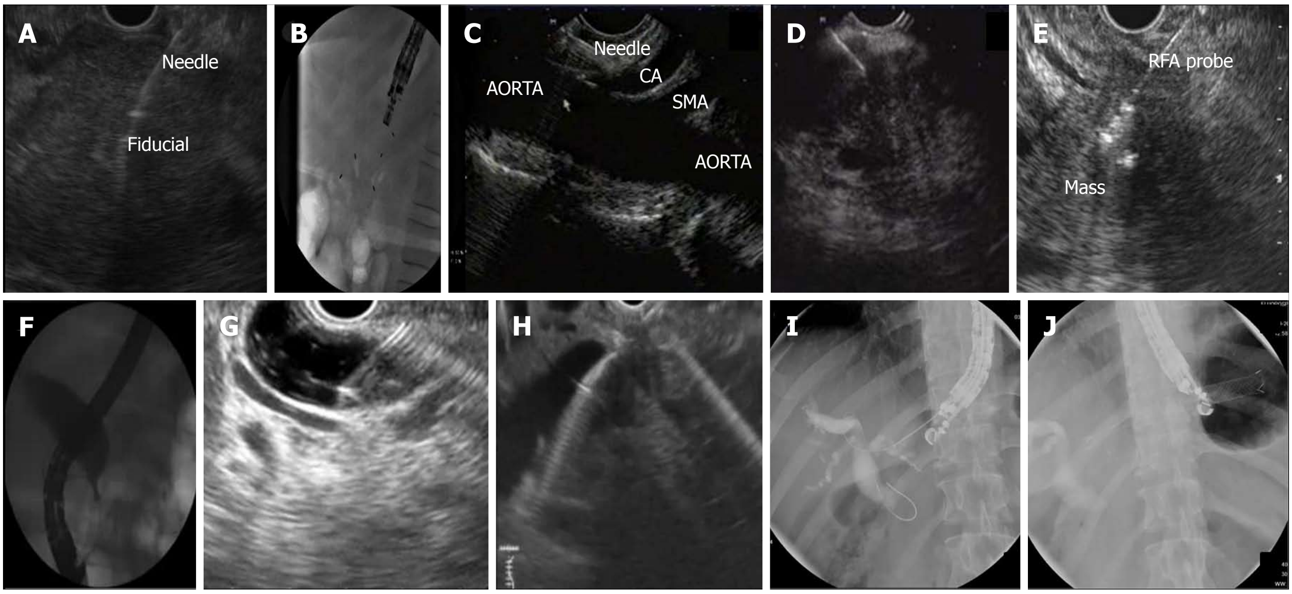

Figure 3 Endoscopic ultrasound guided interventions. A and B: fiducial placement for mass in the head of pancreas (HOP); C: celiac plexus neurolysis (CA-celiac artery, SMA-superior mesenteric artery); D: fine needle aspiration of mass in the HOP; E radiofrequency ablation (RFA) of mass in the HOP; F,G and H: choledochoduodenostomy for biliary stricture due to mass in the HOP; I and J: hepaticogastrostomy and placement of metal stent.

as solid lesions exhibiting hypo-enhancement with a sensitivity and specificity of 88%-96% and 88%-94%, respectively. In particular, 80%-100% of false-negative cases in EUS-FNA are correctly classified by CH-EUS, suggesting its complementary role. In addition, it improves depiction of some subtle lesions in conventional EUS, thus facilitating EUS-FNA. For quantitative perfusion analysis, a time-intensity curve (TIC) for the region of interest can be generated during CH-EUS. The maximum intensity gain and the echo intensity reduction rate from the peak at 1 min obtained by TIC can be used for differentiation of pancreatic adenocarcinoma from other tumors. CH-EUS is also useful for differentiation of invasive intraductal papillary mucinous neoplasms (IPMN) from non-invasive IPMN[55]. Thus, CH-EUS technology is very promising and is likely to play a role in the precise diagnosis of malignant pancreatic lesions.

The detection of various chromosomal abnormalities in FNA aspirates is a field which is rapidly evolving. It is useful in cases with indeterminate results and might help in confirming the diagnosis of a malignancy. Among the earlier studies, telomerase activity was studied by Mishra *et al*[56] which on combination with cytology results increased the sensitivity from 85% to 98% with 100% specificity. The use of fluorescence *in situ* hybridization (FISH) analysis by Kubiliun *et al*[57] on FNA specimens with inconclusive results revealed a sensitivity of 74% for detecting pancreatic cancer which increased to 85% on combining with cytology. Reicher *et al*[58] from US demonstrated the use of detecting K-ras mutation in addition to FISH analysis in precisely identifying 60% of atypical FNAs with final malignant diagnosis yielding 88% sensitivity and 94% specificity with 90% accuracy. The pooled sensitivity of EUS-FNA for the differential diagnosis of pancreatic adenocarcinoma was 80.6%, specificity was 97% and probable sensitivity and specificity were 76.8% and 93.3% for K-ras gene analysis, respectively. For combined EUS-FNA plus K-ras mutation analysis it was 88.7% and 92%, in a meta-analysis by Fuccio *et al*[59]. Overall, K-ras mutation testing applied to inconclusive cases by EUS-FNA reduced the false-negative rate by 55.6% albeit with a false-positive rate of 10.7%. Layfield *et al*[60] in their guidelines mention that many gene mutations (*KRAS*, *GNAS*, *VHL*, *RNF43*, and *CTNNB1*) may be of aid in the diagnosis of cystic neoplasms. The shortcoming of detecting chromosomal abnormalities in FNA specimens is that pancreatic cancers may express multiple mutations, detecting more might increase the sensitivity but with doubtful cost effectiveness.

ROLE OF EUS IN THERAPEUTICS OF PANCREATIC CANCER

The increasing use of EUS as a diagnostic modality has also led to its importance as an interventional tool in the management of pancreatic cancer. It ranges from assisting in radiotherapy, delivery of chemotherapeutic agents to palliation by celiac plexus neurolysis and biliary drainage wherever ERCP fails.

EUS delivery of antitumor agents is largely investigational and is still in experimental stage. The requirement to develop this option is due to pancreatic carcinoma having a poor response to chemotherapeutic agents and radiation; and neoadjuvant chemotherapy can lead to a desmoplastic reaction further impairing drug delivery. Chang *et al*[61] used cytoimplant (Allogenic mixed lymphocyte culture) advanced pancreatic cancer with partial response noted in two patients. TNFerade biologic is a replication-deficient adenoviral vector that expresses tumor necrosis factor-α (TNF-α), regulated by a radiation inducible promoter; inducible by chemotherapy and radiation has been used by various authors. Hecht *et al*[62] had shown one complete response, 3 partial responses, and 12 patients with stable disease, overall 3 survived > 24 mo. Subsequently Herman *et al*[63], reported in the randomized phase Ⅲ trial among patients with locally advanced pancreatic cancer (LAPC) that though it is safe in combination with chemotherapy, it does not increase survival. ONYX-015, an adenovirus which preferentially replicates and kills malignant cells was studied by Hecht *et al*[64] wherein 2 patients had partial regression of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease with 2 patients each having sepsis and duodenal perforation. The injection of immature dendritic cells, which induce T-cell immune response against malignant cells, was used by Irisawa *et al*[65] successfully into the tumors of 7 patients with unresectable pancreatic cancer, with a cohort median survival of 9.9 mo. Thereafter, Hirooka *et al*[66] using the same therapy demonstrated effective responses in three of five patients; 1 had partial remission and 2 had long stable disease of more than 6 mo. This combined therapy was synergistically effective. Despite these studies, much more large prospective studies are required before these techniques are translated into clinical practice.

EUS guided brachytherapy has been carried out with radioactive seeds being placed into the tumour with the help of linear echoendoscope. The most popular radioactive seeds are Iodine 125, palladium 103 and iridium 192; iodine being the preferred radioactive material due to its long half life of 60 d in pancreatic cancers with rapidly dividing cells. Jin *et al*[67] in their experience achieved partial remission in three cases, estimated median survival time of nine months with improvement in pain but no survival benefit.

EUS guided fiducial insertion is being done in pancreatic malignancy to place markers inside the tumor for guiding stereotactic body radiotherapy. These markers can be radioactive spheres, coils or seeds. Its feasibility was shown by Pishvaian *et al*[68] wherein he reported a technical success of 85%. Subsequently in a prospective study by Park *et al*[69] fiducial insertion was successful in 88% of the 57 patients, Sanders *et al*[70] had a success rate of 90% for EUS fiducial insertion in a prospective study of 51 patients while DiMaio *et al*[71] achieved a success rate of 97% with a 22-gauge needle. Law *et al*[72] found this technique safe and feasible to assist intraoperative localization of small pancreatic neuroendocrine tumors. The 2 types of fiducials were compared by Khashab *et al*[73] in 39 patients with advanced pancreatic cancer. Traditional fiducials of 5 mm length had better visibility scores with similar migration rates as compared to viscoil fiducials of 10 mm length.

EUS-guided cryothermal ablation has been studied by Arcidiacono *et al*[74] in 22 patients with unresectable stage Ⅲ pancreatic adenocarcinoma with a feasibility of 73% with insignificant tumor size reduction. Further studies are required to demonstrate progression-free survival and local effects. Recently Pai *et al*[75] used radiofrequency ablation (RF) which was applied with a monopolar RF probe (1.2 mm Habib EUS-RFA catheter) placed through a 19 or 22 gauge FNA needle after FNA was performed in patients with a tumor in the head of the pancreas with a 100% success rate. The response ranged from complete resolution to a 50% reduction in size. Oh *et al*[76,77] used EUS-guided ethanol lavage with paclitaxel injection (EUS-EP) for cystic tumors of the pancreas in two studies and found a 62%-99% resolution rate with adequate safety and feasibility. These data indicate the need for further large prospective studies to ascertain their roles in the management of pancreatic cancer.

EUS guided celiac plexus neurolysis (CPN) provides pain relief, palliation and reduces narcotic use in patients with unresectable pancreatic cancer[78]. The injection of a neurolytic drug into the celiac plexus disrupts the signal transmission to spinal cord and central nervous system. Due to the anatomical location of the celiac plexus around the origin of the celiac trunk and the superior-mesenteric artery, EUS- CPN provides real-time visualization for a safe approach.

EUS-CPN was demonstrated to be safe and effective in alleviating refractory pain due to pancreatic cancer in a meta-analysis of 8 studies by Puli *et al*[79]. Alcohol-based EUS-CPN was found safe and effective in this setting providing pain relief to 73% patients[80]. A recent RCT by Wyse *et al*[81] in 96 patients demonstrated greater pain relief in the early EUS-CPN group at three months than in conventional management group. As compared to opioids, EUS-CPN reduced pain at four and eight weeks and significantly reduced opioid consumption[82]. In addition a single central injection was found to be as effective as bilateral or multiple injections[83,84]. In another comparison between EUS-CPN and EUS-celiac ganglia neurolysis (CGN), Doi *et al*[85] observed higher treatment response rate and complete response rate in the EUS-CGN group compared to the EUS-CPN group.

EUS guided biliary drainage is another important area where therapeutic EUS is helpful. With failed ERCP, biliary drainage can be established by 3 endoscopic methods (1, transluminal biliary drainage with hepaticogastrostomy or choledochoduodenomstomy, 2, EUS antegrade drainage and 3, EUS rendezvous drainage)[86]. In 7% to 13% of patients with pancreatic head malignancy have duodenal stenosis, making ERCP technically challenging or impossible[87].

The role EUS guided biliary drainage in pancreatic cancer in failed ERCP has been recently demonstrated by Weilert[88] in 21 patients, 52% patients with pancreatic cancer wherein he achieved technical success in 20/21 (95.2%) and clinical success 19/21 (90.4%). He noted that EUS-guided anterograde biliary drainage using the intra-hepatic access route had high technical and clinical success with low adverse rate. In a recent study of 208 patients with malignant distal CBD obstruction requiring SEMS placement, authors compared the short-term outcome of single session EUS guided biliary drainage with ERCP[89]. SEMS placement was successful in 97 and 98 patients in the respective groups (93.26% *vs* 94.23%, P = 1.00). The incidence of pancreatitis was higher with ERCP, and EUS group had superior treatment success rates in patients with duodenal stenosis.

CONCLUSION

EUS is rapidly becoming a sensitive and specific modality for diagnosing pancreatic cancer especially on combining with EUS-FNA albeit with difficulty in the presence of chronic pancreatitis. With the advent of newer technology in the form of EUS elastography, CE-EUS, and gene mutations detection in FNA specimens the diagnostic dilemma is better resolved. The availability of interventional EUS has allowed gastroenterologists to make significant difference in management of pancreatic cancer by its various therapeutic options including areas which have been traditionally dealt by surgeons and interventional radiologists. It is likely to become an important modality in the multidisciplinary management of pancreatic cancer.

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REVIEW

Drug eluting biliary stents to decrease stent failure rates: A review of the literature

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Abstract

Biliary stenting is clinically effective in relieving both malignant and non-malignant obstructions. However, there are high failure rates associated with tumor ingrowth and epithelial overgrowth as well as internally from biofilm development and subsequent clogging. Within the last decade, the use of prophylactic drug eluting stents as a means to reduce stent failure has been investigated. In this review we provide an overview of the current research on drug eluting biliary stents. While there is limited human trial data regarding the clinical benefit of drug eluting biliary stents in preventing stent obstruction, recent research suggests promise regarding their safety and potential efficacy.

Key words: Bile ducts; Cholangiocarcinoma; Endoscopy; Pancreas

Core tip: Despite the short life expectancies of patients with biliary tract cancers, biliary stenting suffers from high stent re-obstruction rates, provoking unneeded costs, morbidity and mortality. Drug eluting stents offer the possibility of decreasing stent failure rates from both biliary stent clogging, and external obstruction from tumor and epithelial ingrowth. In this inclusive review we outline the current body of experimental literature on drug eluting stents including bench, animal and human trials, and discuss possible targets for future research.

Shatzel J, Kim J, Sampath K, Syed S, Saad J, Hussain ZH, Mody K, Pipas JM, Gordon S, Gardner T, Rothstein RI. Drug eluting biliary stents to decrease stent failure rates: A review of the literature. *World J Gastrointest Endosc* 2016; 8(2): 77-85 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i2/77.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i2.77

INTRODUCTION

Obstruction of the bile duct results in serious clinical consequences such as cholangitis and death. Biliary stenting is an effective means of relieving obstruction, and is the preferred method of palliating patients with malignancy[1]. Malignant obstructions in particular cause high stent obstruction rates, despite the relatively short lifespan of patients with biliary tract cancers (Table 1). Stent failure is associated with recurrent morbidity, and often necessitates repeat endoscopy with stent retrieval and replacement. These procedures carry an increased risk for procedural complications such as pancreatitis, and can result in additional hospital admissions.

Stent failure can be stratified into four primary etiologies: Internal stent failure from biliary clogging, external failure caused by tumor ingrowth or overgrowth of excessive epithelial or malignant cells, and stent migration. The incidence of each type of failure in malignant obstruction has been documented in several small prospective trials (Table 2). For the purposes of this review, only internal and external failure will be addressed.

Drug eluting stents have been used for several decades in the setting of coronary artery disease to decrease the incidence of stent failure. Currently there have only been a limited number of human trials evaluating drug eluting biliary stents to prevent external obstruction[2,3], none of which showed a significant effect in decreasing stent failure rates. However, only one agent (paclitaxel) has been trialed in humans with malignant obstruction[2,3]. Both trials showed the hybrid stent was safe and well tolerated when compared to traditional stenting. There is a growing body of literature looking at *in vitro* and *in vivo* models of drug eluting biliary stents as prophylaxis against internal and external sources of failure. In this review, we divide stent failure pathophysiology into internal and external mechanisms and analyze the current literature on the use of stent drug elution as prophylaxis against the respective failure types.

INTERNAL STENT FAILURE

Internal stent failure results from the accumulation of obstructing material in the stent lumen. It is a complex process involving microbial colonization and biofilm generation[4]. This process is exacerbated by, but not dependent on, the reflux of duodenal contents into the biliary system.

A normal functioning sphincter of oddi helps to preserve the relative sterility of the biliary tree compared to the duodenum. Stenting across the papilla allows for the reflux of intestinal contents and bacteria into the biliary system[5]. After placement, biliary stents are quickly colonized by a diverse poly-microbial community[6-10]. Aerobic and anaerobic bacteria are readily isolated from occluded biliary stents with *Enterococcus*, *Escherichia coli* and *Klebsiella* the most common aerobic bacteria isolated from biliary sludge, while *Clostridium* is the most common anaerobe isolated[6-8,11]. Anaerobic bacteria may be the first to attach and may play a crucial role on biofilm initiation[7].

Electron microscopy and biochemical analyses of explanted stents has shown that the occluding material is formed by the accumulation of multispecies bacterial colonies, fungi, microbial byproducts, crystals of calcium bilirubinate, crystals of fatty acid calcium salts, and by semi digested fibers arising from duodenal reflux[6,7,12-14]. Surface irregularities in the stent have been postulated to facilitate the initial biofilm generation[6,12,15].

The process of internal failure is self-perpetuating. As the stent lumen narrows with increasing biofilm generation, or external compression, bile flow decreases by an exponential rate. The precipitous decrease in bile flow seen with small decreases in stent diameters is explained by Poiseuille's law, which states that when a fluid with a stable viscosity flows through a tube, halving the radius of the tube will decrease the flow rate to $1^{st}/16^{th}$ the original flow[9] (Figure 1). Viscous fluids also display a parabolic flow, with the lowest flow rates against the surfaces of the tube. Slowing of bile flow promotes both spontaneous and bacteria-driven bile salt precipitation, thus exacerbating the likelihood of internal failure[4]. This has been proven clinically as failure rates have been shown to be well correlated with the diameter of the stent[16].

DRUG ELUTION TO PREVENT INTERNAL FAILURE

Drug insertion into the biliary stent lumen can theoretically improve internal failure rates by decreasing bacterial colonization and biofilm formation. There has been a small amount of research looking at internal drug coating or drug elution to prevent internal failure (Table 3), comprising *in vitro*, *in vivo* animal and one human trial. Drugs selected for analysis can be loosely grouped into two categories: those theorized to inhibit bacterial attachment and biofilm generation and antimicrobials theorized to inhibit bacterial growth and induce sterilization of the biliary tree.

The first published example of incorporating pharmaceuticals into the internal stent lumen was bench modeling done in the late 1990's. An *in vitro* model was developed by submerging test material in culture broth and bile; it was shown that an addition of benzalkonium chloride, a commonly used antiseptic, as well as Teflon, decreased the incidence of microbial colonization[17]. However, these studies did not accurately model the

Table 1 Current stent failure rates

Stent type	Stent failure rates in malignant obstruction
Plastic stents	30%-70%
Self expanding metal stents	19%-46%

Adapted from Ref.[31-37].

Table 2 Causes of stent failure

Causes of stent failure	Percent of total failures
Tumor ingrowth	66%-68%
Epithelial ingrowth	
Biliary clogging	17%-21%
Tumor overgrowth	2%-11%
Stent migration	0%-4%

Adapted from Ref.[31-37].

polymicrobial environment of the biliary tree, utilizing just 3 cultured pathogens.

Several more *in vitro* models have been reported in the literature evaluating luminal drug elution. Of the materials tested, heparin coating has proven promising in both *in vitro* and human trials. Cetta *et al*[18] examined stents internally coated with heparin and hyaluronic acid. The coated stents were then placed in bacterial cultures which were generated from culturing previously occluded biliary prostheses. Compared to uncoated polyurethane stents, heparin coated stents had significantly reduced biofilm formation. Later, some researchers found that stents coated with both hydrophobin and heparin decreased encrustation detected by the electron microscopy compared to hydrophobin alone in their *in vitro* model. This work was followed up by Farnbacher *et al*[19], who devised a prospective human trial. In their study they found that explanted heparin coated stents had significantly decreased rates of luminal encrustation by visual inspection and weight.

Antibiotics, while an intuitive possibility for decreasing bacterial colonization, have failed to show any effect in decreasing internal failure rates when given both systemically or locally through drug elution. There has been a continuous effort since 1989 to identify systemic treatments which could decrease internal stent failure rates, among which antibiotics, ursodiol, mucolytic agents, and anti-inflammatory agents have been trialed (Table 4). Multiple studies as well as meta-analysis[20] have failed to show a direct benefit from any systemic treatment in decreasing internal failure rates.

Along with a lack of benefit when given systemically, antibiotics have also failed to show any benefit when given locally. In 2011, Weickert *et al*[21] analyzed the effect of antibiotic elution on internal failure by incubating stents in human bile. Their experiment examined the combined effect of stents combined with hydrophobin and ampicillin/sulbactam, as well as hydrophobin and levofloxacin showed that the neither antibiotic

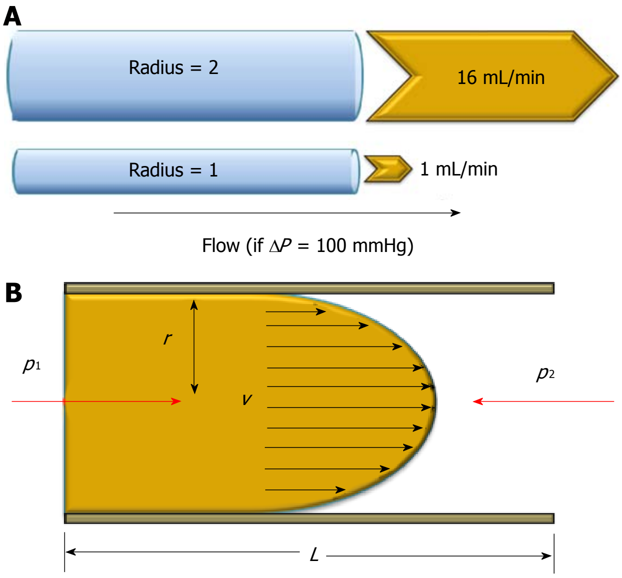

Figure 1 Change in biliary flow determined by stent radius, as described by Poiseuille's law (A) and laminar flow of viscous fluids (B). Flow= (π • pressure difference • radius^4)/(8 • viscosity • length).

reduced the amount of biofilm generation compared to hydrophobin alone. In 2012, Gwon *et al*[22] developed a cefoxitime eluting stent and for testing in a canine model. Upon both gross inspection and analysis with electron microscopy they found no effect from cefotaxime in preventing biofilm development. The reasons behind the lack of local antibiotic efficacy can only be surmised, but may include the selection of resistant organisms in the polymicrobial biliary environment, the inability of antibiotics to permeate through biofilms, or local breakdown and inactivation of antibiotics.

EXTERNAL STENT FAILURE

Biliary obstruction is the first presenting sign of disease in 70% of patients with cancer of the pancreas and biliary system[23]. Pancreatic cancer is common and carries significant morbidity and mortality. In the year 2000 for example, there were 217000 new cases of pancreatic cancer with 213000 pancreatic cancer deaths worldwide[24]. Survival rates are dismal at an estimated five-year rate of 5%[25] and have been generally stagnant with no recent advances improving mortality[26]. Although biliary duct and gallbladder cancers have a lower incidence, their mortality is equally dismal. External stent obstruction is not only a concern in patients with pancreatobiliary malignancy, as there is also a notable population of patients with nonmalignant obstructions at risk for stent failure who could benefit from drug elution as a possible means of decreasing failure risk. Prospective studies on patients with chronic pancreatitis, autoimmune pancreatitis, and liver transplants for instance have shown that respectively up to 20%[27], 83%[28], and 22%-49%[29] of patients developed biliary strictures.

There are two main categories of commercially available biliary stents for endoscopists to select from:

Table 3 Studies evaluating drug elution or coating to prevent internal failure

Ref.	Journal	Study design	Study results
In vitro			
Rees *et al*[17]	*Journal of Hospital Infection* (1998)	*In vitro* - control (polyurethane) - benzalkonium chloride (BZC) - ePTFE (Teflon)	BZC and Teflon reduced the number of organisms attached to stents
Cetta *et al*[18]	*The European Journal of Surgery* (1999)	*In vitro* 5 stents - control (polyurethane) 5 stents - heparin + hyaluronic acid	Heparin and hyaluronic acid coating reduced biofilm development
Weickert *et al*[21]	*Advances in Medical Sciences* (2011)	*In vitro* 7 stents - control (polyethylene) 4 stents - hydrophobin (H) 3 stents - H + ampicillin/sulbactam 3 stents - H + levofloxacin 3 stents - H + heparin	Stents coated with hydrophobin or both hydrophobin and heparin reduced clogging material scanning electron microscopy (SEM) images
Animals			
Gwon *et al*[22]	*Acta Radiologica* (2012)	Canine model 3 stents - control (ePTFE) 3 stents - 10% wt/vol cefotaxime 3 stents - 20% wt/vol cefotaxime	Cefotaxime did not prevent biofilm development (gross inspection, SEM images)
Humans			
Farnbacher *et al*[19]	*Scandinavian Journal of Gastroenterology* (2012)	Randomized prospective 13 stents - control (polyethylene) 13 stents (same patients) - heparin	Heparin is effective in preventing encrustation on stents (encrustation weighed)

plastic or metal-based stents. In regards to malignant obstruction, self-expanding metal stents (SEMS) have been found to have a decreased incidence of cholangitis, stent failure, and overall hospitalizations when compared to plastic stents[30]. Median patency rates for SEMS have been evaluated in several studies and generally found to be at approximately 270 d in malignant obstruction[31-33]. Biliary stents have a sub-optimal failure rate, and will occlude in 30%-70% of patients with plastic stents and in 19%-46% of patient with bare metal stents (Table 1)[31,32,34,35]. The most common cause of failure are tumor or epithelial ingrowth (66%-68%), followed by sludge and clogging (17%-21%), tumor overgrowth (2%-11%), and stent migration (0%-4%) (Table 2)[33,36,37].

From analysis of biopsied obstructing tissue, it was found that 44% of the tissue ingrowth was non-malignant in nature, suggesting epithelial hyperplasia plays a significant role in stent obstruction[35]. Other studies have suggested that up to 50% of SEMS occlude secondary to epithelial hyperplasia[35]. Considering the major mechanisms of stent obstruction, tumor ingrowth, tumor overgrowth, and epithelial hyperplasia, a stent externally coated with agents that effectively hinder tissue growth could theoretically reduce failure rate by 50%-79%. Drug incorporation into the external stent membrane appears to be an intuitive next step in stent development capable of significantly reducing stent obstruction rates[34].

CURRENT RESEARCH ON DRUG-ELUTING BILIARY STENTS TO PREVENT EXTERNAL FAILURE

Drug-eluting stents have been well validated in the intravascular setting and have become a staple in the management of coronary artery disease for several decades. However, despite the theoretical promise of drug-eluting biliary stents (DEBS), there has been little research on the subject to date (Table 5). Ideal agents to incorporate into the stent exterior would serve to (1) effectively inhibit the growth of malignant pancreaticobilary cells; (2) retard the proliferation of biliary epithelial hyperplasia; and (3) display favorable histologic changes when exposed to biliary epithelium, without necrosis or risk of biliary perforation.

ANIMAL MODELS OF DRUG ELUTING BILIARY STENTS

Lee *et al*[38] developed the first published animal models of DEBS in 2005. Their team developed a paclitaxel eluting stent for trial in a porcine model. The decision to use paclitaxel was based on bench data from Kalinowski *et al*[39] which showed that paclitaxel, inhibited human gallbladder cells, human fibroblasts, and pancreatic cells in a dose-dependent fashion. Their model was designed to evaluate drug release dynamics and bile duct histological changes resulting from extended direct stent contact after implantation in pigs for 4 wk. Stents were developed with paclitaxel concentrations of 0%, 10% and 20%. Inflammatory cell infiltration and fibrous reactions were the commonly noted histologic changes which corresponded to the level of paclitaxel incorporated into the stent. Although the model was not designed to evaluate long term failure rates, no pigs showed clinical or laboratory signs of biliary obstruction during the trial. Their results were promising, finding acceptable histologic changes at all drug levels. Epithelial denudation, mucin hypersecretion, and epithelial metaplasia were noted in

Table 4 Trials evaluating systemic treatments to prevent internal failure

Ref.	Journal	Study design	Study results
Humans			
Barrioz *et al*[48]	*Lancet* (1994)	Randomized prospective 25 - conservative treatment 21 - ursodeoxycholic acid and norfloxacin	Drugs were associated with longer stent patency and shorter hospital stay
Coene *et al*[49]	*Scandinavian Journal of Gastroenterology* (1994)	Randomized prospective 60 patients received either co-trimoxazole or N-acetylcysteine	Bile clogging did not correlate with bile viscosity. Mucolytic agents or antibiotics only effective when bile is highly viscous
Smit *et al*[50]	*Gastrointestinal Endoscopy* (1989)	Randomized prospective 30 patients received either placebo or doxycycline or aspirin	Both doxycycline and aspirin reduced the dry weight of sludge. Doxycycline improved patient survival
Halm	*Endoscopy* (2001)	Randomized prospective 26 - ursodeoxycholic acid 26 - ursodeoxycholic acid + ofloxacin	No difference in patient survival or stent occlusion
De Lédinghen *et al*[51]	*Digestive Diseases and Sciences* (2000)	Randomized prospective 29 - conservative treatment 33 - ursodeoxycholic acid and norfloxacin	No difference in stent patency and patient survival
In vitro			
Tsang *et al*[52]	*Journal of Laboratory and Clinical Medicine* (1997)	*In vitro* 4 - porcine bile 4 - porcine bile + ampicillin + sulbactam	Ampicillin and sulbactam inhibited biofilm formation

the bile ducts that were in contact with stents containing 20% weight/volume (wt/v) paclitaxel; there was no incidence of transmural necrosis or perforation in any animal. Furthermore, the amounts of paclitaxel released over 1 wk and over 6 wk were similar, regardless of the concentration of paclitaxel incorporated in the stent. The authors ultimately found that stents with 10% (wt/v) paclitaxel in the covering membrane was superior to those with 20% (wt/v) in regards to histologic changes and drug release dynamics. The 10% (wt/v) paclitaxel stent had a more favorable histologic profile without evidence of epithelial metaplasia or other concerning local changes from excessive cytotoxic effects which could suggest a risk for necrosis or perforation, while still displaying a favorable drug release profile.

There are four other previously published animal studies involving paclitaxel eluting stents. In 2009, Lee *et al*[40] undertook a canine model also to assess biliary duct histological changes, evaluating 20% wt/v paclitaxel DES. The authors noted biliary mucosal hyperplasia in 3/6 dogs who received paclitaxel stents (none in the control group) along with no distinct stent complications. They concluded that more research is warranted to determine the proper concentration of drug to obtain optimal tumor control in and histological remodeling of the biliary duct. In 2012, Jang *et al*[41] used a porcine model to examine a 10% wt/v paclitaxel-eluting biliary stents using a membrane containing Pluronic F-127 in an attempt to bolster drug delivery. They again found acceptable histologic changes based on inflammatory cell infiltration and fibrotic reaction, with no incidence of obstruction or perforation. Paclitaxel was detected for 28 d in porcine serum with the 10% Pluronic concentration. However, released paclitaxel was observed for only 7 d with incorporation of higher or lower concentrations of Pluronic. Most recently, Shi *et al*[42] used a canine model to study the effect of paclitaxel biliary stents when used as biliary-enteric anastomosis following Roux-en-Y cholangiojejunostomy. Histology of the bile duct was observed 1, 3, 6, 9 and 18 wk following the surgery. Paclitaxel-coated stents were found to release paclitaxel for 9 wk, and dogs that had paclitaxel-coated stents placed had less granulation tissue and granular hyperplasia of the biliary-enteric anastomosis. No adverse effects of paclitaxel were observed. Lastly, Bang *et al*[43] recently developed a mouse model xenografted with both pancreatic cancer and cholangiocarcinoma cell lines which they exposed to paclitaxel-eluting membranes, in an attempt to determine the molecular mechanisms of tumor inhibition. Paclitaxel, they discovered, inhibited tumor angiogenesis, through multiple mechanisms including suppression of mammalian target of rapamycin (mTOR) through regulation of hypoxia inducible factor 1 and increased apoptosis, as well as inhibiting tumor-stromal interaction by effecting regulation of CD44, SPARC, matrix metalloproteinase-2, and vimentin.

Besides paclitaxel, two other chemotherapeutics have been evaluated in DEBS animal models. In 2012, Lee *et al*[44] developed a gemcitabine eluting stent membrane applied to a self-expanding Nitinol stent. They performed both *in vitro* modeling using a SK-ChA-1 cholangiocarcinoma cell line as well as *in vivo* modeling using a mouse model with colorectal carcinoma cells (CT-26). They analyzed stents developed with 0%, 8%, 10%, and 12% gemcitabine PU by weight and found the 12% concentration to be superior in terms of tumor inhibition and pro-inflammatory markers in both the *in vivo* and *in vitro* models. The authors concluded that gemcitabine eluting stents show considerable feasibility for the treatment of malignant obstruction[44]. Furthermore, in 2012, Chung

Table 5 Studies evaluating drug elution or coating to prevent external failure

Ref.	Journal	Study design	Study results
Animals			
Lee *et al*[38]	*Gastrointestinal Endoscopy* (2005)	Porcine model 2 pigs - control (metallic) 2 pigs - 10% wt/v Paclitaxel 2 pigs - 20% wt/v Paclitaxel	Paclitaxel-eluting stents caused mild adverse effects, but are safe to use in porcine models
Lee *et al*[40]	*Gastrointestinal Endoscopy* (2009)	Canine model 5 dogs - control (metallic) 6 dogs - 20% wt/v paclitaxel	Paclitaxel-eluting stents caused mild adverse effects, but are safe to use in canine models
Lee *et al*[44]	*International Journal of Pharmaceutics* (2012)	*In vitro*, murine model 5 mice - no stenting 5 mice - polyurethane 5 mice - 0% wt/v gemcitabine 5 mice - 8% wt/v gemcitabine 5 mice - 12% wt/v gemcitabine	Stents coated with gemcitabine reduced the size of subcutaneous tumor *in vitro* and in mice
Chung *et al*[45]	*Journal of Gastroenterology and Hepatology* (2012)	Porcine model 2 pigs - 0% wt/v gemcitabine 2 pigs - 10% wt/v gemcitabine 2 pigs - 15% wt/v gemcitabine 2 pigs - 20% wt/v gemcitabine	Gemcitabine-eluting stents cause mild to severe inflammation, but are safe to use in porcine models
Jang *et al*[41]	*Endoscopy* (2012)	Porcine model 2 pigs - 0% wt/v paclitaxel 2 pigs - 0% Pluronic + 10% taxol 2 pigs - 10% Pluronic + 10% taxol 2 pigs - 20% Pluronic + 10% taxol	Greater patency observed when stents were coated with pluronic with paclitaxel. Stents are safe to use in porcine models
Kim do *et al*[46]	*International Journal of Nanomedicine* (2013)	*In vitro*, murine model 10 mice - control (no stenting) 10 mice - PCL film 10 mice - sorafenib-loaded film	Sorafenib-loaded film inhibited the growth of human cholangiocarcinoma cells *in vitro* and in mice
Shi *et al*[42]	*European Journal of Gastroenterology and Hepatology* (2013)	Canine model 10 dogs - control (no stenting) 10 dogs - Poly-L-lactic acid coated metallic stents (PLLA) 10 dogs - PLLA + 1 mg paclitaxel/stent 10 dogs - PLLA + 2 mg paclitaxel/stent	No adverse effects less granulation tissue and glandular hyperplasia in dogs with paclitaxel stents
Bang *et al*[43]	*Gastroenterology Research and Practice* (2015)	Murine model 8 mice - control (polyurethane) 8 mice - control + Pluronic 8 mice - Pluronic + 5% paclitaxel 8 mice - Pluronic + 10% paclitaxel	Tumor angiogenesis inhibited in mice with Paclitaxel stents through multiple molecular mechanisms
Humans			
Suk *et al*[2]	*Gastrointestinal Endoscopy* (2007)	Randomized prospective 21 patients - 10% wt/v paclitaxel	Paclitaxel-eluting stents are safe and effective. Occlusion in 9 patients, mean patency was 429 d
Jang *et al*[3]	*Digestive Diseases and Sciences* (2013)	Randomized prospective 46 patients - control (metallic) 60 patients - 10% wt/v paclitaxel	No significant differences in stent patency or patient survival, but stents proved safe to use in humans

et al[45] developed a porcine model to analyze gemcitabine eluting stents, analyzing 0%, 10%, 15% and 20% gemcitabine wt/v drug DEBS. They found mild to severe inflammation in the 15% and 20% groups compared to mild inflammation in the 10% group. Fibrous reactions in the submucosal layer did not differ among groups and no biliary obstruction, necrosis or perforations were observed during the study. They found that the 10% GEM stents produced mild histologic changes and are likely most appropriate for clinical application.

Most recently in 2013, Kim do *et al*[46] loaded sorafenib on PCL film, which was then wrapped around a metal biliary stent. They cultured human cholangiocellular carcinoma cells with the PCL films in order to examine the effect of sorafenib on angiogenesis and tumor cell growth. Additionally, a mouse model was developed using human cholangiocarcinoma cells. The study concluded that sorafenib successfully inhibited local angiogenesis and tumor cell growth both *in vitro* and in murine models.

HUMAN TRIALS OF DRUG ELUTING BILIARY STENTS

There have been limited human trials involving DEBS. The initial human trial of paclitaxel DEBS was a single arm trial of 21 patients undertaken by Suk *et al*[2] in 2007 in which a mean patency of 429 d and a mean survival of 350 d were found. Occlusion was observed in 9 patients due to bile sludge or clogging in 4, tumor overgrowth in 3, and tumor in-growth in 2. Furthermore, cumulative patency rates at 3, 6, and 12 mo were 100%, 71%, and 36%, respectively. Blood levels of paclitaxel were monitored in 6 patients showing systemic levels were low, peaking between 1-10 d, suggesting systemic effects are minimal compared to local effects. This trial showed promising safety and efficacy data and prompted a follow up prospective trial[3], comparing a 10% wt/v paclitaxel eluting bare metal stent with a traditional covered metal stent. Stents were 5-8 cm in length and 10 mm in diameter in both groups. The study was altered due to a patient preference for the DEBS, and the planned randomized controlled trial was changed to consecutively enrolling 60 patients to the paclitaxel-coated stent arm and then enrolling 46 patients to standard covered SEMS[41]. Mean duration of stent patency was 199 ± 235 d in the paclitaxel-DEBS group and 149 ± 99 d in the covered SEMS group. Mean survival was 270 in the in the paclitaxel-DEBS arm *vs* 260 d in the control arm. The rates of cholangitis, pancreatitis, and stent migration were similar between the two groups. Although there was a trend towards improved patency and survival in the DEBS arm, the results did not display statistical significance. The authors concluded that although no significant difference was detected with paclitaxel DEBS, they were shown to be equally safe in human use, and further research is needed. The relatively small number of patients, as well as the shift from a prospective concurrent randomized trial to a trial with staggered accruement likely inhibited the power of the study to detect a clinical benefit from paclitaxel eluting biliary stents. These studies aside, there are multiple avenues for future human research, as well as a significant need to perform large prospective trial to evaluate the effectiveness of drug eluting biliary stents, both with paclitaxel and innumerous other compounds.

CONCLUSION

The amount of direct research involving drug eluting biliary stents has been limited, with only a few drugs having been directly examined. Considering the myriad of possible drugs which could decrease the incidence of internal failure, external failure, or both, there is ample room for further research. As described earlier, small amounts of luminal narrowing from external compression can have exponential effects on the rate of biliary flow, resulting in a significantly increased propensity for internal failure. Drug elution has theoretical benefit in decreasing internal stent failure rates, and heparin coating in particular has shown promise in small studies, which warrants further research. However, antibiotic elution has not shown a benefit in decreasing biofilm formation, which parallels trials looking at the use of systemic antibiotics to prevent stent failure. This may be secondary to multiple possible etiologies including the inability of antibiotics to permeate within biofilms, or the polymicrobial environment of the biliary tree which may quickly lead to bacterial resistance.

Only three drugs, paclitaxel, gemcitabine and sorafenib have been evaluated as possible candidates to decrease the incidence of external failure, where paclitaxel is the sole drug evaluated in human trials. There are multiple drugs which theoretically could show a clinical benefit in decreasing stent failure rates in both malignant and nonmalignant sources of biliary stenosis. Development of an effective drug eluting stent would likely be cost effective due to the high costs involved in stent failure and has the possibility of directly decreasing patient morbidity and mortality. The high costs, and extensive time and labor requirements of large animal modeling, as well as the lack of an established reproducible bench model have likely inhibited the process of stent development thus far. Despite this, the raw theoretical benefit is evident, where the demand for new devices that reduce restenosis rates with their associated morbidity and mortality is ever present.

Among the possibilities for future DEBS research, the possibility of combination drug stents holds theoretical promise. In order to maximize stent patency rates, the ideal stent would feature both internal and external drug elution. Also, previously trialed drugs which failed to show efficacy as a single agent may have added efficacy when combined with other agents such as heparin or antibiotics, which could prove to have increase efficacy when used in concert. Future animal and human trials will benefit from the analysis of drug combinations.

One of the main limitations to the development of DEBS is the lack of cheap, reproducible models which accurately reflects the human bile duct. Internal stent failure can be reasonably modeled on the bench top by systems which propel biologically active bile through the stent[47]. Biofilm development can then be measured by direct inspection, weight and electron microscopy[17-19,21,22]. This model may be used to select optimal agents for further analysis. However, there are no cheap reproducible models which accurately depict the human biliary ducts tolerance to direct contact with drug elution. Drug eluting stents, particularly those with external drug elution, require animal modeling in order to assess histological changes resulting from the stent. As there are no adequate small animal models available for biliary stenting, this has previously been performed with porcine or canine modeling. This has multiple downsides including the high costs of endoscopists or surgeons to place stents, veterinarians, and the animal husbandry required for the several weeks while stents incubate in the bile duct. As the large animal model is also required to establish the ideal drug elution dosage based on histologic changes, costs inhibit the number of drug dosages trialed. Future investigators would benefit from the development of more streamlined and standardized bench top and animal models.

In conclusion, although the current research on DEBS is limited, promise is evident and holds the possibility for significantly increasing the rates of long-term stent patency. Drugs that inhibit malignant cells and non-malignant epithelia hyperplasia, while displaying reasonable histologic tolerance after exposure to the biliary epithelium, should be further examined. Previous models that are well defined can be implemented to streamline further research. There is an obvious need in this population to decrease morbidity, and DEBS hold the possibility of a significant improvement in outcomes. Further analysis of both new pharmaceuticals and further modeling of current and combinatory drug eluting stents is needed.

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REVIEW

Submucosal tunnel endoscopy: Peroral endoscopic myotomy and peroral endoscopic tumor resection

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Abstract

Peroral endoscopic myotomy (POEM) is an innovative, minimally invasive, endoscopic treatment for esophageal achalasia and other esophageal motility disorders, emerged from the natural orifice transluminal endoscopic surgery procedures, and since the first human case performed by Inoue in 2008, showed exciting results in international level, with more than 4000 cases globally up to now. POEM showed superior characteristics than the standard 100-year-old surgical or laparoscopic Heller myotomy (LHM), not only for all types of esophageal achalasia [classical (Ⅰ), vigorous (Ⅱ), spastic (Ⅲ), Chicago Classification], but also for advanced sigmoid type achalasia (S1 and S2), failed LHM, or other esophageal motility disorders (diffuse esophageal spasm, nutcracker esophagus or Jackhammer esophagus). POEM starts with a mucosal incision, followed by submucosal tunnel creation crossing the esophagogastric junction (EGJ) and myotomy. Finally the mucosal entry is closed with endoscopic clip placement. POEM permitted relatively free choice of myotomy length and localization. Although it is technically demanding procedure, POEM can be performed safely and achieves very good control of dysphagia and chest pain. Gastroesophageal reflux is the most common troublesome side effect, and is well controllable with proton pump inhibitors. Furthermore, POEM opened the era of submucosal tunnel endoscopy, with many other applications. Based on the same principles with POEM, in combination with new technological developments, such as endoscopic suturing, peroral endoscopic tumor resection (POET), is safely and effectively applied for challenging submucosal esophageal, EGJ and gastric cardia tumors (submucosal tumors), emerged from muscularis propria. POET showed up to know promising results, however, it is restricted to specialized centers. The present article reviews the recent data of POEM and POET and discussed controversial issues that need further study and future perspectives.

Key words: Achalasia; Heller myotomy; Laparoscopic myotomy; Per-oral endoscopic myotomy; Natural orifice transluminal endoscopy surgery; Endoscopic submucosal dissection; Submucosal endoscopy; LES; Transluminal technique; Minimally invasive surgery; Peroral endoscopic tumorectomy; EndoFLIP

Core tip: Submucosal tunnel endoscopy: Peroral endoscopic myotomy (POEM) and peroral endoscopic tumor resection (POET), constitutes a novel terrain for miniinvasive endoscopic treatment of diseases, where the surgical alternatives are totally incomparable, particularly in elderly. POEM showed exciting results in international level in treating all types of achalasia [classical (Ⅰ), vigorous (Ⅱ), spastic (Ⅲ)], including advanced sigmoid type, failed surgical or laparoscopic Heller myotomy cases, and other esophageal motility disorders (diffuse esophageal spasm, nutcracker and jackhammer esophagus). POET was spawned from the success of POEM, and slowly expanded worldwide to treat muscularis based esophageal, esophagogastric junction and cardia submucosal tumors. Submucosal tunnel endoscopy further inspired other applications and opened promising future perspectives.

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INTRODUCTION

Peroral endoscopic myotomy (POEM)[1] is a novel, incisionless, minimal invasive endoscopic surgical procedure, which has been derived from the era of natural orifice transluminal endoscopic surgery (NOTES)[2], intended for long-term recovery from symptoms of esophageal achalasia.

POEM has successfully spread internationally, with more than fifty centers to have performed POEM worldwide[3], following the excellent initial results from pioneering centers[1,4] and definitely open the era of submucosal tunnel endoscopy in clinical practice. POEM has been extended to treat not only all types of esophageal achalasia [classical (Ⅰ), vigorous (Ⅱ) or spastic (Ⅲ), Chicago classification[5]], but other spastic esophageal motility disorders as well[6-9].

There were modest variations among centers in technique and periprocedural management, which are currently under investigation, but all centers uniformly reported excellent efficacy and safety outcomes[3]. POEM has been also extended to include failure of previous therapies, such as botulin toxin injection (BTI) or pneumatic balloon dilatation (PBD)[10] or failed surgical or laparoscopic Heller myotomy (LHM)[11,12], advanced sigmoid-type achalasia[13-15], and also after failure of previous POEM[13]. Up to know more than 4000 POEM cases have been successfully performed worldwide, and currently there is an explosion of publications regarding POEM[3].

As an extension of the POEM technique and submucosal tunnel endoscopy, peroral endoscopic submucosal tumor resection (POET) is also introduced, and is currently increases in experience, however restricted to specialized centers[16,17].

Successful POET of esophageal and gastric SMTs is possible, due to direct access through the submucosal tunneling far from the mucosal entry, followed by successful mucosal closure even for inadvertent mucosal tunnel perforations with many techniques, such as standard clips, combined clip-endoloop technique[18], the over-the-scope clips (OTSC)[19], and finally the most recent technological progress of the endoscopic suturing device (OverStitch™; Apollo Endosurgery Austin, Texas)[20].

POET is far less invasive than the surgical alternatives, which are either gastrotomy or gastrectomy and esophagectomy for gastric and esophageal SMTs respectively, while POET can be also applied in case of contraindications or serious comorbidities[16]. However, further international experience with longer follow-up is necessary and awaited. Finally, POEM also opened other applications as well, such as endoscopic gastric pyloromyotomy for refractory gastroparesis[21].

POEM

Historical perspective of POEM

The concept of endoscopic myotomy for treatment of achalasia, was first reported in case series in 1980[22], but it was only in 2008 when Inoue *et al*[1] performed the first successful clinical case of endoscopic myotomy in humans with achalasia, based on experimental data by Pasricha *et al*[23], Sumiyama *et al*[24] and Perretta *et al*[25]. Inoue *et al*[1] coined the term POEM and subsequently extended its use to treat not only achalasia, but other spastic esophageal motility disorders as well[26].

Indications and contraindications

Currently, all types of symptomatic esophageal achalasia [classical (Ⅰ), vigorous (Ⅱ) or spastic (Ⅲ), Chicago classification[5]] diagnosed by high quality (preferably high resolution) esophageal manometry[5] can be treated by POEM[27], including failure of previous therapies, such as BTI or PBD[10] or failed surgical or LHM[11,12], advanced sigmoid-type achalasia[13-15] and also after failure of previous POEM[3,13] (Table 1). POEM has been also reported in post-gastric bypass patients with achalasia[28].

According to international IPOEMS database 43% of subjects had prior intervention such as PBD, BTI or LHM[3]. Previous therapies make POEM technically more challenging due to the presence of inflammatory fibrosis, adhesions and scars[12].

Maselli *et al*[29] also reported the first successful clinical case of POEM in a 3-year-old child with achalasia and Down syndrome, while lately other groups also reported POEM in children and adolescents[30,31], making

Table 1 Indications and contraindications of peroral endoscopic myotomy

Indications
Absolute indications
Primary idiopathic achalasia of all types [classical (Ⅰ), vigorous (Ⅱ), spastic (Ⅲ)] (Chicago Classification)
Relative indications
Other hypertensive motor disorders (diffuse esophageal spasm, nutcracker or jackhammer esophagus). HRTM necessary
Failed surgical myotomy (POEM at the opposite site manly posterior POEM)
Failed pneumatic balloon dilatation
Failed previous POEM. Redo POEM at the opposite site mainly posterior POEM necessary
Advanced sigmoid type achalasia with mega esophagus (bilateral POEM may be necessary)
Children with achalasia (relative indication in experienced hands and specialized centers only)
Elderly with achalasia and comorbidities and non-surgical candidates (relative indication in experienced hands and specialized centers only)
Contraindications
Absolute contraindications
Severe cardiopulmonary disease or other serious disease
Pseudoachalasia
Failure in creating the submucosal tunnel because of severe fibrosis and adhesion
Relative contraindications
Severe esophagitis and/or very large ulcer in the lower esophagus
Recent endoscopic treatment such as EMR, ESD

POEM: Peroral endoscopic myotomy; HRTM: High resolution topographic manometry; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

age, no limitation for POEM. Currently, the pioneer centers[1,11] have no exceptions when considering the application of the POEM.

Moreover, Inoue first extended the indications of POEM to other spastic esophageal motility disorders, such as diffuse esophageal spasm, nutcracker, and jackhammer esophagus[7,8,32]. According to international survey (IPOEMS), 28% of the reported POEMs performed for other esophageal motility disorders, than achalasia[3]. In these disorders POEM permitted the longer myotomy required, which cannot be achieved *via* the laparoscopic approach[6-8,32].

POEM contraindications, according to the consensus, include severe pulmonary disease, esophageal irradiation, esophageal malignancy, bleeding disorder, including coagulopathy and recent esophageal surgery or endoscopic intervention, including endoscopic mucosal resection and endoscopic submucosal dissection (ESD)[3].

POEM procedure

POEM starts with a mucosal incision, followed by submucosal tunnel creation crossing the EGJ and myotomy inside the tunnel and away from the mucosal entry. Finally the mucosal entry is closed with endoscopic clips. The equipment required for POEM are the same used for ESD, while carbon dioxide insufflation is obligatory through the entire procedure.

It is recommended to use spray catheter for reinjection or the injection needle to remain inside the plastic sheath, to prevent damage to the muscular layer or to mucosal flap. The width of the tunnel should be about one-third of the circumference of the esophagus. A challenge with POEM concerns the identification of the EGJ while in the tunnel, which is discussed below. At the completion of myotomy smooth passage of the endoscope through the EGJ provides confirmation of complete myotomy. Figure 1 demonstrates the critical steps of POEM.

One day postoperatively, gastroscopy and esophagogram should be routinely performed to confirm mucosal integrity and exclude complications. Adequate esophageal empty controls the efficacy of myotomy and enables oral intake. In uncomplicated cases, patients begin by drinking liquid on day 1, a soft diet on postoperative day 2, and a normal diet on postoperative day 3, while an intravenous infusion of antibiotics should be delivered for one to three days after POEM, followed by an additional four days of oral antibiotics.

The debatable issues of POEM that need further clarification are presented in detail below (Table 2).

Knives

Currently, an important issue for discussion regarding POEM is: Which knife should be used? Inoue *et al*[1] introduced the triangular TT-knife, that has the advantage of permitting selective dissection of the circular muscle layer, which is the responsible muscle for achalasia, while the thin outer longitudinal muscle may remain as intact as possible, as another safety margin from mediastinum and as a guide to keep a correct dissection plane.

The flat triangular base of the TT-knife is safely touched to the longitudinal layer permitting catching and selective dissection of circular muscle bundles, while lowering the risk of damage to surrounding structures, particularly for inexperienced operator (Figure 1E).

Other knives have been also successfully used for POEM, with the Water-jet (WJ) and ERBE knives the most competitive to TT-knife[33]. They have the advantage of flushing during POEM, which, according to single center, comparative studies, resulted in shorter procedure time, mostly due to less replacement of accessories and permitted full-thickness myotomy[33,34]. The authors

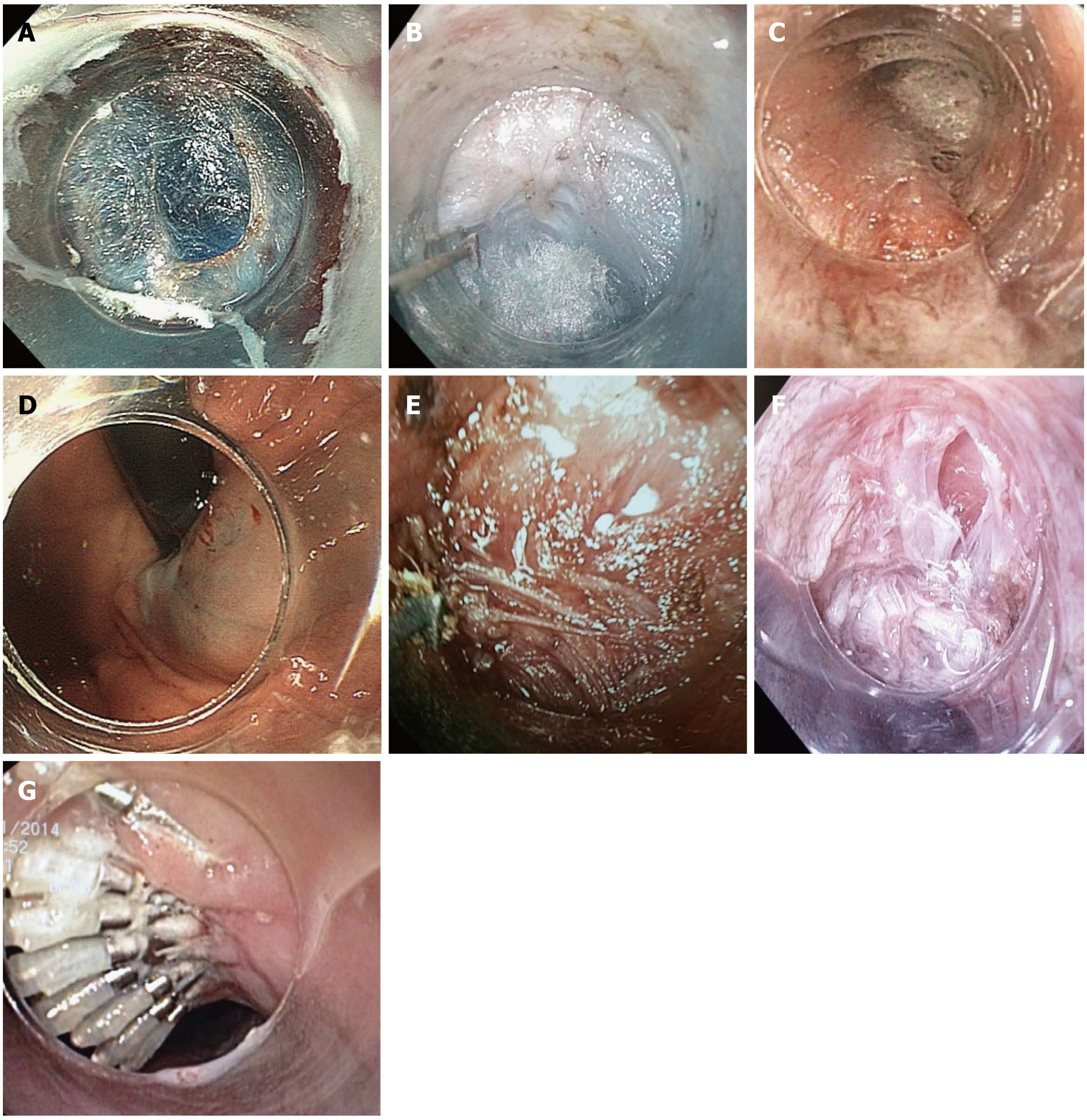

Figure 1 Peroral endoscopic myotomy stages. A: Mucosal entry after longitudinal incision at the 2-o'clock position; B: Submucosal tunneling. Ectopic innermost longitudinal muscle bundles in front of the circular muscle layer are recognized; C: Palisade vessels at the EGJ inside the tunnel; D: Blue dye at retroversion in the stomach confirms tunnel extension to gastric side; E: The sharp tip of the TT-knife is used to catch circular muscle bundles and then retract them toward the esophageal lumen; F: Longitudinal muscle is identified at the bottom of myotomy site. Longitudinal muscle fibers split each other and a gap is recognized, creating an unintentional, partly full-thickness myotomy; G: Mucosal closure with endoscopic clips. EGJ: Esophagogastric junction.

comparing WJ to TT-knife also reported larger injection volume and fewer bleeding episodes with WJ, which attributed to easier reinjection[33,34]. However, reinjection is important only during submucosal tunnel creation and not during myotomy, which is the most important and durative part of POEM.

Lastly, a simple and efficient modified POEM technique using TT-knife and a new method of injecting dyed saline through an integrated water jet channel, to avoid exchanging the knife for a spray catheter, which is time consuming, has been described[35].

As POEM is an innovative technique, operating time is not anymore a taboo, while the significant time variation between different groups and within the same group related to obvious inhomogeneity of achalasia patients and irrespective of the knife used, made comparative studies difficult.

In contrary, while TT-knife permits also full-thickness myotomy, selective circular myotomy is more difficult using WJ or ERBE knife, because of the round tip of the knife that does not permit easy catching of individual muscle fibers. These knives are found more appropriate to perform intentional full-thickness myotomy, although not necessary, for treating achalasia.

To our knowledge there is no sufficient international independent data, comparing different knives and up to know no knife has been proved to be more efficacious, although the largest international experience is with the less expensive TT-knife in terms of safety and efficacy.

Coagulation parameters

High frequency electrosurgical energy generator (V/O

Table 2 Issues of peroral endoscopic myotomy that need further study

TT-knife *vs* ERBE knife *vs* other knives
Posterior *vs* anterior myotomy *vs* bilateral myotomy
Selective circular *vs* full thickness myotomy
EndoFLIP technique *vs* classical tricks to evaluate adequacy of myotomy
Mucosal closure clips *vs* OverStitch
POEM *vs* LHM or surgical myotomy
GERD after POEM (treatment necessary, *e.g.*, antireflux procedure, PPIs?)
Training system for POEM
How the risk of mishaps related to POEM can be diminished?

POEM: Peroral endoscopic myotomy; LHM: Laparoscopic Heller myotomy; GERD: Gastroesophageal reflux; PPIs: Proton pump inhibitors.

300D ERBE; Tubingen, Germany) that enables a spray-coagulation mode with noncontact tissue dissection was the standard preference of Inoue *et al*[1] for both submucosal tunneling and myotomy during POEM. The spray-coagulation mode makes the submucosal dissection during tunnel creation much easier, faster, and with less bleeding. Settings can be individually adjusted during the operation.

However, other coagulation modes (*i.e.*, forced coagulation) are also acceptable during submucosal dissection and myotomy, with comparable quality to spray coagulation, in terms of safety and efficacy during POEM with excellent results.

CO_2 insufflation

After frequent serious complications with room air, the POEM groups have been converted to exclusively carbon dioxide insufflation during POEM[1]. Currently, CO_2 gas insufflation through the endoscope, during POEM, in concordance to laparoscopic techniques, is mandatory not only to reduce mediastinal emphysema, but also to reduce the risk of air embolization.

Intratracheal intubation with positive pressure ventilation should be maintained at higher pressures than those generated by endoscopic CO_2 insufflation, to reduce the risk of mediastinal emphysema during submucosal endoscopy[26,27]. Mild subcutaneous emphysema, mediastinal emphysema or pneumoperitoneum after POEM, however, should not be considered as complications but as part of this procedure in concordance to pneumomediastinum or pneumoperitoneum after laparoscopic surgery.

Circular vs full thickness myotomy

One of the major concerns during POEM was how deeply the muscle layer should be divided. In surgical myotomy, full-thickness myotomy is performed, as the surgeon cut from outside first the external longitudinal muscle layer to approach the inner circular muscle layer.

In initial series of POEM performed by Inoue *et al*[1] and subsequently by other groups[36-39], muscle cutting was intended to dissect only the circular muscle bundles, which is the responsible muscle for achalasia, while the thin longitudinal muscle layer was left intact as a safety margin between submucosal space and mediastinum.

Full-thickness myotomy is not necessary for treating esophageal achalasia and other esophageal motility disorders, and selective circular myotomy can solve the problem, according to excellent results from more than 3000 selective circular POEM cases. So intentional full-thickness myotomy is not recommended to treat achalasia and other esophageal motility disorders.

However, complete true selective circular myotomy is not possible as longitudinal muscle bundles are naturally thin enough to be widely stretched and split each other during POEM, only by mild compression of the endoscope tip, creating partially full-thickness gaps, without clinical relevance or consequences[26].

With the increasing experience in POEM and the development of sophisticated endoscopic techniques for closing mucosal gaps, some specialized centers performed intentionally full-thickness myotomy, even for achalasia, although not necessary[40,41]. However, no significant difference to selective circular myotomy was found in all parameters studied (symptom relief, procedure related parameters, manometry) except of reduced procedure time in the group of full-thickness myotomy.

In terms of safety however, nobody knows the real risks of potential complications in inexperienced hands and the consequences of the severe capnomediastinum and capnoperitoneum, following full-thickness myotomy than selective circular myotomy. Moreover, the gastroenterologist who performs POEM is not familiar to mediastinal anatomy and may have higher risk of complications, such as making accidental injuries to structures beyond the esophageal wall.

However, full-thickness myotomy opened new perspectives in the era of NOTES for further investigation, as structures beyond the esophageal wall, such as mediastinum and retroperitoneum are directly endoscopically accessible and also structures, such as the angle of His and vagus nerve[42] may be recognized during POEM. Potential future endoscopic procedures could be endoscopic retroperitoneoscopy or mediastinoscopy in a similar fashion to laparoscopy and thoracoscopy. However, these areas need further investigation.

Myotomy length

Myotomy length in POEM is also another controversial issue for discussion. POEM permitted control of myotomy length to be as long as we wish, and achievement of longer myotomy than any surgical myotomy[8,26]. In initial POEM cases, a relatively short myotomy was performed, however long enough to achieve complete release of high LES pressure and resolve achalasia symptoms. Based on clinical results, the recommended myotomy length during POEM should to be a minimum of 7 cm, with 2 cm gastric extension.

With the introduction of high resolution topographic manometry (HRTM)[43] and Chicago classification[5], achalasia is accurately classified in three major groups, which permitted better pre-POEM evaluation of these patients.

Based on these manometric studies, patients with type Ⅱ (vigorous, panesophageal pressurization) and Ⅲ (spastic) achalasia, with chest pain because of spasm and/or another high-pressure zone, or other mixed esophageal motility disorders, such as diffuse esophageal spasm, nutcracker and jackhammer esophagus[7-9], longer myotomy of more than 7 cm is necessary for appropriate symptom resolution.

Khashab *et al*[9] recently reported the international multicenter experience from 73 patients with spastic esophageal disorders with mean myotomy length 16 cm and maximum up to 25 cm. However, myotomy length should be individualized, based on HRTM results before POEM.

According to the consensus from IPOEMS and other studies, POEM has significant efficacy in nutcracker esophagus, hypertensive LES, diffuse esophageal spasm and type Ⅲ (spastic) achalasia, because in those disorders often a longer myotomy is required than cannot be achieved *via* the laparoscopic approach[3,6,7].

Identification of EGJ

Another fundamental issue in POEM is the extension of myotomy beyond the EGJ about 2-3 cm at the gastric side. So identification of the EGJ in the submucosal space during POEM has significant importance. As clear markers for identifying the EGJ, should be checked: (1) the insertion depth of the endoscope from the incisors; (2) a marked increase of resistance when the endoscope approaches the EGJ, followed by a prompt easing when the endoscope enters the gastric submucosal area; (3) the working space in the submucosal tunnel becomes gradually narrower when the endoscope approaches closely to the LES; (4) endoscopic visual identification of palisade vessels in the submucosal layer (Figure 1C); (5) a change of vasculature in the submucosal layer in the esophageal submucosal space few vessels are observed, while gastric submucosal vasculature suddenly becomes rich looking like a spider web and finally; and (6) the ectopic innermost longitudinal muscle bundles in front of the circular muscle layer at the level of the EGJ, finding in more than 30% of cases[44].

Tattooing at the gastric cardia using indocyanine green (ICG) before POEM is reported to be one trick for identifying EGJ during POEM by recognition of the green dye at the EGJ within the submucosal tunnel[32]. However, tattooing may be impractical, time consuming, and confusing particularly in sigmoid type achalasia with dilated and helicoid esophagus. However, this issue may need further study.

Orientation within the submucosal space

Ensuring that the submucosal tunnel stays in line with the esophagus is another issue with significant importance, especially in esophageal motility disorders with tight contractions during POEM and sigmoid and dilated esophagus. There is little data regarding orientation during submucosal tunneling, and although this issue is very important it is not included in up-to-date protocols.

According to Inoue *et al*[26], when the cap-fitted endoscope introduced into the submucosal space and then pushed, tends to advance only in line with the esophagus and its round tip tends to move to the center of the elliptical cross-section of the submucosal tunnel.

However, this is not always the case, especially during anterior myotomy to the lesser gastric curvature, because there are no objective markers to sustain correct direction and inexperienced endoscopists may easily loose the orientation, when they are inside the submucosal space (tornado tunnel).

Orientation within submucosal space may be easier during posterior myotomy to the greater gastric curvature because the existence of more objective guiding anatomic markers, such as the ankle of His, and the compression from the spinal cord[13]. However this issue needs further confirmation in comparative studies.

Myotomy site

Another question regarding POEM, is on which side myotomy should be done? In initial POEM cases, Inoue *et al*[1] performed anterior myotomy, to avoid damage to the angle of His and sling muscle bundles that are located at opposite direction at the greater gastric curvature, which might be a natural barrier to postoperative reflux of gastric contents. Since then anterior myotomy has been established and accepted by most endoscopists worldwide[36-39]. In fact, the International Peroral myotomy survey (IPOEMS), showed that 14 of 16 centers preferred the anterior approach[3].

Alternatively, posterior myotomy at 5 o'clock position, leading to the greater gastric curvature, is a promising safe modification of the POEM technique, with high rates of technical and clinical success, according to few centers[13,45]. Posterior myotomy has the theoretical advantage of easy access to EGJ and better orientation within the submucosal tunnel, because of spinal cord and the ankle of His[13].

Moreover, anterior myotomy is precluded by previous procedures such as failed surgical Heller myotomy or by other anatomic considerations that obscure the normal dissection planes[12,13]. Also, in patients with advanced sigmoid type achalasia with megaesophagus, the identification of the EGJ may be difficult during anterior myotomy, resulted in an incomplete gastric myotomy and poor symptom relief[13].

Posterior myotomy may be especially useful in cases of redoPOEM[32], POEM post-Heller myotomy[11,12] or when the EGJ is difficult to recognize because of supervening anatomic constraints or in sigmoid type achalasia with megaesophagus (Figure 2)[15]. However, no comparative studies have been yet published. A multicenter prospective single blind randomized clinical trial is currently underway, to investigate the optimal technique to myotomy (anterior *vs* posterior approach)

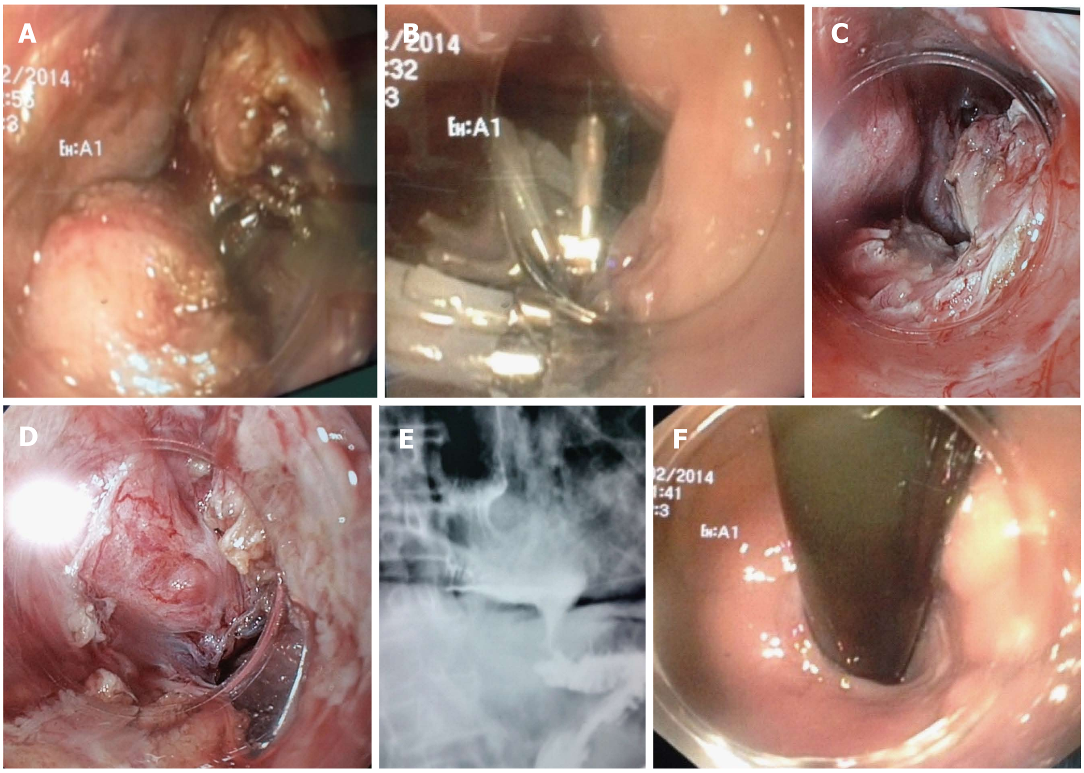

Figure 2 Bilateral peroral endoscopic myotomy in advanced sigmoid (S2) type achalasia with mega esophagus and severe dysphagia in a 74-year-old male with 35-year-old history of achalasia. A: Anterior myotomy. Circular muscle is too thick; B: Closure of the mucosal entry by clips after anterior POEM; C and D: Posterior myotomy at the opposite site. We recognize the mucosal flap and myotomy site; E: Esophagogram after redo-posterior POEM showed sigmoid and dilated esophagus but satisfactory passage of contrast; F: Open EGJ at retroversion. POEM: Peroral endoscopic myotomy; EGJ: Esophagogastric junction.

for POEM.

Mucosal closure

Maintaining the integrity of the mucosal flap and the reliable closure of the mucosal entry during POEM is paramount in preventing leakage of esophageal contents into the mediastinum. Most centers employ clips for closure of the mucosal entry of the tunnel[1,36-39]. When a completion of the closure with standard clips is unsuccessful, the combined clip-endoloop technique has been successfully applied, comparable to endoscopic full-thickness resection in other areas of the GI tract[18].

Alternatively, in failed cases, successful mucosal closure has been reported with the OTSC in two POEM cases[19], and fibrin sealant[46], however these techniques are more expensive.

There are also few groups who have also successfully used an endoscopic suture device (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas) for closure of inadvertent mucosal tunnel perforations, particularly for mucosal flap injuries at the EGJ[20]. These groups[11,20] are also more comfortable with full-thickness myotomy, because they have the possibility to close any perforation either by clipping or by suturing. They reported on 25 mucosal closures without statistically significant differences in closure time, complications or mean costs[34], however these results are debatable. Moreover, there are no comparative studies between different methods of mucosal closure, also regarding the cost-effectiveness.

Endoluminal Functional Lumen Imaging Probe system

During POEM the endoscopist is able to immediately assess the adequacy and completeness of myotomy by passing the endoscope through EGJ at the end of the procedure[26]. The rationale of POEM is to extend myotomy 2-3 cm to the gastric side in order to cut all responsible for achalasia, circular muscle fibers at the EGJ. However, endoscopic measurements of adequate myotomy are subjective and empirical, often imprecise and may be affected by many biases.

Some POEM groups assess the EGJ distensibility quantitatively, immediately at the end of the procedure, with the EndoFLIP (Endoluminal Functional Lumen Imaging Probe) system, trying to objectively confirm the adequacy of myotomy, however without clear results and no real benefit[47,48]. The EndoFLIP (Crospon Ltd., Galway, Ireland) system, uses impedance planimetry for real-time measurements of the EGJ diameter, through a specific balloon-tipped catheter[48].

The rationale of the EndoFLIP use during POEM is that the possibility to measure the diameter of the EGJ before and after POEM may reveal cases of incomplete myotomy, before the closure of mucosal entry as it was the case in one patient reported by Familiari *et al*[48]. The endoscope was inserted again in the submucosal tunnel and additional muscular bundles were cut at the

EGJ.

According to these studies, EndoFLIP was found to be potentially useful during LHM, but no real benefit was proved in POEM cases[48,49]. Obviously, the effects of myotomy on the diameter of EGJ are often unpredictable and not really controllable with POEM. Some authors studied the EndoFlip technique, concluded that EndoFLIP during POEM may be impractical and the real role, if any, should be evaluated in further multicenter studies[48]. To our opinion EndoFLIP may be confusing, time consuming, troublesome, especially in advanced, sigmoid type achalasia and costly.

POEM in sigmoid-type achalasia

Sigmoid type achalasia subdivided into S1 and S2 subtypes based on radiological signs on computed tomography. In S1 achalasia, the esophageal lumen is tortuous, but the direction is still downward. S2 type is an extremely advanced sigmoid form, where the esophageal lumen is tortuous and turns upwards[1].

Sigmoid type 2, (S2) was initially considered as an exclusion criterion for POEM. In this very advanced form of achalasia, the maximal tortuosity of the esophageal lumen does not allow smooth food passage, which occurs by gravity when the patient is upright. It was hypothesized that simple myotomy could not relieve symptoms and straightening of the curved esophagus was recommended in addition to laparoscopic myotomy[1].

However, based on the excellent initial results, Inoue *et al*[1] first proceeded to successful POEM in 9 patients with sigmoid-type achalasia, and reported them in his initial publication[1]. Since then other groups also reported successful POEM in advanced sigmoid achalasia[14,15,50].

Currently sigmoid type of achalasia is not yet considered as a contraindication for POEM, although it may produce even more technical difficulties, especially in remaining perpendicular to circular layer during myotomy. Moreover, in advanced sigmoid type (S2) achalasia, which is usually presented in advanced age, with multiple comorbidities, and contraindications for major surgery such as esophagectomy, and with a history of potential multiple previous therapies, such as PBD or even surgery, POEM may be the only available therapy. In these advanced sigmoid type (S2) achalasia, with potential extremely thick circular muscle layer, posterior or bilateral POEM[15] (Figure 2), may be the more appropriate approach, however without definite literature data. Further international experience in this specific subgroup is necessary and is awaited.

POEM for failed surgical myotomy

Although surgical or LHM resulted in good-excellent long-term results in 90% of achalasia patients, failures do occur[51]. According to Gockel *et al*[51] the most common causes of surgical myotomy failures are persistent achalasia or early recurrence due to inadequate or incomplete myotomy; early scarring or fibrosis; early fusion or healed myotomy; while other causes are tight fundoplication; peptic stricture due to gastroesophageal reflux (GERD); late recurrence due to progression to advanced sigmoid megaesophagus; diffuse esophageal spasm; progression to esophageal cancer; and others.

Treatment of failed surgical myotomy is a challenging, difficult urgent problem, with controversial data[51]. Redo Heller myotomy has lower efficacy and more postoperative complications, because it is more technically demanding due to the presence of adhesions, fibrosis, and scars from previous surgery according to Wang and Li[52].

Onimaru *et al*[12] and Zhou *et al*[11] reported successful rescue POEM on 10 and 12 achalasia patients respectively, with persistent or recurrent symptoms after previous surgical myotomy, with excellent (> 90%) short-term results and without complications.

Both LES resting pressure and symptom score were improved in short-term. The authors have not encountered any difficulties in extending the adequate POEM myotomy down to the stomach because of the presence of fundoplication.

In the rescue POEM, myotomy was performed at the axis opposite to the previous myotomy (mainly posterior axis), to avoid facing scars and submucosal fibrosis from previous surgery. In cases which the axis of previous surgical myotomy could not be clearly identified, myotomy was made at the standard 2 o'clock axis at the proximal esophagus and then rotated to a different axis at the area of the EGJ[12]. Rescue POEM, however, is highly demanding procedure compared to standard POEM and may be better performed by experts.

POEM *vs* surgical myotomy for primary achalasia

As the positive international experience with POEM increases, with explosion of international centers performing POEM, there is a criticism in the literature regarding the superiority of POEM to alternative standard 100-year-old surgical or LHM[53]. One of the major arguments for surgical myotomy is that "the approach is outside the mucosa"[54]. However intact mucosa is not any more a "taboo" in the modern era of NOTES as mucosal gap can be safely and effectively closed after the procedure, according to excellent results from more than 4000 POEM cases worldwide, up-to date[1,3,4,36-39]. Moreover, with surgery anatomical structures around EGJ are permanently cut and mobilized, and LHM should always be accompanied with partial fundoplication due to risk of severe GERD. Advantages and disadvantages of POEM *vs* LHM are presented in Table 3.

Furthermore, POEM permitted endoscopists to approach and cut the responsible muscle of achalasia (the circular muscle layer at the EGJ), through the submucosal space with the most delicate mode, leaving the surrounding structures intact[1].

Few non-randomized studies[53,55-57] exist comparing POEM to LHM, with conflicting results[55]. A recent meta-analysis of comparative studies between LHM and POEM showed equivalent short-term outcomes and similar results for adverse events, perforation rate, operative time and a non-significant trend toward a reduced length of hospital stay in the POEM group[54,58].

Table 3 Advantages and disadvantages of peroral endoscopic myotomy *vs* laparoscopic Heller myotomy

	POEM	LHM
Advantages of POEM		
Myotomy length	Longer myotomy up to 25 cm	Short myotomy maximum 6 cm
	Minimally invasive method	Invasive (major surgery)
Hospitalization	Less hospitalization (1-5 d)	Longer hospitalization > 5 d
Myotomy depth	Selective circular myotomy possible	Only full-thickness myotomy
Other esophageal motility disorders	Effective for esophageal spasm, nut cracker and jackhammer esophagus	Combined laparoscopic and thoracoscopic approach is necessary to obtain equivalent myotomy
Sigmoid achalasia	Effective in all types of achalasia even in end-stage, sigmoid type (S2) achalasia with megaesophagus	Major surgery such as esophagectomy may be necessary
Elderly patients	Effective in elderly with comorbidities and contraindications	Contra indication for surgery
In failed surgical	POEM after failed surgical myotomy is effective	Redo-surgery often with high rates of failure and complications
Cost	Lower hospitalization and lower cost	Higher cost in combination to surgical procedure
GERD	Less common and lower severity. No antireflux procedure (fundoplication) necessary at the moment. Further study necessary	Fundoplication necessary and routinely performed Complications from fundoplication
	Does not preclude surgery	POEM more difficult after LHM
	Bilateral POEM possible	
Disadvantages of POEM		
	POEM	Surgery
Follow-up	Short follow-up (novel technique)	Longer follow-up
	POEM restricted to specialized centers	Common surgical or laparoscopic procedure overall available
Training	Difficult (no so many centers)	Overall available

POEM: Peroral endoscopic myotomy; LHM: Laparoscopic Heller myotomy; GERD: Gastroesophageal reflux.

Further, randomized comparative studies of LHM and POEM are required. However, conducting studies comparing a novel endoscopic procedure mainly performed by gastroenterologists to a standard LHM performed exclusively by surgeons, in a population of achalasia with large inhomogeneity regarding type, stage and severity are extremely difficult.

All studies comparing POEM to LHM have not focused to specific subgroups of achalasia patients, *i.e.*, end-stage achalasia, with sigmoid type and megaesophagus with contraindications for major surgery. In these particular cases, as well as in other mixed esophageal motility disorders, POEM is the potential only acceptable treatment, according to up-to date positive experience[11,13,15,26]. The exciting results from POEM make objective, comparative studies to LHM difficult, with many ethical issues also emerged.

POEM after failure of previous POEM

Failure of POEM to control achalasia symptoms, does not exclude future surgery (LHM), because POEM does not involve adjacent tissues surrounding the lower esophagus[13].

The most common causes of POEM failures are persistent achalasia or early recurrence due to inadequate or incomplete myotomy; end-stage, sigmoid type (S2) achalasia with megaesophagus, where one side (mainly anterior) myotomy is not sufficient and overlooked mixed esophageal motility disorders that need longer myotomy[13]. In these failed POEM cases, redo-POEM at the opposite (posterior) direction is recommended and it has been successfully reported[13]. Longer follow-up, with greater number of patients and further studies focusing on failed POEM are necessary.

POEM RELATED COMPLICATIONS

Acute or late POEM related complications varied greatly among different reports[59] (Table 4). According to recent pooled analyses, minor complications include: Gas-related complications, such as capno/pneumoperitoneum (30%), subcutaneous emphysema (32%), and capno/pneumomediastinum (10%-22%)[39,58-60]. Major operative adverse events include tunnel mucosal perforation resulted to mediastinal or peritoneal leak, acute peritonitis, pleural effusion, GI fistula (0.3%), postoperative bleeding (1.1%) and a single death (1/4000 POEM cases, 0.025% mortality)[58].

Major bleeding in the tunnel is unusual but may require reentry for hemostasis, longer hospitalization time or even blood transfusion[29,46,61]. Post-POEM reflux esophagitis reported in 19% of patients, although there is controversy in the literature regarding incidence and severity of post-POEM GERD[58].

Gas related complications

Minor pneumomediastinum, or mild subcutaneous emphysema, just after POEM, could be as high as 100%, with incidence between 10%-22%[39,59,60], however, without clinical significance or requirement of special

Table 4 Complications of peroral endoscopic myotomy[58]

Common complications
Gas-related complications (minor)
Subcutaneous emphysema (31.6%)
Capno/pneumomediastinum (10%-22%)
Capno/pneumothorax (11%)
Capno/pneumoperitoneum (30.6%)[58]
Mucosal injury-perforation (mediastinal or peritoneal leak) (0.3%) (major)
Mediastinitis (insufficient data)
Peritonitis (insufficient data)
Retroperitoneal abscess (2 proved cases reported)
Pleural effusion (insufficient data)
Pneumonitis (insufficient data)
GI fistula (insufficient data)
Fever (temperature > 38 ℃)
Severe postoperative pain
Rare complications
Delay postoperative bleeding (1.1%)
Hematoma within the tunnel
Submucosal infection
Mortality (0.025%) (Single death/4000 POEM cases)

POEM: Peroral endoscopic myotomy; GI: Gastrointestinal.

treatment, and should not be considered as a complication. This phenomenon should be considered similar to the pneumomediastinum seen post thoracoscopic surgery or post-ESD[26,60,62].

However, gas-related complications may cause discomfort, which is usually relieved through conservative treatment, while in more severe cases vast gas accumulation may occur in the chest, abdominal cavity, mediastinum or under the skin, while acute respiratory and circulatory failure may occur. In such setting emergency invasive interventions of deflation *via* subcutaneous puncture and if necessary closed thoracic drainage should be taken for symptom relief[26,41,45].

Severe pneumothorax (up to 2.5%[45]) need chest tube placement, reported in the very early series of POEM[4], when air was insufflated instead of carbon dioxide gas, while thereafter no such severe complication is reported, at least from pioneering centers[6,11,15].

Furthermore, despite the theoretical dangerous "downside", according to centers with large number of POEM cases, although long myotomy have been performed up to 25 cm[8], no clinically severe mediastinitis has been reported at the moment[4,11,26].

Selective circular myotomy is preferred by most researchers trying to preserve longitudinal muscular layer in order to reduce the chance of gas entry into the thoracic and abdominal cavity. Full-thickness myotomy, however did not increase the occurrence of gas-related complications, although further studies are necessary[41].

Sigmoid-type esophagus was found to be independent risk factor for the occurrence of gas related complications, due to esophageal twisting, which might form a state of high pressure within the tunnel, so as to cause such complication as subcutaneous emphysema, pneumothorax and pneumoperitoneum[59].

Tunnel mucosal perforation

Mucosal tear during POEM, particularly at the high-pressure zone of the EGJ or cardia, which are considered as true perforations, have been also reported (0.3%), particularly in early POEM series[4,12,26,32,58]. These complications were usually treated conservatively with observation, prolonged fasting and longer intravenous antibiotic therapy. In two cases with sub diaphragmatic abscess, external drainage was necessary, with optional outcome thereafter.

The mucosal defects have been adequately closed by multiple clips[12,26,32], fibrin sealant[46], or by the clip-endoloop technique[18] and lately by endoscopic suture device (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas)[20]. Temporary dysphagia is also reported in one patient after multiple clipping at the EGJ[26].

POEM-related mortality

According to International POEM group, only a single, unpublished[58], POEM related death is currently reported and outside from the large POEM volume Asian centers, that reported no deaths[32,50]. So, POEM related mortality at the moment, is estimated to be 0.025% (one out of 4000 POEM cases globally). However, POEM related mortality should be compared to mortality of the surgical alternatives, which are the surgical, or LHM. According to recent (2015) study on national outcomes, the mortality rate of LHM was (4/1237) 0.3%[63] (almost 10-times more than POEM), with 2.4% major complications, 3.1% readmissions and 2.3% reoperation[63].

Moreover, the existing international experience from great number of patients, showed that POEM is a totally safe procedure, applied safely and effectively to all age spectrum from children to octogenarians, and also to patients with severe co-morbidities and contraindications for surgery[1,36-39,45,59,64,65]. However, future prospective, randomized, comparative, multicenter studies, on POEM related complications, also focusing on 30-d mortality rate after POEM (procedure and not procedure related), are necessary and awaited.

GERD after POEM

LHM is routinely accompanied by antireflux procedure, to prevent postoperative GERD, because the natural antireflux mechanisms are impaired, while in POEM no antireflux procedure is recommended, since the hiatal attachments are left untouched and the flap-valve mechanism intact[1].

Theoretically to minimize the risk of post-POEM reflux, anterior myotomy has been recommended, to avoid damage to the angle of His, and the oblique muscle layer of the EGJ, which are natural barriers to postoperative gastric reflux, located posterior laterally[1]. Sigmoid-type esophagus was found to be independent risk factor for the occurrence of GERD after POEM[59].

There are controversial results regarding post-POEM GERD, with incidence varied between 5%-46%

Table 5 Efficacy and complications of peroral endoscopic myotomy

Ref.	Patients (*n*)	Mean age (yr)	Eckardt score (pre/post)	LES pressure (pre/post) (mmHg)	Follow-up (mo)	Efficacy	Objective GERD evidence *n* (%)
Onimaru *et al*[12], Yokohama, Japan	300	45 (3-87)	6.13/1.33	27.3/13.4	12	98%	10%
Zhou *et al*[4], Fudan, China	42	44 (10-70)			2.5 (1-6)	100%	
Minami *et al*[32], Nagasaki, Japan	28	52 (19-84)	6.7/0.7	71.2/21	16	100%	Esophagitis 39.3%
Swanström *et al*[65], Portland, Oregon	18	59 (22-88)	6/0	45/16.8	6	94%	Esophagitis grade 1 28% +pH study 46%
Costamagna *et al*[39], Rome, Italy	11	41 (23-68)	7.1/1.1	45.1/16.9	3	100%	
Chiu *et al*[64], Hong Kong, China	16	47 (22-87)	5.5/0	43.6/29.8	3	100%	+pH study 3/15 (20%)
Hungness *et al*[53], Chicago, Illinois	18	38 (22-69)	7/1	19/9	63	89%	Esophagitis LA 33.3% A 13.3% B 13.3% C 6.7%
Von Renteln *et al*[60], European, CT	70	45	6.9/1	27.6/8.9	12	82%	Esophagitis 42% LA class A 29.2% B 12.3%
Stavropoulos *et al*[85], Mineola, New York	100	52 (17-93)	7.8/0.2	44.2/17.6	13.3	96%	17/53 (32%)
Verlaan *et al*[37], Amsterdam, The Netherlands	10	43	8/1	20.5/6.8	3	100%	60% LA class A 30% B 30%

GERD: Gastroesophageal reflux.

in published series[3,4,12,32,36-39,45,53,61,64,66] (Table 5). Inoue *et al*[1] and other initial multicenter studies[1,36-39,45,59], reported no symptomatic or mild endoscopic (LA grade A) post-POEM GERD, and concluded that GERD is minor or no problem after POEM. In contrary, according to a recent European multicenter study, GERD was the most common adverse event after POEM, with esophagitis diagnosed in 42% of patients, though usually mild[60].

There is controversy between studies and within the same study regarding the definition of post-POEM GERD. GERD can be defined on base of symptoms, 24-h pH monitoring and endoscopy data. Familiari *et al*[48] reported incidence of GERD of 57% based on pH monitoring, 33% based on endoscopic findings and 14% based on symptoms. This discrepancy is found to all studies, however, they all agree that GERD after POEM is not severe and can be successfully treated with proton-pump inhibitors.

In the largest POEM series with longer follow-up, the risk of GERD after POEM varies between 10%-30%, with average 10%, with excellent control under proton pump inhibitors (PPIs)[32]. Although this issue needs further long-term studies, at the present no antireflux procedure is recommended during POEM.

Efficacy of POEM

The overall results of POEM worldwide, showed excellent symptom improvement (using Eckardt score pre- and post-POEM) between 82%-100%, (mean 90%)[1,3,4,36-39]. Efficacy of POEM was also studied using manometry and timed barium esophagogram, showing significant improvement in LES pressure and esophageal emptying in 66% and 80% post-POEM, respectively[12,26,37,38,53,58] (Table 5). However, more data on long-term efficacy of POEM is needed, and awaited.

Training in POEM

As POEM constitutes a new endoscopic, pure NOTES procedure, which opens the era of submucosal endoscopy, emerged important ethical and training issues. Although theoretically POEM may have dangerous "downside" this has not been yet proved according to successful international experience from more than 4000 POEM cases globally. However, in order to diminish the risk of mishaps an appropriate training program for acquiring adequacy for performing safe and effective POEM is urgently needed.

A simple, cheap and reproducible, non-survival porcine animal model has been established for training in POEM, without the need for concern about complications[67-69]. Pig is the most appropriate animal model for training in POEM, due to its similarities to the human anatomy, while the porcine esophagus has the advantage of easy mobilization due to absence of tight junctions to surrounding organs.

However, there are significant differences between the porcine and human esophagus, particularly in patients with achalasia. Human submucosa is more hard than porcine's and esophageal circular muscle layer in achalasia is thicker, with multiple high-pressure contractions, while in cadaveric pig model the muscle is thin and without any contraction. Thus, mucosotomy and submucosal tunneling dissection are difficult in porcine due to tissue pliability and poor tissue distention[68].

The low incidence of achalasia (0.3%-1% per 100000 population)[70], in combination with the risk of serious complications, related to the technically demanding POEM procedure, has made training difficult[68,71]. Neither gastroenterologists nor surgeons are absolutely familiar with submucosal endoscopy. While endoscopists are familiar with endoluminal procedures and more experienced in handling endoscope within the natural lumen, surgeons, are familiar with laparoscopic/thoracospocic procedures and can more easily recognize the structures beyond the mucosa[68,71].

POEM however is a procedure that requires both capabilities. Good endoscope manipulation, recognition of luminal structures and surgical knowledge of extraluminal structures especially vessels, nerves and mediastinal anatomy. Moreover, delicate skills are also needed[68,71]. With the worldwide expansion of centers starting performing POEM training program, in POEM procedure is more urgent. Until recently, there are no standard training guidelines for training. The pioneers in POEM proposed a two stage training system for POEM.

First is preclinical training, during which the experienced trainee -which is familiar with handling GI endoscope, has perfect knowledge of esophageal and EGJ anatomy, knowledge of the pathophysiology of achalasia and knowledge of the POEM procedure, including set up of device and patient care during perioperative period- has to follow observation of POEM performed by specialists, and then practice in the animal or cadaveric model, about 46 (range 12-154) hours, according to recent international consensus[26,27,67-69,71]. Some other centers proposed use of clinical proctor system with 2 median number of proctored cases[71].

Second step is the clinical training, with POEM in humans with achalasia, performed under careful guidance and observation by specialists, and finally, performance of POEM in humans, with 20 POEM procedures needed to cover the learning curve[67,68,71]. However, there is still controversy in the literature regarding POEM operator background and training program focusing on "learning curve", while objective, neutral studies in this issues are difficult[72-74].

POET

Historical perspective

The exciting results of POEM[1,3,11,36-39] for esophageal achalasia, has further inspired other endoscopic miniinvasive treatments, such as POET[16,17] for *en bloc* resection of SMTs using the submucosal tunnel technique, particularly for esophageal, EGJ and gastric cardia tumors originating from the muscularis propria.

Endoscopic resection of SMTs originating from the mucularis mucosa (such as leiomyomas) and possibly the submucosa, has been also reported, with a variety of other techniques[75], from simple snaring to endoscopic submucosal dissection (ESD), because the muscle layer can be preserved[76,77]. Tumors however, originating from the muscularis propria have to be resected by thoracoscopy or laparoscopy[78].

Endoscopic snare full-thickness resection with adequate closure of the perforation with OTSC[19], or clips and an endoloop[18] or endoscopic suturing[20] has been successfully reported for small gastric SMTs (diameter < 2-3 cm)[79]. ESD has been also reported for the removal of EGJ SMTs, with satisfactory results[80]. Endoscopic partial resection using the unroofing technique has been also safely and effectively applied for definite pathological diagnosis of small SMTs[81].

The EGJ, however, is a difficult location for endoscopic resection because it is adjacent to the diaphragm, complicating the endoscopic resection with movement from breathing as well as esophageal peristalsis, in combination with narrow lumen or sharp angle, while SMTs of the EGJ are often irregular, lobulated and may grow annylarly, with potential increased risks of perforation and mediastinal infection, especially for SMTs originating from the muscularis propria. Conventional endoscopic muscularis excavation causes large mucosal defects which are difficult to close and often result in strictures[17].

Submucosal tunnel endoscopy, permitting approach to SMTs through a submucosal tunnel, tumor dissection within the tunnel, "*en bloc*" removal through a mucosal opening far from the tumor, and finally mucosal closure by clips. Submucosal tunnel endoscopy, permitted a controlled, standardized assess to previously taboo spaces, such as the muscle layer, mediastinum and peritoneum, which has been popularized with POEM[1,3,11,36-39].

Xu *et al*[17] and Inoue *et al*[16], based upon the POEM concept for treatment of achalasia, further described the technical principles for POET and performed the first successful POET clinical cases for esophageal, EGJ and gastric cardia SMTs originating from the muscularis propria. Since then POET has been used by other centers[16,17,82,83] as well. However, further international experience is necessary and awaited before the popularization of POET.

Indications and contraindications

The absolute and relative indications and contraindications of POET are described in Table 6. POET for esophageal, EGJ or gastric cardia SMTs, is far less invasive than, the technically demanding and invasive, surgical alternatives, which are either partial proximal gastrectomy for EGJ SMTs and esophagectomy for esophageal SMTs, while for lesions in the middle or distal stomach can be resected easily *via* laparoscopic approach[16,27] (Table 7). Moreover, surgical resection of cardia SMTs, have high risk of esophageal stricture development.

Based on the experience from specialized centers[16,27,80,82], absolute indication for POET includes suspected or confirmed gastrointestinal stromal tumor (GIST) and leiomyoma of the esophagus, gastric cardia and EGJ larger than 2-3 cm, if they are causing symptoms, increasing in size on follow-up or have high risk features on biopsy, endoscopic ultrasound (EUS) or computed tomography[16,27]. SMTs lower than 2 cm are low risk lesions and life-long surveillance by endoscopy/EUS is indicated. Some authors stated that in these small size (<

Table 6 Indications and contraindications of peroral endoscopic tumor resection

Absolute indications
Suspected or confirmed GIST of the esophagus and gastric cardia larger than 2-3 cm and lower than 5 cm, and tumor growth on follow-up
Suspected or confirmed leiomyoma of the esophagus and gastric cardia larger than > 2-3 cm and < 5 cm
Esophageal or gastric cardia SMTs in elderly with comorbidities and non-surgical candidates completed the above criteria (only in experienced hands and specialized centers)
POET does not exclude surgery. Complete histological diagnosis possible with POET
Relative indications
Esophageal and gastric SMT more than 5 cm (full-thickness resection using submucosal tunnel technique possible) (in experienced hands and specialized centers only and within studies)
Contraindication
Suspected or proved malignancy of SMTs

GIST: Gastrointestinal stromal tumor; POET: Peroral endoscopic tumor resection; SMT: Submucosal tumor.

Table 7 Advantages and disadvantages of peroral endoscopic tumor resection *vs* surgery

Advantages of POET		
	POET	Surgical myotomy
	Minimally invasive method	Invasive (major surgery)
Hospitalization	Less hospitalization (1-5 d)	Longer hospitalization > 5 d
	Specimen for complete histology possible	
	Does not preclude surgery	
Elderly patients	Effective in elderly with comorbidities and contraindications (only specialized centers)	Contra indication for surgery
Cost	Lower hospitalization and lower cost	Higher cost in combination to surgical procedure
Disadvantages of POET		
	POET	Surgery
Follow-up	Short follow-up (novel technique)	Longer follow-up
POEM	POET restricted to specialized centers	Common surgical or laparoscopic procedure overall available
Training	Difficult (only few centers worldwide)	Overall available
Outcome	Complete curable resection may be not possible in malignant GIST cases	Complete resection possible

GIST: Gastrointestinal stromal tumor; POET: Peroral endoscopic tumor resection; POEM: Peroral endoscopic myotomy.

2 cm) SMTs, POET may offer definitive histologic diagnosis by achieving en bloc resection and may eliminate the need for life-long surveillance[40], however the current surveillance practice has not yet changed. Contraindication for POET is suspected or confirmed malignancy. In suspected malignant cases, EUS puncture is indicated for tissue diagnosis and if malignant, the patients were primarily referred for surgical resection.

POET is also advantageous because it could be also applied in case of contraindications for the above-mentioned major operations, particularly in patients with serious comorbidities[16]. Although, initial experience of POET in a small series of patients and from specialized centers, was exciting in terms of safety and efficacy, further international experience with greater number of patients and longer follow-up is necessary and awaited.

POET procedure

The general set up of POET is the same as during POEM procedure[1], including longitudinal mucosal incision, entrance to the submucosal space, creation of the sub-mucosal tunnel, and approaching the SMTs. Only the final step is different and individualized based on the specifics of each case (Figure 3).

In POET the initial 2-cm longitudinal mucosal incision, is made at approximately 5 cm orally to the proximal margin of the SMT. The submucosal tunnel is created in the same way as Inoue *et al*[1] first described for POEM. The submucosal tunnel advanced towards the SMT and then extended beyond the tumor to prepare enough space to finally resect the tumor under direct vision.

In the final stage of POET the SMT is enucleated using combination of electrocautery knives [TT-knife and insulated tip (IT) knife] after dissection of muscle fibers connected to the SMT. The IT-knife is useful to dissect from the distal to proximal direction, and to mobilize the SMT. Then, extraction of the mobilized SMT is followed by suctioning the tumor into the cap device and removes it through the mucosal entry. Finally, the mucosal entry was closed tightly in similar manner as in POEM[1], mainly with endoscopic clips. Endoscopic suturing is alternatively used in difficult cases, by other groups[40].

The follow-up includes gastroscopy the following day to evaluate the mucosal integrity and contrast media swallow to check for leakage, and if normal started clear liquid diet and gradually regular diet the next days. Annual endoscopic follow-up was then recommended.

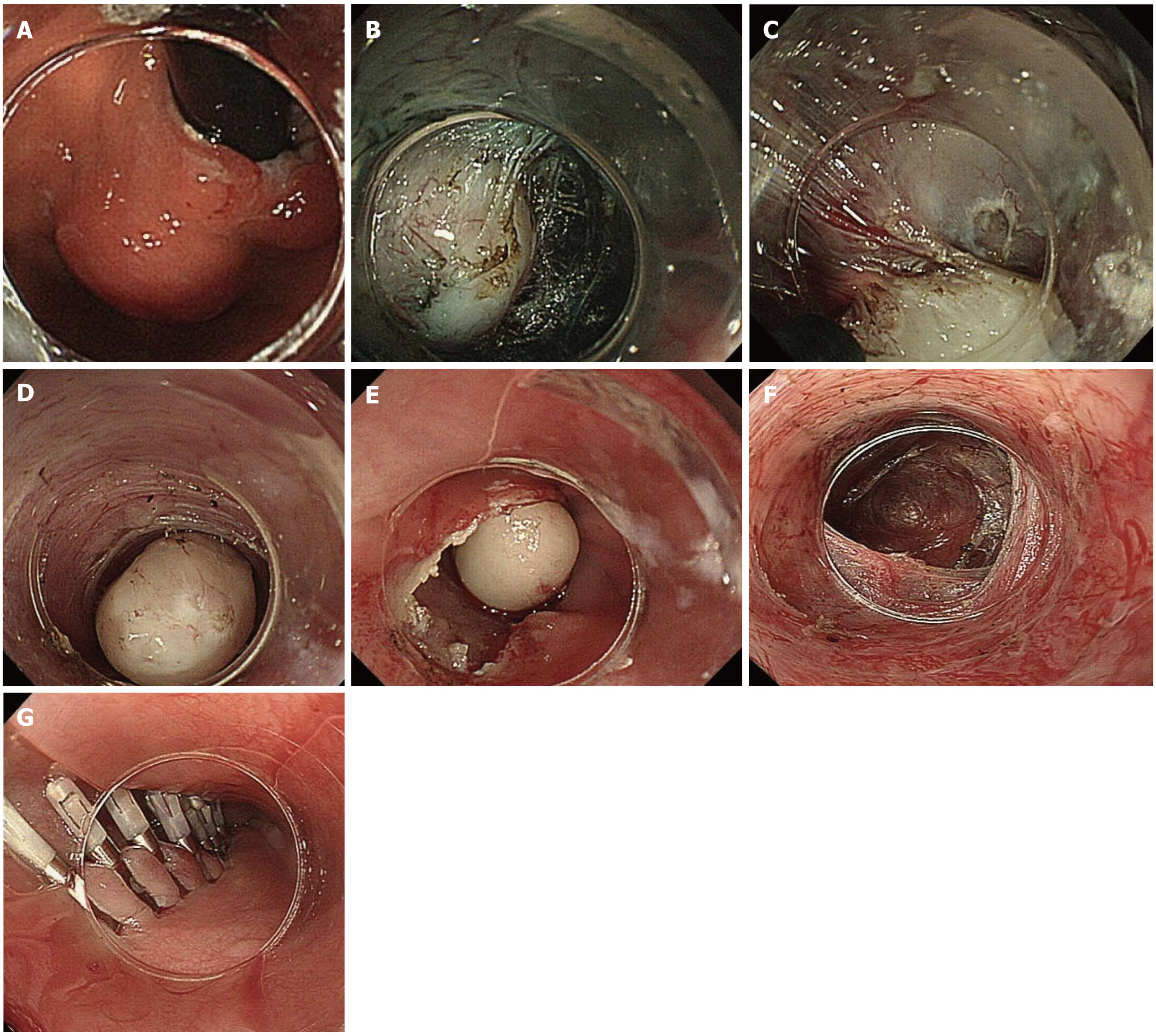

Figure 3 Schema of stages of peroral endoscopic tumor resection. A: Gastric cardia SMT in retroversion view; B: Submucosal tunneling. After initial mucosal incision approximately 5 cm proximal to the edge of the SMT, saline and indigo carmine are injected to create a mucosal bleb. A submucosal tunnel is created by dissecting the submucosal fibers. Submucosal dissection is advanced beyond the distal tumor edge; C: Tumor excision. The submucosal tumor is dissected from the muscle layer. All muscle bundles that connect to the submucosal tumor are cut with the triangle-tip knife; D and E: Removal of the submucosal tumor. The totally mobilized tumor is extracted from the submucosal space (D) through the mucosal incision (E). The submucosal tumor is caught tightly by endoscopic suction at the tip of its distal attachment. Submucosal tumors generally have an oval shape, which enables smooth removal out through the mucosal entry; F: Submucosal tunnel after removal of SMT; G: Closure of the mucosal entry incision. After confirmation of complete hemostasis in the submucosal tunnel (F), the mucosal entry is tightly closed with hemostatic clips. POET: Peroral endoscopic tumor resection; SMT: Submucosal tumor.

POET efficacy and related complications

Inoue *et al*[16] described successful complete POET in seven patients, four cardia and three esophageal SMTs, without complications. Histologically, one GIST, five leiomyomas and one aberrant pancreas were found. Only in the rare case of aberrant pancreas, additional mucosal resection was required, while in the other six tumors, resection margins were clear. No short-term complications reported[16].

POET also showed excellent results in long-term, according to a recent report from a pioneering center with large number of patients (290 patients with 4 years follow-up), showing no residual tumor, local tumor recurrence or distant metastasis[82]. According to literature available to us, no POET-related deaths were currently reported.

However, taking into account that POET is a relatively new technique with potential dangerous “downside”, future international, prospective, multicenter studies, focusing also on complications (procedure and not procedure related), are necessary and awaited. At the moment POET is restricted only to pioneering centers and within protocols. On the other hand, POET should be also considered as endoscopic surgical procedure and should be compared to surgical equivalents, which are for esophageal and EGJ lesions the esophagectomy

Table 8 Future perspectives of submucosal tunnel endoscopy

Endoscopic vagotomy?
Endoscopic thoracoscopy?
Endoscopic retroperitoneoscopy?
Endoscopic peritoneoscopy?
Endoscopic sympathectomy

and esophagogastrectomy, respectively.

Submucosal tunnel endoscopy opened other possibilities as well, such as exploration of peritoneal and thoracic cavities through transgastric peritoneoscopy[84] (Table 8). Lastly, another application of submucosal tunnel endoscopy, is the peroral pyloromyotomy as a potential treatment of gastroparesis using endoscopic submucosal tunneling similar to the concept of POEM[21].

CONCLUSION

Submucosal tunnel endoscopy, including POEM and POET, constitutes a novel terrain for minimal invasive endoscopic treatment of various diseases, such as achalasia and other esophageal motility disorders and esophageal, EGJ and gastric cardia SMTs, which showed exciting results in international level, and superior characteristics than the standard 100-year-old surgical alternatives.

Technological advancements in the era of NOTES, such as endoscopic suturing techniques, permitted endoscopists to become more aggressive, with submucosal tunnel endoscopy including endoscopic full-thickness resections, to be performed safely and successfully. Submucosal tunnel endoscopy opened many possibilities for miniinvasive endoscopic treatment in diseases where the surgical equivalents in terms of aggressiveness are totally incomparable, particularly in elderly patients with co-morbidities.

POEM has been globally popularized, with excellent results even from small centers, while it has been extended further to become the treatment of choice not only for all types of achalasia [classical (Ⅰ), vigorous (Ⅱ), spastic (Ⅲ)], including advanced sigmoid (S1 and S2) type, but also for failed surgical or LHM cases, and other esophageal motility disorders (diffuse esophageal spasm, nutcracker and jackhammer esophagus).

POET was spawned from the success of POEM, and slowly expanded worldwide to safely and successfully treat muscularis propria based SMTs in challenging locations in esophagus, EGJ and gastric cardia, with minimally invasive endoscopic procedure.

However, larger number of patients and long-term outcome of POEM and more experience of POET is necessary and is awaited. POEM and POET inspire many other NOTES interventions utilizing the submucosal tunnel approach.

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REVIEW

Endoscopic ultrasound-guided interventions in special situations

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Abstract

Endoscopic ultrasound (EUS) was introduced in 1982 and has since become a popular advanced procedure for diagnosis and therapeutic intervention. Initially, EUS was most commonly used for the diagnosis of pancreatobiliary diseases and tissue acquisition. EUS was first used for guided cholangiography in 1996, followed by EUS-guided biliary drainage in 2001. Advancements in equipment and endoscopic accessories have led to an expansion of EUS-guided procedures, which now include EUS-guided drainage of intra-abdominal abscesses or collections, intravascular treatment of refractory variceal and nonvariceal bleeding, transmural pancreatic drainage, common bile duct stone clearance, enteral feeding tube placement and entero-enteric anastomosis. Patients with surgically altered upper gastrointestinal anatomies have greatly benefited from EUS also. This systematic review describes and discusses EUS procedures performed in uncommon diseases and conditions, as well as applications on more vulnerable patients such as young children and pregnant women. In these cases, routine approaches do not always apply, and thus may require the use of innovative and unconventional techniques. Increased knowledge of such special applications will help increase the success rates of these procedures and provide a foundation for additional advances and utilizations of the technique.

Key words: Children; Endoscopic ultrasonography; Intra-abdominal abscesses; Pregnancy; Special situation; Surgically altered anatomy; Therapeutic; Uncommon

Core tip: This article reviews the clinical applications of endoscopic ultrasound-guided interventions reported to date, including drainage of intra-abdominal collections, gallbladder and pancreas. Procedures used in pregnant women and children are also described. The aim of this review was to promote knowledge of special clinical applications in which endoscopic ultrasound is applicable.

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INTRODUCTION

Human endoscopic ultrasound (EUS), first described in 1982 by Dimagno *et al*[1], has become a popular procedure for diagnosis and therapeutic intervention. Since the first report on EUS-guided cholangiography, advances in equipment and the development of endoscopic accessories have led to a substantial growth in the number and types of EUS-guided therapies[2]. These techniques allow for real-time visualization of structures beyond the endoscopic view, thus increasing the success rate and minimizing complications associated with the procedures. As a result, EUS has also been applied to uncommon or special clinical scenarios recently, such as intra-abdominal abscesses or collections, refractory variceal and non-variceal bleeding, and transmural pancreatic drainage. Furthermore, pregnant women and children have greatly benefited from EUS applications. The aim of this review was to identify and highlight these additional uses for EUS. The PubMed database was searched for human studies written in the English language and published between 1990 and March 2015. The following keywords were used either alone or in combination with EUS: Children, pregnancy, pancreatic drainage, surgically altered anatomy, refractory bleeding and angio-therapeutic interventions, tumor ablation, tumor injection, anti-tumoral therapy, and common bile duct (CBD) stone. The references in the identified articles were also searched for potentially relevant studies. The initial search identified 196 articles, of which 89 full-text articles were considered to be related to this topic and were chosen for review and analysis.

COMMON EUS-GUIDED INTERVENTIONS

Currently, the most common EUS applications are for diagnosing pancreatobiliary disease and tissue acquisition. EUS provides a precise evaluation of the pancreas, peripancreatic organs, CBD and gallbladder. Soon after its original use for pancreatic pseudocyst drainage, EUS was utilized for biliary drainage in cases were endoscopic retrograde cholangiopancreatography (ERCP) had failed. In fact, EUS produced superior outcomes in patients with post-surgical altered anatomy, according to both technical and clinical success rates compared to enteroscopic-based ERCP-related procedures (89%-100% *vs* 50%-95%, respectively)[3-11]. The complication rates in the EUS-guided procedure, such as procedures with a transpapillary approach, using transgastric or transduodenal routes for EUS-guided rendezvous, or a transmural approach in EUS-guided hepaticogastrostomy or choledochoduodenostomy, were in an acceptable range (25%-35%)[5-11]. However, despite their relative success and routine performance, the feasibility and possibility of complications should always be considered when performing these advanced procedures[12,13]. EUS-guided pancreatic pseudocyst drainage is commonly accepted in the treatment of fluid collection due to acute pancreatitis; however, this particular application will not be reviewed in the present article.

SPECIAL EUS-GUIDED INTERVENTIONS

EUS-guided interventions have also been utilized when dealing with uncommon diseases or conditions. More susceptible patients, such as young children and critically ill or pregnant patients, have greatly benefited from EUS-guided procedures. Since these groups of patients usually require alternative approaches, each application will be reviewed and described in detail.

EUS-guided pancreatic drainage

EUS-guided pancreatic duct drainage is one of the most difficult and advanced endosonography-based interventions. This procedure is associated with relatively high complication rates, up to 43%[14-20], and thus should be carried out only by dedicated and highly skilled endoscopists with extensive experience in therapeutic ERCP and EUS procedures. Although similar to EUS-guided biliary drainage, EUS-guided pancreatic drainage is limited to patients in whom ERCP has failed, such as those with symptomatic chronic pancreatitis and pancreatic duct obstruction (due to stone or stricture).

EUS-guided pancreatic duct drainage can be performed in two ways: EUS-guided rendezvous of the pancreatic duct and EUS-guided pancreaticogastrostomy. For EUS-guided rendezvous of the main pancreatic duct, the approach involves puncture from a gastric site and guidewire manipulation until it is passed down to the ampulla, followed by guidewire grasping and scope exchange. For EUS-guided pancreaticogastrostomy, the main pancreatic duct is punctured using a transgastric approach, which is followed by neo-tract creation-dilation and stent insertion from the pancreatic duct through the gastric cavity. The success of both of these procedures is due in part to improvements in the techniques and use of the proper instruments (dilating catheters, dilating balloons, or cauterizing devices for pancreatogastric tract creation). The case series and case reports[21-26] involving EUS-guided pancreatic duct drainage are shown in Table 1.

EUS-guided biliary interventions due to surgically altered anatomy

ERCP with overtube-assisted enteroscopy has a success rate average of 75% with 3%-5% complication rates, while percutaneous biliary drainage, with similar success rate, has 0.5%-15% complication rates, including 0%-4.9% mortality[27,28]. Currently, EUS-guided biliary drainage is a preferred alternative treatment option when the patient with surgically altered anatomy prefers internal drainage. Approximately one-third of the patients

Table 1 Clinical details of case series on endoscopic ultrasound-guided pancreatic duct drainage

Ref.	Technical success	Clinical success	Complications
Shah *et al*[21] (*n* = 25)	Pancreatography, 100% Pancreatic rendezvous, 50% Pancreatic duct intervention, 71%	N/A	10.5% (pneumoperitoneum, severe pancreatitis)
Ergun *et al*[22] (*n* = 20)	Pancreaticogastrostomy, 79% Rendezvous, 100%	Long-term, 72% Mean FU time = 7 mo FU range: 3 mo to 120 mo	10% (bleeding, peripancreatic collection) Long-term: Stent dysfunction 50% (plastic stents in all cases)
Will *et al*[23] (*n* = 12)	Pancreaticogastrotomy and rendezvous, 69%	73.2% FU range: 1 mo to 72 mo	42.9% (bleeding, perforation, pain)
Tessier *et al*[24] (*n* = 36)	Pancreaticogastrostomy and pancreaticobulbostomy, 92%	69.4% Mean FU time = 14.5 mo FU range: 4 mo to 55 mo	13.2% (fluid collection, hematoma)
Fujii *et al*[25] (*n* = 43)	Pancreaticogastrostomy, (antegrade: 18, retrograde: 14) overall: 74%	83% Mean FU time = 23 mo	Major: 6% (bleeding, perforation), overall: 24%
Barkay *et al*[26] (*n* = 21)	Pancreatography, 86% Pancreatic duct drainage, 48%	70% Mean FU time = 1 yr	2% (peri-pancreatic abscess, guidewire shearing)

N/A: Data not available; FU: Follow-up.

who undergo EUS-guided pancreatic duct drainage and one-fifth who undergo EUS-guided biliary drainage have surgically altered anatomies. This is typically due to a preceding Whipple's operation (pancreaticoduodenectomy-choledochojejunostomy and pancreatojejunostomy), post-gastrectomy, or other internal bypass surgeries. Prior to the advent of EUS procedures, the only treatment options for these patients were percutaneous drainage or repeat surgical operations. Advancements in EUS techniques provided alternatives, including EUS-guided rendezvous followed by ERCP or enteroscopy-assisted ERCP, EUS-guided transmural drainage procedures (hepaticogastrostomy, choledochoduodenostomy, or pancreaticogastrostomy), and EUS-guided antegrade stent insertion. The techniques for these EUS-guided interventions are the same as the ones used for conventional (non-altered anatomy) cases, with technical and clinical success rates of 85%-100% and acceptable complications[28]. The EUS-guided biliary drainage is performed as follows: the punctured site is first localized (intra or extra-hepatic bile duct), followed by a neo-tract creation (either by cauterization or non-cauterization methods), neo-tract dilation (either by graded dilation or balloon dilatation techniques) and finally a stent placement (either plastic or metallic stents)[5,6,28,29]. Details of the case series and case reports involving EUS-guided interventions in patients with surgically altered upper gastrointestinal anatomy are shown in Table 2.

EUS-guided CBD stone clearance

The conventional CBD stone removal fails in 5%-10% of cases[30,31], half of which require other treatments such as intraductal therapy (laser lithotripsy or electrohydraulic lithotripsy)[32,33]. Patients with a surgically altered anatomy are at an increased risk for clearance failure. Itoi *et al*[29] reported a case series of 5 patients with surgically altered upper gastrointestinal anatomy who underwent EUS-guided transhepatic antegrade CBD stone removal. The success rate of complete CBD stone clearance in one session was 60%. The group used transgastric (3 cases) or transjejunum (2 cases) puncture of the CBD with a 19- or 22-gauge needle and a contrast study to evaluate the CBD stones. Next, a guidewire was introduced, traversing the ampulla down to the duodenum, and the papilla was dilated in an antegrade fashion *via* inflation of a balloon catheter to push the stones down until they passed the ampulla. In cases of incomplete CBD stone clearance, a stent was inserted.

A randomized controlled trial showed an equivalent success rate of EUS-guided CBD stone removal compared to standard ERCP for the treatment of small (< 10 mm) CBD stones[34]. The success rate was calculated based on the CBD clearance rate, procedure time, and complications. In the trial, CBD cannulation was performed only under EUS guidance to demonstrate the feasibility of EUS-only CBD stone removal. Hence, the need for fluoroscopy was eliminated, providing a feasible alternative for treatment of pregnant patients or in bedside procedures performed in the intensive care unit.

EUS-guided enteral feeding tube placement and enteric anastomosis

EUS guidance can be utilized for placement of enteral feeding tubes, such as in the case of gastrostomy or internal anastomosis. Khashab *et al*[35] described a case report involving EUS-guided gastroenterostomy. For this technique, the desired duodenal or seminal loop closest to the EUS curvilinear echoscope was identified, and the lumen was punctured to allow passage of a 0.035-inch guidewire. The sphincterotome was inserted over the guidewire for infusion of water (< 500 mL to avoid metabolic derangement), and the gastroenteric tract was dilated in preparation for placement of the anastomotic stent. There is a risk of leakage with this technique due to the mobility of the small bowel, particularly the jejunum. A recent report by Ikeuchi *et al*[36] described an endoscopic treatment in a patient with afferent loop syndrome who underwent surgical bypass. The neo-gastrojejunal

Table 2 Clinical details of case series on endoscopic ultrasound-guided biliary drainage due to surgically altered anatomy

Ref.	Etiology	Procedure (technical success rate, %)	Complications
Iwashita *et al*[28] (*n* = 7)	Stone (*n* = 5) Stricture (*n* = 1) Malignant (*n* = 1)	Stone removal, 100% Dilation, 100% Stent placement, 100% (SEMS)	Minor: 28%
Itoi *et al*[29] (*n* = 14)	Stone (*n* = 14)	Single session clearance, 60% Overall clearance, 71.4%	None

SEMS: Self-expandable metallic stent.

tract was created using a curvilinear echoscope, and a 19-gauge needle passed from the stomach into the bowel lumen. After guidewire insertion, the two lumens were stabilized, and a lumen-apposing metal stent was inserted and deployed. This neo-type of lumen secures the tract and prevents leakage, the most common problem encountered with this type of procedure. Recently, Itoi *et al*[37] reported a case series of EUS-guided gastrojejunostomy using a special gastrojejunal tube with balloon fixation technique. This specific instrument was developed to stabilize the jejunal lumen allowing for easier creation of a neo-gastrojejunal tract while minimizing the occurrence of complications, especially of leakage or perforation. Firstly, the gastroscope with overtube was inserted into the strictured region, followed by placement of a guidewire *via* the strictured region to the jejunum. After the scope was removed, a special gastrojejunal tube with balloon fixation was inserted over the guidewire down to the jejunum (in the same fashion as a naso-jejunal tube placement). Secondly, the two balloons were inflated separately using contrast media followed by water infusion through the catheter (the opening of the water channel was located between these two balloons) to form a fixed jejunal segment-like tubular structure that was easy to find with an echoscope. Therefore, this particular jejunal segment was fully dilated and very close to the gastric wall. Then, EUS was performed to locate the puncture site, which appeared on the endosonographer as a sausage-like hypoechoic structure very close to the gastric wall. A 19-gauge needle was used to puncture into that segment and a guidewire was inserted and looped. Finally, a single-step lumen-apposing stent with cautery enable-access catheter unit (Hot AXIOS stent; Xlumena Inc., Mountain View, CA, United States) was inserted over the guidewire and deployed. EUS-guided gastrojejunostomy performed by Itoi *et al*[37] appears to be safer than two other techniques mentioned previously. The new incoming type of lumen-apposing stent is currently being developed, aiming at the possibility of greater ease of deployment compared to the previous model[38].

EUS-guided intra-abdominal abscess and collection drainage

EUS-guided drainage of an intra-abdominal abscess was first reported by Giovannini *et al*[39] in 2001. EUS-guided procedures have also been reported in the drainage of pelvic and hepatic abscesses (tuberculous, pyogenic/ruptured, and concealed), as well as for prostatic, mediastinum, sub-phrenic and retroperitoneal abscesses[40-50]. These procedures use the curvilinear echoscope to locate the abscess and verify that it is well formed. After ensuring that there are no intervening blood vessels, the abscess is punctured and contents aspirated with a 19-gauge needle. Next, a guidewire is inserted into the abscess and a contrast agent is injected to allow for visualization. Then, a small-caliber sphincterotome or catheter is inserted to flush the abscess cavity with saline (50 mL). The tract is then gradually dilated using either a graded dilation technique or a balloon dilation to allow for insertion of a 7 Fr, 8.5 Fr or 10 Fr straight stent, or a single/double pigtail stent with or without nasal-abscess drainage catheter for routine flushing of saline to enhance the drainage. Follow-up studies are still needed to verify resolution of the abscesses. The size of abscesses involved varied from 4 cm to 12 cm in diameter, and the time for resolution of these abscess ranged from 3 mo to 10 mo. Details on the case series involving EUS-guided intra-abdominal abscess drainage are shown in Table 3.

EUS-guided arteriovenous interventions

In 2000, Lee *et al*[51] was first to report EUS-guided injection of cyanoacrylate for stoppage of gastric variceal bleeding. In 2008, Levy *et al*[52] combined the glue injection with microcoil embolization to treat refractory gastric variceal bleeding. Since then, there have been additional reports demonstrating success of this procedure, with variceal and non-variceal re-bleeding rates of < 10% in most cases[53-58]. A similar clinical outcome was reported by Kinzel *et al*[59] for a 31-year-old man with duodenal variceal bleeding.

Kuramochi *et al*[60] used EUS to demonstrate the increased risk of recurrence of esophageal varices in high-risk patients who exhibited anterior branch dominance and flow velocity of 12 cm/s. EUS was found to be a very sensitive tool for early detection of heightened portal pressure, observed as dilation of the collateral circulation and small gastroesophageal varices, which are often missed *via* endoscopic evaluation[61]. EUS has been shown to improve the detection and diagnosis of gastroesophageal varices and collateral veins. Furthermore, EUS can be used as an endoscopic therapy of gastroesophageal varices, such as EUS-guided sclerotherapy of esophageal collateral vessels and EUS-

Table 3 Case series on endoscopic ultrasound-guided abscess drainage

Ref.	Location of abscesses/size	Route of drainage	Complete resolution/complications
Mandai *et al*[40] (n = 4)	Post-operative abscess/4.5 cm to 7.0 cm	TG	100%/none
Hadithi *et al*[41] (n = 8)	Perirectal (n = 6), Perisigmoid (n = 2)/4.0 cm to 9.0 cm	TR	100%/none
Puri *et al*[42] (n = 30)	Periprostatic (n = 4) Perirectal (n = 19) Perisigmoid (n = 7)/2.5 cm to 5.4 cm	TR/TS	93.4%/none Re-intervention 16.5%
Varadarajulu *et al*[43] (n = 25)	Perirectal (n = 19), Perisigmoid (n = 6)/5.0 cm to 6.9 cm	TR/TS	96%/none Re-intervention 3%
Wehrmann *et al*[44] (n = 20)	Para-esophageal (n = 15)/> 2 cm	TE	95%/mortality 7%

N/A: Data not available; TG: Transgastric route; TR: Transrectal route; TS: Transigmoid route; TE: Transesophageal route.

Table 4 Case series on endoscopic ultrasound-guided interventions in gastrointestinal oncology

Ref.	Diseases	Therapeutic interventions	Clinical response rate	Complications
Pai *et al*[70] (n = 8)	Pancreatic cyst (n = 6) Pancreatic NET (n = 2)	RFA	100% Complete, 20%	20% (pain)
Park do *et al*[71] (n = 11)	Pancreatic NET (n = 11)	Alcohol injection volume: 0.5 mL to 7.0 mL Mass size: 9 mm to 19 mm	61.50% Single session, 53.3%	36.30% (pancreatitis, pain)
DeWitt *et al*[72] (n = 22)	Pancreatic cyst (n = 22)	Alcohol + Paclitaxel Cyst size: 15 mm to 43 mm	Complete, 50% No response, 25%	13% (pancreatitis, peritonitis)
Oh *et al*[73] (n = 14)	Pancreatic cyst (n = 14)	Alcohol + Paclitaxel Mass size: 17 mm to 52 mm	Complete, 78%, No response, 7%	7% (pancreatitis)
Wang *et al*[74] (n = 23)	Pancreatic cancer (n = 23)	I^{125} seed	Partial pain control at 12 wk, 77.8%	12.50% (constipation, nausea/vomiting)

RFA: Radio frequency ablation; NET: Neuroendocrine tumor.

guided cyanoacrylate (glue) injection of gastric varices. EUS can also provide knowledge on the efficacy of pharmacotherapy of portal hypertension. Furthermore, EUS can provide assessment and prediction of variceal recurrence after endoscopic therapy and assessment of portal hemodynamics, such as the E-Flow Doppler ultrasound study of the azygous and portal veins. Additionally, Giday *et al*[62,63] demonstrated the feasibility of portal vein puncture for measuring pressure and injection of contrast agents without inducing liver injury in an animal model. This was followed by a case report by Buscaglia *et al*[64] describing EUS-guided insertion of an intrahepatic portosystemic shunt. Matthes *et al*[65] demonstrated the feasibility of EUS-guided portal vein embolization using Enteryx, a swine model. However, there is no report in the literature of these invasive portal vein interventions being applied in a clinical setting as of yet.

EUS-guided interventions in gastrointestinal oncology

Patients with pancreatobiliary malignancy who were not surgical candidates benefited from EUS-guided interventions for local control and treatment of tumors. Many treatment applications have been used in these cases, including ablative therapy (by absolute alcohol injection), thermal ablative therapy using radio frequency ablation, or cold therapy by the cryo-based probe, or a combination of the techniques. In all these techniques, the catheter was introduced through the echoscope channel, localizing the treatment location under EUS guidance[66,67]. Intra-tumoral injections of cell products such as tumoral dendritic cells, TNFerade or brachytherapy using I^{125} have also been reported[68,69]. However, the clinical outcomes of these therapeutic platforms were not impressive. Although newer treatment modalities, such as new cell types and new chemical situations, are being developed, there is yet too little information available for a reasonable discussion in this review. The large case series on local tumor treatments are shown in Table 4[70-74].

EUS in pregnancy

The incidence of pancreatobiliary disease, including choledocholithiasis, in pregnant women, is estimated to be 2%-6%[75]. However, ERCP, the conventional method for CBD clearance, is not appropriate for these patients due to risks associated with fluoroscopy. Thus, EUS-guided CBD stone removal with or without intraductal visualization *via* spyglass or cholangioscopy represents a suitable alternative. With this method, CBD diagnosis can be confirmed *via* radial EUS, followed by intraductal evaluation or CBD cannulation *via* duodenoscopy[76-78]. The position of the CBD stone can be confirmed through detection of aspirated bile content allowing for a complete stone removal and/or a stent placement to avoid recurrence.

EUS in children

EUS-guided interventions are equally feasible in pediatric patients. However, compared to adults, the child's organs and ducts are smaller, requiring extra care by the endoscopists who perform the procedures. The first EUS-guided intervention in a pediatric patient was reported in 1993, and it used a fine-needle aspiration (FNA)[79]. Since then, additional advanced procedures have been performed in pediatric patients[80,81]. In 2009, Attila *et al*[82] reported a case series of EUS procedures performed in 38 children. Of these, 30% of the cases used EUS with FNA, which established the correct diagnosis in 75% of the patients who underwent FNA without any complication. Recently, Scheers *et al*[83] also reported a case series of EUS procedures in 48 children. In this case series, 13 therapeutic EUS procedures, including 9 combined EUS-ERCP procedures, were performed without adverse events. The authors also proposed that the adult endoscopes and accessories can be used safely in children > 3 years of age (or > 15 kg body weight) and that a single endoscopic treatment session is feasible in children.

CONCLUSION

EUS-guided interventions can be used to treat various conditions, with favorable outcomes in most cases. In addition to pancreatic and biliary draining procedures, EUS guidance has been utilized in CBD stone clearance, enteral feeding tube placement, enteric anastomosis, and intra-abdominal abscess drainage. Such techniques are particularly well suited for patients with altered anatomy, pregnant women, or children. Increased knowledge of such special applications will help increase the success rates of these procedures and provide a foundation for additional advances and utilizations of EUS.

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ORIGINAL ARTICLE

Retrospective Study

Evidence to suggest adoption of water exchange deserves broader consideration: Its pain alleviating impact occurs in 90% of investigators

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Institutional review board statement: The study protocols relative to this retrospective study and the use of their data were reviewed and approved by the local Ethics Committee of the St. Barbara Hospital, Vitkovice Hospital and N. S. di Bonaria Hospital.

Informed consent statement: Patients agreed to the study by written consent at enrollment, even if the analysis used anonymous clinical data. For full disclosure, the details of the study are published on the website of the Institution of the St. Barbara Hospital under the section "Archivio Delibere" (Resolutions Archive).

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Abstract

AIM: To determine variations in colonoscopy real-time insertion pain among investigators using three different insertion techniques.

METHODS: From March 2013 through June 2014, 18-85-year-old diagnostic and 50-70-year-old screening patients were enrolled at each center to on-demand sedation colonoscopy with water exchange (WE), water immersion

(WI) and insufflation with air or CO_2 for insertion and withdrawal [air or carbon dioxide (AICD)]. Data were aggregated for analysis. Primary outcome: Variations in real-time maximum insertion pain (0 = none, 1-2 = discomfort, 10 = worst).

RESULTS: One thousand and ninety-one cases analyzed: WE (n = 371); WI (n = 338); AICD (n = 382). Demographics and indications were comparable. The WE group had the lowest real-time maximum insertion pain score, mean (95%CI): WE 2.8 (2.6-3.0), WI 3.8 (3.5-4.1) and AICD 4.4 (4.1-4.7), $P < 0.0005$. Ninety percent of the colonoscopists were able to use water exchange to significantly decrease maximum insertion pain scores. One investigator had high insertion pain in all groups, nonetheless WE achieved the lowest real-time maximum insertion pain score. WE had the highest proportions of patients with painless unsedated colonoscopy (*vs* WI, $P = 0.013$; *vs* AICD, $P < 0.0005$); unsedated colonoscopy with only minor discomfort (*vs* AICD, $P < 0.0005$), and completion without sedation (*vs* AICD, $P < 0.0005$).

CONCLUSION: Aggregate data confirm superiority of WE in lowering colonoscopy real-time maximum insertion pain and need for sedation. Ninety percent of investigators were able to use water exchange to significantly decrease maximum insertion pain scores. Our results suggest that the technique deserves consideration in a broader scale.

Key words: Colonoscopy; Painless colonoscopy; Water immersion; Water exchange; Colonoscopy pain

Core tip: Randomized controlled trials (RCTs) have shown water exchange (WE) to have considerable advantage in decreasing colonoscopy insertion pain. Assessment of individual investigators' performance using WE in RCTs is usually not reported. We assessed the performance of individual investigators in 3 RCTs comparing WE, water immersion and gas insufflation (with air or carbon dioxide) during insertion, to determine whether observations are reproducible across investigators and what factors might contribute to variations. Aggregate data show that individual investigators had significant variations in insertion pain scores and use of adjunct maneuvers together with short insertion time, but the pain alleviating impact of WE occurs in 90% of them. WE has the highest proportions of patients with painless unsedated colonoscopy; complete unsedated colonoscopy with only minor discomfort and completion without sedation.

Cadoni S, Liggi M, Falt P, Sanna S, Argiolas M, Fanari V, Gallittu P, Mura D, Porcedda ML, Smajstrla V, Erriu M, Leung FW. Evidence to suggest adoption of water exchange deserves broader consideration: Its pain alleviating impact occurs in 90% of investigators. *World J Gastrointest Endosc* 2016; 8(2): 113-121 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i2/113.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i2.113

INTRODUCTION

Water exchange (WE) and water immersion (WI) are two colonoscopy techniques that entail infusion of water to distend the lumen during the insertion phase. Randomized controlled trials (RCTs) have shown WE (airless insertion, infused water aspirated predominantly during insertion to clear the view and minimize distension) to have considerable advantage in decreasing colonoscopy real-time maximum insertion pain when compared with WI (water infused as adjunct to insufflation, and aspirated predominantly during withdrawal without attempting to maximize colon cleanliness during insertion) and air[1-3] or carbon dioxide insufflation[3,4]. WE is a relatively new technique, and requires new maneuvers not entirely intuitive to colonoscopists[5]. In spite of this, in a previous report focused on individual investigators' performance[6], WE has shown reproducibility and repeatability in decreasing maximum insertion pain, usually not reported in RCTs. Some of the factors associated with difficult colonoscopy (*e.g.*, prior abdominal surgery, low body mass index) and insertion pain are favorably influenced by WE[2,3,7,8].

We assessed the performance of individual investigators in three recently completed RCTs in a multinational setting, to determine whether the effect of WE in reducing real-time maximum insertion pain is reproducible across investigators and what factors (*e.g.*, use of adjunct maneuvers of loop reduction and abdominal compression, insertion time, *etc.*) might contribute to variations among them.

MATERIALS AND METHODS

Patient-related and procedure-related factors were collected prospectively at our centers (NCT01781650, 01780818, 01954862): St. Barbara Hospital, Iglesias (Italy); N. S. di Bonaria Hospital, San Gavino Monreale (Italy) and the Vitkovice Hospital, Ostrava (Czech Republic).

From March 2013 through June 2014, 18-85-year-old diagnostic and 50-70-year-old screening patients were enrolled and randomized to WE, WI or insufflation with air or carbon dioxide (AICD) at each site. Sedation was available on-demand at patients' request[2,3]. Local Ethics Committees approved the protocols. Written informed consent was obtained from all patients at enrollment. All authors had access to the study data, reviewed and approved the final manuscript. Statistical review of the study was performed by a biomedical statistician.

Study procedures

Colonoscopies were performed by 10 board-certified endoscopists, five with experience in about 10000 AICD, 260 WE and 120 WI. One investigator had experience in about 7200 AICD, 260 WE, 800 WI. The last four investigators had experience in about 3000-7000 AICD and 150 WE. One had experience in 800 WI, the remaining three in 90 WI.

A split-dose bowel preparation was used to clean the colon[2,3]. Enrolled patients were assigned to the different insertion techniques by computer-generated lists, with block allocation and stratification based on participating endoscopists. Group assignment was kept in sealed envelopes that were opened just before the start of the procedure. The patients, but not endoscopists and assisting nurses, were blinded to the insertion method used: The monitors were concealed from patients' view. Endoscopists were blinded to insufflation gas used: Light source and insufflators were concealed from the view. At discharge patients were asked to guess which insertion method had been used (infusion of water or insufflation), and investigators which gas had been insufflated. If no more than half of the responses were correct, their blinding was considered adequate[2,3].

Colonoscopy began with the patients in the left lateral position without premedication. High-resolution wide-angle variable-stiffness adult video colonoscopes (Olympus HD 180) were used. Variable stiffness was used at the discretion of the investigators, but its record was not kept[2,3]. Cardiopulmonary function was monitored throughout.

In patients randomized to WE and WI, insufflation was turned off before starting the procedure. After the rectosigmoid junction was reached, the colon was irrigated with water at 37 ℃ using flushing pumps[2,3].

Water exchange involved infusion of water during insertion to distend the lumen to the minimum required to reach the cecum. When opaque water was encountered, infusion and near-simultaneous suction were applied until clear water was in front of the instrument. Residual air pockets, feces and infused water were removed predominantly during insertion[2,3].

Water immersion involved the infusion of water during the insertion phase to aid passage to the cecum without attempting to clear the colon contents, with limited use of insufflation when necessary[2,3]. Infused water was removed predominantly during withdrawal.

In the AICD group colonoscopy was performed in the usual fashion with the minimal insufflation required to reach the cecum[2,3]. In all arms insufflation was used during withdrawal to obtain adequate distension of the lumen for exploration[2,3].

In all groups loop reduction, position change and abdominal compression were applied in that sequence as needed when the instrument failed to advance, and not per protocol at determined anatomic locations. Cecal intubation was defined as reaching beyond the ileocecal valve with adequate visualization of the appendix orifice.

Pain assessment and sedation

Pain was assessed using a numeric rating scale (NRS) with faces outlines and verbal descriptors, with a score 0 = absence of pain, 1-2 = simply "discomfort", 10 = the worst possible pain. Before the procedure, a nurse explained the NRS to the patients. They were informed that the request for pain information was meant to assess the need and dosage of sedation[2,3], and to let the colonoscopist be alerted to the need to use maneuvers to minimize discomfort (*e.g.,* removal of colonic content, loop reduction, change in patient position and/or abdominal compression). At the discretion of the assisting nurse, at irregular intervals, patients were asked about discomfort or pain several times during the procedure and encouraged to report it spontaneously. Responses were recorded and the real-time maximum insertion pain score noted. On-demand sedation was offered at a NRS score ≥ 2 (discomfort). If patients accepted, sedation was started with an intravenous dose of 2 mg of midazolam, with step-ups of 1 mg (up to 5 mg) if the patients continued to report pain[2,3]. To avoid bias by the colonoscopist, medication was administered based on the patients' confirmation that the pain was no longer tolerable, and not at the discretion of the endoscopist. No other analgesic or sedative medications were administered. At discharge, a blinded nurse recorded patients' recalled maximum insertion pain using the same NRS in the absence the personnel who performed the procedure.

Study endpoints

The primary outcome was real-time maximum insertion pain score recorded during the insertion phase of colonoscopy. Secondary outcomes included recalled pain at discharge, individual performance of investigators in terms of several procedural outcomes; analysis of painless unsedated colonoscopy, unsedated colonoscopy completed with only discomfort (NRS = 1-2), and complete unsedated colonoscopy with any pain score.

Statistical analysis

Standard descriptive statistics were used to assess the distribution of the study variables and to compare them. Pain values were computed using mean at 95%CI and analyzed by using the *t*-test and analysis of variance (ANOVA) where appropriate. *P* values < 0.05 were considered significant.

RESULTS

The database stored data relative to 1091 patients randomly allocated to WE (n = 371), WI (n = 338) or AICD (n = 382). Overall, demographics, body mass index (BMI), previous abdominal surgery and indications were comparable (Table 1).

In greater detail, age was comparable among the study groups and individual investigators. Abdominal pain had comparable proportions among methods and individual investigators, except for Investigator number 1 and Investigator number 8 that had significantly higher proportions in the WE group. The other indications were comparable among methods, except for Anemia (0.048).

Table 2 shows that female patients were equally

Table 1 Water-aided colonoscopy and insufflation colonoscopy: Baseline characteristics and indications of 1091 patients

	WE (n = 371)	WI (n = 338)	AICD (n = 382)	P value[1]
Age, yr, mean (± SD)	59 (12.2)	59 (11.6)	59 (12.0)	0.627
Females, n (%)	149 (40.2)	140 (41.4)	151 (39.5)	0.873
Males, n (%)	222 (59.8)	198 (58.6)	231 (60.5)	
BMI, mean (± SD)	26.7 (4.8)	26.5 (4.7)	26.4 (4.7)	0.607
Previous abdominal surgery, n (%)	141 (38.0)	116 (34.3)	116 (30.4)	0.087
Indications for colonoscopy, n (%)				
Abdominal pain	68 (18.3)	52 (15.4)	59 (15.4)	0.127
Bleeding	90 (24.3)	89 (26.3)	108 (28.3)	0.076
Change in bowel habits	73 (19.7)	64 (18.9)	60 (15.7)	0.977
Anemia	8 (2.2)	12 (3.6)	7 (1.8)	0.048
Diverticulosis	4 (1.1)	5 (1.5)	7 (1.8)	0.787
Other	46 (12.4)	37 (10.9)	46 (12.0)	0.403
Screening	82 (22.1)	79 (23.4)	95 (24.9)	0.361

[1]ANOVA. n: Number of patients; WE: Water exchange for insertion, insufflation with air or CO_2 for withdrawal; WI: Water immersion for insertion, insufflation with air or CO_2 for withdrawal; AICD: Insufflation with air or CO_2 for insertion and withdrawal; SD: Standard deviation.

Table 2 Variations among investigators

	Real-time maximum insertion pain, mean (95%CI)			P value					
	WE (n =371)	WI (n = 338)	AICD (n = 382)						
All investigators	**2.8 (2.6-3.0)**	**3.8 (3.5-4.1)**	**4.4 (4.1-4.7)**	**< 0.0005[1] WE *vs* WI < 0.0005[2] WE *vs* AICD < 0.0005[2] WI *vs* AICD 0.002[2]**					
Investigator	**WE**	**WI**	**AICD**	**Females (%)**	**BMI (± SD)**	**Previous abdominal surgery (%)**	**Abdominal compression (%)**	**Loop reduction (%)**	**Insertion time, min (± SD)**
1	2.1 (1.7-2.5)	4.0 (3.4-4.7)	4.7 (4.1-5.3)	46.3	26.1 (4.9)	51.3	57.5	61.3	13 (6.5)
2	2.9 (2.4-3.3)	3.3 (2.8-3.9)	4.1 (3.5-4.7)	32.9	27.0 (4.8)	46.8	67.1	63.3	11 (5.5)
3	2.3 (1.0-3.6)	2.3 (1.0-3.6)	4 (2.9-5.2)	28.6	27.5 (4.4)	7.1	57.1	7.1	11 (4.4)
4	2.4 (1.7-3.2)	1.9 (0.6-3.3)	2.8 (2.0-3.5)	28.6	25.6 (4.2)	10.7	71.4	21.4	15 (6.7)
5	2.9 (1.8-4.0)	3.7 (2.3-5.1)	3.5 (2.2-4.8)	46.2	24.6 (3.3)	7.7	92.3	84.6	9 (2.8)
6	2.4 (1.6-3.3)	2.6 (1.5-3.7)	3.5 (2.5-4.5)	60.9	28.4 (6.8)	13.0	73.9	52.2	10 (4.0)
7	2.4 (1.6-3.2)	3.7 (2.3-5.1)	4.3 (3.0-5.6)	17.6	26.4 (2.5)	41.2	64.7	82.4	12 (7.2)
8	2.8 (2.0-3.6)	2.4 (1.7-3.0)	2.4 (1.4-3.3)	50.0	25.6 (4.0)	35.7	92.9	92.9	15 (5.2)
9	2.9 (2.3-3.5)	4.1 (3.4-4.9)	6.0 (5.3-6.7)	37.7	28.4 (5.2)	45.9	36.1	34.4	9 (3.1)
10	5.3 (4.4-6.2)	7.1 (6.3-8.0)	7.0 (6.2-7.9)	50	27.2 (5.6)	35.7	21.4	10.7	8 (3.0)
P values	< 0.0005[1]	< 0.0005[1]	< 0.0005[1]	0.074[1]	0.025[1]	< 0.0005[1]	< 0.0005[1]	< 0.0005[1]	< 0.0005[1]

[1]ANOVA; [2]χ^2. n: Number of patients; WE: Water exchange for insertion, insufflation with air or CO_2 for withdrawal; WI: Water immersion for insertion, insufflation with air or CO_2 for withdrawal; AICD: Insufflation with air or CO_2 for insertion and withdrawal; SD: Standard deviation; BMI: Body mass index.

distributed among study groups and individual investigators. There were significant differences in terms of BMI within the WE and WI groups (P = 0.025 and P < 0.0005, respectively). The AICD group had the lowest proportion of patients with previous abdominal surgery, comparable among individual investigators (P = 0.405). Among the 10 individual investigators there were significant differences in terms of use of abdominal compression, loop reduction and cecal intubation time.

Primary outcome analysis

The number of patients examined by each colonoscopist

Table 3 Water exchange for insertion group, significant factors associated with increased pain score of Investigator number 8 *vs* all the other investigators, *n* (%)

	Investigator number 8 (*n* = 28)	All other investigators (*n* = 343)	*P* value
Abdominal pain as indication, females and males	11 (39.3)	57 (16.6)	0.003[1]
Females with abdominal pain as indication	9 (32.1)	21 (6.1)	< 0.0005[1]
Females with previous abdominal surgery, any indication for colonoscopy	6 (21.4)	24 (7.0)	0.018[1]

[1]χ^2.

Table 4 Investigator number 8, significant differences associated with increase in real-time maximum insertion pain score among methods, *n* (%)

	WE (*n* = 28)	WI (*n* = 28)	AICD (*n* = 24)	*P* value
Females and males, abdominal pain as indication	11 (39.3)	2 (7.1)	7 (29.2)	0.017[1] WE *vs* WI 0.004[2] WE *vs* AICD 0.446[2] WI *vs* AICD 0.064[2]
Females with abdominal pain as indication	9 (32.1)	1 (3.6)	3 (12.5)	0.008[1] WE *vs* WI 0.005[2] WE *vs* AICD 0.059[2] WI *vs* AICD 0.352[2]
Females with abdominal pain as indication and previous abdominal surgery	6 (21.4)	1 (3.6)	1 (4.2)	0.031[1] WE *vs* WI 0.043[2] WE *vs* AICD 0.069[2] WI *vs* AICD 0.911[2]

[1]ANOVA; [2]χ^2; *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO_2 for withdrawal; WI: Water immersion for insertion, insufflation with air or CO_2 for withdrawal; AICD: Insufflation with air or CO_2 for insertion and withdrawal; SD: Standard deviation; BMI: Body mass index.

ranged from 12 to 80 per group.

Table 2 shows the analysis of the performance of the individual investigators. There were significant differences of mean real-time maximum insertion pain score among WE, WI and AICD, mean (95%CI): WE 2.8 (2.6-3.0), WI 3.8 (3.5-4.1) and AICD 4.4 (4.1-4.7), *P* < 0.0005; differences were significant also within each study group. WE consistently showed the lowest real-time maximum insertion pain scores, and with the exception of Investigator number 8, who showed WE to have higher pain scores than all the other insertion techniques, the trend that WE was the least painful was observed in all the rest of investigators, regardless of their prior experience with the insertion technique used (Table 2). The WE group showed significant variations in terms of BMI, previous abdominal surgery, abdominal compression, loop reduction and insertion time among individual investigators.

Table 3 shows that, compared with all the other investigators, the WE group of Investigator number 8 had a significantly higher proportion of patients with abdominal pain as indication (39.3% *vs* 16.6%, *P* = 0.003), cohort that included mostly irritable bowel syndrome (IBS) patients; and a significantly higher proportion of female patients (32.1% *vs* 7.0%, *P* < 0.0005) with a significantly higher incidence of previous abdominal surgery: 21.4% *vs* 7.0%, *P* = 0.018 (Table 3).

The same analysis across Investigator's number 8 study groups (Table 4) showed that his WE group had a higher proportion of cases with abdominal pain as indication (ANOVA among groups *P* = 0.017; WE 39.3% *vs* WI 7.1%, *P* = 0.004); in particular women (ANOVA among groups *P* = 0.008; WE 32.1% *vs* WI 3.6%, *P* = 0.005; *vs* AICD 12.5%, *P* = 0.059). This WE group of female patients with abdominal pain as indication showed also a higher incidence of previous abdominal surgery (ANOVA among groups *P* = 0.031): WE 21.4% *vs* WI 3.6%, *P* = 0.043; *vs* AICD 4.2%, *P* = 0.069. The comparisons of WE *vs* AICD lacked enough power (type II error) to show significance.

Investigator number 10, with infrequent use of loop reduction or abdominal compression and short mean insertion time (Table 2), had high real-time maximum insertion pain scores in all groups, but the use of WE brought insertion pain down in this investigator: ANOVA among groups *P* = 0.004.

Secondary outcomes analysis

Compared with AICD and WI, WE had the highest proportion of patients with painless unsedated colonoscopy (Table 5): 13.5%, *vs* WI 7.7% (*P* = 0.013); *vs* AICD 6.0% (*P* < 0.0005). Compared with AICD, WE and WI showed a significantly higher proportion of unsedated colonoscopies with only discomfort, corresponding to NRS values of 1-2: WE 36.1%, *vs* WI 31.4% (*P* =

Table 5 Pain during insertion, patients' tolerance and sedation, *n* (%)

	WE (*n* = 371)	WI (*n* = 338)	AICD (*n* = 382)	*P* value
Painless unsedated colonoscopy[2]	50 (13.5)	26 (7.7)	23 (6.0)	WE *vs* WI 0.013[1] WE *vs* AICD < 0.0005[1] WI *vs* AICD 0.374[1]
Unsedated, completed with only discomfort[2]	134 (36.1)	106 (31.4)	87 (22.8)	WE *vs* WI 0.180[1] WE *vs* AICD < 0.0005[1] WI *vs* AICD 0.009[1]
Completed without sedation	321 (86.5)	287 (84.9)	292 (76.4)	WE *vs* WI 0.537[1] WE *vs* AICD < 0.0005[1] WI *vs* AICD 0.004[1]
On-demand sedation	50 (13.5)	51 (15.1)	90 (23.6)	WE *vs* WI 0.537[1] WE *vs* AICD < 0.0005[1] WI *vs* AICD 0.004[1]

[1]χ^2; [2]Pain score based on numeric rating scale (NRS): 0 = absence of pain, 1-2 = discomfort, 10 = maximum pain. *n*: Number of patients; WE: Water exchange for insertion, insufflation with air or CO_2 for withdrawal; WI: Water immersion for insertion, insufflation with air or CO_2 for withdrawal; AICD: Insufflation with air or CO_2 for insertion and withdrawal; SD: Standard deviation.

0.180); *vs* AICD 22.8% (*P* < 0.0005); WI *vs* AICD *P* = 0.009 (Table 5). WE and WI achieved also a significantly higher proportion of procedures completed without sedation: WE 86.5%, *vs* WI 84.9% (*P* = 0.537); *vs* AICD 76.4% (*P* < 0.0005); WI *vs* AICD *P* = 0.004 (Table 5). Accordingly, WE and WI showed low proportions of patients requesting on-demand sedation: WE 13.5%, *vs* WI 15.1% (*P* = 0.537); *vs* AICD 23.6% (*P* < 0.0005); WI *vs* AICD *P* = 0.004 (Table 5).

Procedural outcomes

Cecal intubation rates (WE 98.7%, WI 97.9% and AICD 97.9%; *P* = 0.692) and total procedure times [minutes (± standard deviation, SD): WE 23 (9.7), WI 22 (11.7) and AICD 22 (11.0), *P* = 0.177] were comparable. A complete report has already been presented elsewhere[2,3]. Comparisons of amount of water infused and aspirated during insertion and during withdrawal attested to the correct application of WE and WI methods[2,3].

DISCUSSION

In this study aggregate data confirm superiority of WE in lowering insertion pain compared with WI and AICD. The pain alleviating impact of water exchange shows the lowest mean real-time maximum insertion pain scores in 90% of the investigators, despite their pain scores were significantly different within the WE, WI and AICD groups, and regardless their significantly different individual performances in terms of use of adjunct maneuvers and insertion time (Table 2). A plausible explanation of the effect of WE in decreasing real-time maximum insertion pain is the avoidance of the variable elongation of the colon induced by different amounts of insufflated gas, with the associated loop formation[9] that leads to insertion pain[10]. Full understanding, however, will require additional investigation.

Previous abdominal surgery is associated with higher colonoscopy pain score[11-14] or with difficult procedures[15]. The AICD group showed the lowest proportion of patients with previous abdominal surgery and had comparable BMI values among individual investigators; nevertheless, AICD pain scores were almost invariably higher than the other two groups (Table 2). Compared with WE, WI had a lower proportion of patients with previous abdominal surgery; and yet also WI showed a trend toward higher pain scores than WE (Table 2).

With the exception of Investigator number 8, the consistent pattern of pain scores being lowest in the WE group qualifies WE as the best method for achieving low pain scores during the insertion phase of colonoscopy, with a reproducible effect among different colonoscopists. Several factors contributed to the aberrant finding of Investigator's number 8 higher real-time maximum insertion pain score in the WE group compared with the WI and AICD groups: His WE group had a significantly higher proportion of female patients with abdominal pain as indication (this cohort comprised IBS cases) and with previous abdominal surgery. All these are risk factors for difficult[15] or painful colonoscopy[1,11-14,16-22], with expected laborious intubation and increased need for sedation[11,22,23].

Moreover, Investigator number 8 had experience in only 150 WE and 90 WI procedures. WE is a relatively new technique, and requires new maneuvers not entirely intuitive to colonoscopists. Collectively, all these factors contributed to the higher real-time maximum insertion pain score achieved in his WE group of patients.

Our data show that WE is effective in achieving significantly higher proportions of painless unsedated procedures, completion with only minor discomfort or without sedation. These two last outcomes are also achieved by WI.

Unsedated colonoscopy represents an important option for many patients[24,25] and has important implications in terms of patient satisfaction, medical related complications[26,27] and cost savings in health care systems, particularly in settings where the use of sedation is discretionary and targeted also to low-risk patients[28,29].

The scheduled unsedated option may also have an impact on no-show due to lack of an escort, improving patients' adherence to colonoscopy, particularly important in screening settings[30].

Promotion of on-demand sedation colonoscopy and successful completion of the unsedated option minimizes institutional resources and lessens patients' burdens[6,31].

Multiple published reports have indicated colonoscopists around the world were able to harness the pain reduction impact of WE[2,3,7,8,32-40].

The limitations of our study require comment. The endoscopists and the nurse assistants were not blinded to the WE and WI insertion techniques. However, interactions with patients were standardized, colonoscopists' bias was minimized and pain recording was very accurate[2,3]. The unblinded real-time maximum insertion pain scores obtained during colonoscopy were internally validated by correlating them with the blinded recalled maximum insertion pain scores recorded at discharge: the Pearson correlation range was 0.6-0.9 (P < 0.0005)[2,3]. The blinded pain recording after the procedure validated the unblinded one collected during the examination[2,3]. Mean correct patients' guesses about insertion method used (36%) and investigators' about insufflated gas (41%) confirmed their adequate blinding[2,3].

Our study has certain notable features. To the best of our knowledge, it has the largest sample of multiple individual investigators' real-time maximum insertion pain scores obtained in a head-to-head randomized controlled comparison of WE, WI and AICD. Patients were recruited from a routine clinical setting in different community hospitals at multinational sites. The important finding is the reproducibility and repeatability of WE in attenuation of maximum insertion pain when compared with WI and AICD.

In summary, in this head-to-head randomized controlled comparison of WE, WI and AICD with reliable real-time maximum insertion pain scores, minimization of investigators' bias and adequate patient blinding, despite variations in pain scores by individual investigators, WE is superior to WI and AICD in attenuating real-time maximum insertion pain.

We conclude that the high proportion of colonoscopists able to use WE to decrease insertion pain in the current study, as well as in previous published reports, suggest that the technique deserves consideration in a broader scale.

COMMENTS

Background

Water exchange (WE) and water immersion (WI) are two colonoscopy techniques that entail infusion of water to distend the lumen during the insertion phase. WE is characterized by airless introduction to the cecum, infused water is aspirated predominantly during this phase to clear the view and minimize distension. In WI water is infused as an adjunct to insufflation and aspirated predominantly during withdrawal, without attempting to maximize colon cleanliness during insertion. Randomized controlled trials (RCTs) have shown WE to have considerable advantage in decreasing colonoscopy real-time maximum insertion pain when compared with WI or with air or carbon dioxide insufflation. WE shows its beneficial effect in decreasing colonoscopy pain also in patients presenting with factors associated with difficult and painful colonoscopy (*e.g.*, prior abdominal surgery, low body mass index).

Research frontiers

The authors assessed the performance of individual investigators in three recently completed RCTs in a multinational setting, to determine whether the effect of WE in reducing real-time maximum insertion pain is reproducible across investigators, and what procedural factors (*e.g.*, use of adjunct maneuvers of loop reduction and abdominal compression, insertion time, *etc.*) might contribute to variations among them.

Innovations and breakthroughs

The study has the largest sample of multiple individual investigators' real-time maximum insertion pain scores obtained in a head-to-head randomized controlled comparison of WE, WI and air or carbon dioxide (AICD). Patients were recruited from a routine clinical setting in different community hospitals at multinational sites. The data confirm superiority of WE in lowering insertion pain compared with WI and AICD. Its pain alleviating impact shows the lowest mean real-time maximum insertion pain scores in 90% of the investigators, despite their significantly different insertion pain scores within the WE, WI and AICD groups, along with significantly different individual performances in terms of use of adjunct maneuvers and insertion time.

Applications

WE achieves higher proportions of painless unsedated procedures, or completed with only minor discomfort, decreasing the need for sedation. Promotion of on-demand sedation colonoscopy and successful completion of the unsedated procedures lessens patient's burdens.

Terminology

WE: A colonoscopy insertion technique that entails airless insertion; water is infused to facilitate progression of the instrument to the cecum and is aspirated predominantly during this phase to clear the view and minimize distension. WI: A colonoscopy insertion technique that entails infusion of water as an adjunct to insufflation to help reaching the cecum; water is aspirated predominantly during withdrawal, without attempting to maximize colon cleanliness during insertion.

Peer-review

The article described the difference in colonoscopy real-time maximum insertion pain among WE, WI and AICD and among individual investigators in routine clinical settings. It is useful to analyze colonoscopy pain produced by different techniques in order to reduce the suffering of patients. It is a meaningful research in clinical practice. The study had a logical design in methods, the analysis of the difference of pain among WE, WI and AICD was detailed and produced credible results.

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