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Review Article

Third space endoscopy: Current evidence and future development

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A B S T R A C T

Therapeutic endoscopy has evolved tremendously over the past decades and the development of submucosal endoscopy opens the third space for treatment of gastrointestinal diseases. This review focused on the recent development in third space endoscopy, with introduction of its development from peroral endoscopic myotomy (POEM) to beyond. Two recent randomized trials comparing POEM against pneumatic dilation and laparoscopic Heller myotomy (LHM) demonstrated significantly better relief of dysphagia for POEM compared to pneumatic dilation, while POEM achieved similar outcomes compared to LHM. Apart from achalasia, third space endoscopy is now developed to manage spastic esophageal motility disorders, esophageal diverticular diseases, gastroparesis, and Hirschsprung's disease. Subepithelial tumors can also be resected through tunneling and endoscopic full-thickness resection. In future, third space endoscopy will be one of the major areas in development of diagnostic and therapeutic endoscopy using novel imaging technologies and therapeutic devices.

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Keywords: Peroral endoscopic myotomy; Peroral endoscopic tumor resection; Submucosal endoscopy; Submucosal tunneling endoscopic resection; Third space endoscopy

Introduction

In the past 70 years, rapid advancement in endoscopy has crucial impact on the management of gastrointestinal (GI) diseases.¹ Today, endoscopy represents the standard of practice for diagnosis and treatment of pathologies within the GI lumen. Traditionally, endoscopic interventions have been confined to within the lumen, which is known to endoscopists as “the first space”.² From first polypectomy for treatment of colorectal polyp in 1969 by Dr. Shinya,³ endoluminal interventions have seen tremendous progress with more aggressive techniques for endoscopic resections like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).^{4,5}

Imbued with visionary imagination, pioneers in endoscopy aimed to perform “No Scar” flexible endoscopic surgery within the peritoneal space. Natural orifice transluminal endoscopic surgery (NOTES), which began in 2004 with the idea of transgastric peritoneoscopy,⁶ had been mostly a proof of concept development in transvaginal and transgastric procedures.⁷ Nevertheless, endoscopic exploration into the peritoneal space, the “second space”² of endoscopy, has paved way to the development of im-

portant technical advances in the field. One particularly important technique designed for safe breaching of the GI wall, submucosal tunneling, was first described in porcine models by Sumiyama et al⁸ in 2007. The submucosal endoscopy with mucosal flap safety valve (SEMF) technique opened a novel submucosal world for endoscopic intervention. Pasricha et al⁹ conducted a preclinical research on submucosal endoscopic myotomy in animal models using the principles of SEMF. Inoue and colleagues performed the first human peroral endoscopic myotomy (POEM) for management of achalasia in 2008.¹⁰ The same group published the world's first series of POEM for treatment of achalasia in 17 patients,¹¹ demonstrating POEM as an effective and safe treatment, unleashing a decade of innovation and research in submucosal endoscopy—the third space for endoscopy.

In this review, we will look into the current state and future perspective of submucosal endoscopy, also known as “third space endoscopy” amongst other names such as “submucosal endoscopy” or “submucosal endoscopic surgery”.² These procedures are based on endoscopically creating the third space, i.e., submucosal space, between the muscularis mucosa and the muscularis propria, while keeping the mucosal flap intact thus enabling intervention

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up to the muscularis propria level or further into the mediastinum or peritoneum^{12,13} while preventing GI luminal content leak. Latest evidence on third space endoscopic procedure such as POEM, submucosal tunnel endoscopic resection (STER), and endoscopic full-thickness resection (EFTR) will be covered, based on literature search on PubMed/MEDLINE and EMBASE with keywords including: third space endoscopy; submucosal endoscopy; peroral endoscopic myotomy; STER; and EFTR. All types of articles including prospective randomized trial, case control studies, retrospective cohort studies and case series as well as systematic reviews and meta-analysis were included in this review.

Endoscopic Submucosal Dissection: The Progenitor

ESD¹⁴ is the first endoscopic procedure that involved direct visualization and dissection at the submucosal space. Its development was to overcome limitations of EMR in achieving en-bloc resection of neoplasia larger than 20 mm. Today, ESD is well established and extensively applied¹⁵ for treatment of esophageal superficial squamous cell carcinoma (SCC), gastric superficial neoplastic lesions,¹⁶ and early colorectal neoplasia. Systematic reviews and meta-analyses showed that ESD obtained high en-bloc resection rates, high histological complete resection rates, and lower recurrence rates for esophageal superficial SCC¹⁵ as well as superficial gastric neoplastic lesions.¹⁷⁻¹⁹

POEM for Achalasia: The Archetype of Third Space Endoscopy

Achalasia is the most common primary esophageal motility disorder characterized by failure of lower esophageal sphincter (LES) relaxation and esophageal aperistalsis. Over the past decade, POEM was successfully translated from a clinical novelty into an established treatment option for achalasia patients,²⁰ with clinical studies confirming the its efficacy (Fig. 1). Table 1 summarized the currently available reviews which pooled outcomes from case series of POEM, which reported high clinical success and reasonable safety profile.²¹⁻²⁶

Compared to conventional treatments including endoscopic pneumatic dilatation and laparoscopic Heller myotomy (LHM), POEM has the advantage of achieving the definitiveness of myotomy without surgical incisions. Recent randomized trial provided quality clinical evidence in comparing the outcomes of POEM to the established endoscopic and surgical treatments. Ponds et al²⁷ conducted a prospective randomized trial comparing POEM against pneumatic dilatation for patients with achalasia. Among 133 patients randomized to either treatment, those treated by POEM had significantly higher rate of relief of dysphagia compared to pneumatic dilatation at 24 months after treatment (92% vs 54%; $P < 0.01$). Werner et al²⁸ conducted a randomized controlled trial (RCT) comparing POEM against LHM plus Dor's fundoplication, recruiting 112 patients in the POEM arm and 109 patients in the LHM arm. Clinical success (defined as Eckardt score ≤ 3) at 2-year follow-up was noted to be 83.0% in POEM group

Fig. 1. Peroral endoscopic myotomy for treatment of achalasia. (A) Mucosal incision in anterior approach using Triangle Tip knife. (B) Development of submucosal tunnel from esophagus to gastric cardia. (C) Selective inner circular myotomy starting from esophageal side. (D) Selective inner circular myotomy extending to the high gastroesophageal junction. (E) Closure of mucosal incision using endoclips. (F) Complete closure of the mucosal incision using endoclips.

Table 1 Summary of the Results of Systematic Reviews on Clinical Outcomes of Peroral Endoscopic Myotomy (POEM)

Author	Search period	Studies included	No. of cases	POEM operative time (min)*	Clinical success	Complication (%)	Mean follow-up GERD duration (mo)	GERD (%)
Barbieri et al (2015) ²¹	2010–2013	16	551	156 (42–112)	93% as defined by clinically relevant improvement in dysphagia	Adverse event (14)	6	13
Talukdar et al (2015) ²²	2005–2014	19	1,045	NA	Significant reduction in Eckardt score overall effect size (Z) of -7.95 ($P < 0.0001$)	Bleeding (1.0) Mediastinal emphysema (5.2) Perforation (2.3) Pleural effusion (17.4) Pneumonia (9.9) Pneumoperitoneum (16.2) Pneumothorax (8.7) Subcutaneous emphysema (21.8)	6.5	10.9
Akintoye et al (2016) ²³	Up to 2014	27	1,733	88 ± 6	97% as defined by Eckardt score < 3	Bleeding (0.6) Esophageal perforation (0.3) Mucosal injury (9.4) Pleural effusion (9.5) Pneumoperitoneum (13) Pneumothorax (5.4) Subcutaneous emphysema (11)	8.8	15
Crespin et al (2017) ²⁴	Up to February 2015	19	1,310	NA	89.4% defined as Eckardt score < 3 in all studies except one using Eckardt score < 4	Mucosal perforation (9.0) Pleural effusion (10.1) Pneumonia (7.9) Pneumoperitoneum (16.9) Pneumomediastinum (4.4) Pneumothorax (5.3) Subcutaneous emphysema (10.0)	11.1	NA
Andolfi and Fisichella (2019) ²⁵	2008–2018	20	449	NA	95.8% defined by relevant clinical improvement of dysphagia	NA	20.9	NA
Li et al (2019) ²⁶	Up to November 2017	10	373	66.7 (17.9–220)	92.9% defined as Eckardt score ≤ 3	Mediastinal emphysema (5.6) Mucosal perforation (7.2) Pneumothorax (1.9) Pneumoperitoneum (5.6) Subcutaneous emphysema (4.0) Others (4.0)	30.0	10.2

GERD, gastroesophageal reflux disease; NA, not available.

*Values are presented as median (range) or mean $\pm$ standard deviation.

and 81.7% in LHM plus fundoplication group ($P = 0.007$ for non-inferiority). The POEM group had shorter procedure time by 13.81 minutes (95% confidence interval [CI], 6.26–21.36). There was no difference between the two groups in terms improvement of LES integrated relaxation pressure or the Gastrointestinal Quality of Life index. Another recent RCT by Moura et al²⁹ compared POEM against LHM, recruiting 20 patients into either arm. The study noted no statistically significant difference between the two groups in terms of Eckardt score, height of barium contrast column, LES pressure, and adverse events rate at 1 year, with the POEM group having significant shorter operative time (95.7 vs 218.7 minutes, $P < 0.001$).

However, gastroesophageal reflux disease (GERD) after POEM remains a significant sequela after POEM, affecting range of 10.2% to 15% of patients^{23,26} in the systematic reviews summarized in Table 1. The incidence of GERD was especially higher in Western series compared to those in Asia, up to 72.2% in one study.³⁰ This phenomenon was reproduced in the aforementioned randomized trials, with POEM arm more likely to develop reflux esophagitis than the pneumatic dilatation arm (41% vs 7%, $P = 0.002$),²⁷ LHM arm (64.6% vs 11.1%, $P = 0.002$),²⁹ or LHM with Dor's fundoplication arm (44% vs 29%; odds ratio, 2.00; 95% CI, 1.03–3.85)²⁸ respectively. In view of such outcome, there are now novel attempts of adding endoscopic transperitoneal partial fundoplication to the standard POEM (POEM + F) in order to mini-

mize GERD complications. A case series of 21 patients³¹ has demonstrated its technical feasibility, with no major adverse events noted. POEM + F describes an anterior fundoplication technique and is better suitable with anterior POEM, and might not be suitable in patients with prior POEM due to submucosal fibrosis.³¹ Further studies are needed for assessment on postoperative GERD symptoms, as well as the durability of the fundoplication wrap.

Submucosal Tunnel Endoscopic Resection/Peroral Endoscopic Tumor Resection for Gastrointestinal Subepithelial Tumors

Apart from functional disorders, submucosal endoscopy emerged as a therapeutic option for subepithelial tumors (SETs) of the GI tract.^{32,33} Recently, SETs are increasingly diagnosed, one of the major reasons is due to the increasing performance of diagnostic endoscopy. SETs of the GI tract include a spectrum of different pathologies arising from subepithelial tissues, including gastrointestinal stromal tumor (GIST), leiomyoma, lipoma, schwannoma, as well as ectopic pancreas. Peroral endoscopic tumor resection (POET)¹³ and submucosal tunneling endoscopic resection (STER) had been reported for treatment of SETs in esophagus, gastroesophageal junction and stomach. The technique of POET/STER evolved from POEM with similar initial steps of submucosal tunneling development, while the mucosal entrance

Fig. 2. Submucosal tunnel endoscopic resection for treatment of subepithelial tumors at the cardia of stomach. (A) Development of submucosal tunnel after mucosal incision over distal esophagus to approach subepithelial tumor at gastric cardia. (B) Identification of proximal margin of the subepithelial tumor within submucosal tunnel. (C) Dissection around the lateral border of the gastric subepithelial tumor using dual knife. (D) Further dissection at the inferior border of gastric subepithelial tumor over the adherent part at muscularis propria. (E) Endoscopic retrieval of the subepithelial tumor using net. (F) Complete closure of the mucosal incision at the esophageal side with endoclips.

would be closer to the submucosal tumor (SMT) (Fig. 2). The dissection should be performed over lateral side of the submucosal tumor, and a submucosal space should be developed distal to the tumor prior to complete dissection at the muscularis propria so as to allow space for tumor manipulation. For most of the procedures, there would be a bridge into the adventitial layer or the serosa upon dissection at the base of tumor over muscularis propria, while keeping integrity of mucosa avoided a full thickness perforation (Fig. 2).

Two systematic reviews^{34,35} summarizing the results of current observational studies on STER were shown in Table 2. Majority of the SETs resected were leiomyoma, accounting for 76.9% of all lesions based on 28 observation studies.³⁵ The results demonstrated high clinical efficacy of STER with excellent complete resection rates ranging from 97.5% to 99.8%, and high en-bloc resection rates from 94.6% to 92.1%. No tumor recurrence was reported in follow-up period ranging from 1 to 32 months. Subcutaneous emphysema with or without pneumomediastinum was the commonest encountered complication with a pooled prevalence of 14.8% (95% CI, 10.5–20.5) from 17 studies, and this complication commonly occurred for STER performed over the esophagogastric junction. Most of the emphysema were managed conservatively³⁶; Chen et al³⁷ reported that only 10% of STERs required intervention for complications. Risk factors for STER-related complications^{33,37} included overlying ulcerated mucosa,³⁷ SETs with irregular borders,³⁶ tumor involvement with deep portion of muscularis propria layer,³⁸ long procedure time, and insufflation with air.³⁷

Endoscopic Full-Thickness Resection

While the performance of STER avoided full thickness perforation through preservation of mucosa, the dissection is usually close to the tumor border, with difficulty confirming dissection completeness during the procedure.³⁹ This contributes a significant risk of incomplete resection to submucosal tumor especially for GIST. In difficult cases, the close margins of dissection could cause injury to tumor capsule and potentiate tumor seeding. EFTR could achieve better en-bloc resection and avoid the risks of bridging of tumor capsule during STER. The technique of EFTR can be classified into three approaches (Fig. 3)⁴⁰: (1) non-tunneled exposed EFTR; (2) tunneled-exposed EFTR; and (3) non-exposed EFTR. The term “exposed” refers to any temporary exposure of the GI tract lumen to the peritoneal cavity. Exposed EFTR involved creation and closure of luminal defects during the resection, which can be subdivided into tunneled and non-tunneled exposed EFTR. Tunneled-exposed EFTR is similar to STERs, and closure of the mucosal flap entry site after complete full thickness resection will suffice. Exposed non-tunneled EFTR is performed with a similar approach as ESD with dissection around the submucosal tumor first at the submucosal layer, then the tumor is completely resected through the muscularis propria to serosa to achieve en-bloc resection (Fig. 4). In exposed EFTR, closure of luminal defect is achieved by either clips application, clip and loop technique,⁴¹ endoscopic suturing devices,^{42,43} and prototype endoscopic staplers.⁴⁴ One of the major difficulties for exposed non-tunnel EFTR

Table 2 Summary of Systematic Reviews on Clinical Outcomes of Submucosal Tunnel Endoscopic Resection (STER) for Treatment of Subepithelial Tumors

Author	Search period	Studies included	No. of cases	Follow-up duration (mo)	Mean tumor size (cm)	Mean operative time (min)	Complete resection rate (%)	En-bloc resection rate (%)	Tumor recurrence (%)	Complication
Jain et al (2017) ³⁴	Up to February 2016	16 studies: -4 prospective -9 retrospective -3 case reports	703 patients 736 lesions: -465 esophageal -146 EGJ -125 gastric	1–32	2.1 (0.6–5.5)	Esophageal or EGJ lesions: 120.1 (15–365) Gastric lesions: 86.7 (25–320)	99.8	92.1	0	272 adverse events (37.0%) -Air leak: 1 (0.1%) -Bleeding: 6 (0.8%) -Chest pain: 4 (0.5%) -Esophageal diverticulum: 2 (0.2%) -Esophageal pleural fistula: 1 (0.1%) -Mucosal injury/laceration: 4 (0.5%) -Perforation: 17 (2.3%) -Pneumomediastinum: 16 (2.2%) -Pneumoperitoneum: 19 (2.6%) -Pneumothorax: 44 (6.0%) -Subcutaneous emphysema: 101 (13.7%) -Subphrenic infection: 1 (0.1%) -Thoracic/pleural effusion: 56 (7.6%)
Lv et al (2017) ³⁵	Up to November 2015	28 studies: -8 prospective -20 retrospective	1,041 patients 1,085 lesions: -712 esophageal -95 EGJ -141 cardia -137 gastric	7.1 (1.9–18.0)*	1.9 (0.5–7)	55.8	97.5	94.6	0	263 adverse events -Bleeding: 8 -Perforation: 18 (5.6%) -Pneumoperitoneum: 42 (6.8%) -Pneumothorax: 48 (6.1%) -Subcutaneous emphysema and pneumomediastinum: 147 (14.8%)

Values are presented as mean (range).

EGJ, esophagogastric junction.

*Median of mean follow-up (range).

Fig. 3. Illustrations on different types of endoscopic full-thickness resection (EFTR). (A) Exposed non-tunnelled EFTR. 1: Direct incision from mucosa, submucosa to muscularis propria. 2: Complete resection of the subepithelial tumor. 3: Closure of mucosal incision with clips or over-stitch. (B) Exposed tunnelled EFTR. 1: Development of submucosal tunnel proximal to the subepithelial tumor. 2: Dissection of subepithelial tumor within the submucosal tunnel with full thickness dissection to peritoneal cavity. 3: Closure of the mucosal entrance after complete dissection of the subepithelial tumor with endoclips. (C) Non-exposed EFTR with full-thickness resection device (FTRD). 1: Endoscopic localization of the subepithelial tumor and assessment of the tumor size fitting with FTRD device. 2: Aspiration of the subepithelial tumors using suction or tissue retraction device within the distal attachment cap, followed by application of the over-the-scope clip for complete closure of the gastrointestinal wall before resection. 3: Complete full thickness resection of the subepithelial tumor with snare. Data from the article of Liu et al (*Surg Endosc.* 2013;27:4354-9).³⁶

Fig. 4. Endoscopic full-thickness resection for treatment of gastric gastrointestinal stromal tumor (GIST). (A) Gastric GIST located at posterior wall of cardia. (B) Half circumferential mucosal incision distal to the GIST. (C) Extending the submucosal dissection to muscularis propria. (D) Full-thickness incision over muscularis propria into peritoneal cavity. (E) Retraction of the submucosal GIST using clip and string technique, and exposure of serosal margin of the GIST. (F) Full-thickness closure using over-stitch suturing device.

is to achieve safe closure of the defect upon which the luminal insufflation would be compromised upon complete resection of tumor. Our technique utilized tumor retraction with clip and line so as to minimize gas leakage during dissection, and luminal closure with overstitch endoscopic suturing.

Non-exposed EFTR avoids full thickness perforation by retracting the segment containing the target lesion into the lumen, allowing approximation and fixation of two serosal surfaces before resection.^{40,45} One of the advances in achieving non-exposed EFTR is the development of a full-thickness resection device (FTRD) which combines resection and closure by the over-the-scope clip (OTSC) device. FTRD achieved EFTR through grasping and pulling of target lesion into the transparent hood, followed by deployment of OTSC to close approximate GI wall prior to resection of the lesion above the clip.⁴⁶ FTRD is limited by the size of specimen achieved and the size of the device which hindered its deployment in narrowed part of the GI tract. Non-exposed EFTR does not utilize principles of third space endoscopy, therefore it will not be further covered in this review. We identified 11 retrospective cohort studies reporting short and mid-term outcomes of exposed EFTR of gastric SMTs, as summarized in Table 3.^{47–57} Majority of the resected SMTs were confirmed to be GIST histologically. While the sample size of each series is still small, the published data demonstrated high complete resection rate (90.3%–100%). There were very few major complications with 15 cases of GI bleeding events (3.6%) and 3 cases of perforation (0.07%) on pooled analysis. Abdominal distention and discomfort from the pneumoperitoneum after EFTR resulting upon full thickness resection was up to 20%.⁵⁰ Postoperative fever amenable to conservative management was also between 0% to 17% (5 out of 30), likely from intraoperative peritoneal contamination as sub-group analysis demonstrated a correlation between lower incidence of postoperative fever and shorter operative time.⁵⁴ The size of resected gastric SMTs ranged from 0.6 to 6.0 cm, and endoscopists reported technical difficulties of EFTR for both extremes of sizes. Small SMTs < 0.5 cm are difficult to identify, while large SMTs create issues of difficult closure of large luminal defect, longer operative time and inability of specimen retrieval per orally.⁵⁴

Oncologically, these cohort studies demonstrated no significant residual tumor or rate of local recurrence upon re-assessment endoscopy in short-term follow-up. In terms of long-term outcome of endoscopic resection of gastric GIST, two recent series with median follow-up period of 36 months and 57 months reported low recurrence of 1.7% (1 out of 60 patients)⁵⁸ and 0% (0 out of 225 patients)⁵⁹ respectively.

Apart from gastric lesions, EFTR has also been applied to lesions in other parts of the GI tract. However, full thickness resection in esophagus, duodenum, and colorectal tract presents greater challenges in closing large defects with higher incidence of leaks,⁶⁰ therefore current data on exposed EFTR are lacking. In these regions, FTRD offered a technically less demanding approach with encouraging results of clinical success in achieving non-exposed EFTR.^{61–63} A 2019 multicenter study of 114 patients receiving EFTR with FTRD for colorectal lesion reported lateral and deep R0 resection up to 90% and 92%, respectively,⁴⁶ with 11% experiencing adverse clinical events (only 1 patient with major bleeding and 1 patient with perforation).

Emerging Indications: Myotomy in Upper GI Tract and Beyond

Submucosal tunnel opened the third space for development of novel procedures. Apart from POEM for treatment of achalasia,

numerous innovative procedures had been developed for treatment of GI diseases. These procedures included G-POEM for gastroparesis, D-POEM for esophageal diverticulum, Z-POEM for Zenker's diverticulum, per rectal endoscopic myotomy for Hirschsprung disease.

POEM for Other Spastic Esophageal Motility Disorders

With the establishment of POEM in achalasia management, the next logical step is to expand its indication to other spastic esophageal disorders (SED) include type III achalasia, diffuse esophageal spasm (DES), and nutcracker/Jackhammer esophagus. While these disorders vary in manometric findings and pathophysiology, with the former two associated with loss of neural inhibition and the latter caused by cholinergic activation,⁶⁴ they share similar symptomatology of dysphasia, regurgitation, and chest discomfort. By adjusting length and location of myotomy,¹⁰ POEM achieved high clinical success of treatment of these disorders as demonstrated in a meta-analysis of 8 observational studies.⁶⁴ POEM achieved high clinical success rates of 92%, 88%, and 72% and adverse events rate of 11%, 14%, and 16% for treatment of type III achalasia, DES, and Jackhammer esophagus respectively. A more recent meta-analysis⁶⁵ demonstrated a promising pooled clinical success rate of 89.6% for SEDs. However, both meta-analyses could only include a paucity of cases of DES and Jackhammer esophagus due to the lower disease incidence. Further prospective studies with higher case volume and longer-term outcomes should be conducted to confirm the effectiveness of POEM for these motility disorders.

Z-POEM and D-POEM for Esophageal Diverticular Diseases

Third space endoscopy allowed endoscopic approach to treatment of esophageal diverticular diseases through creation of submucosal tunnel and dissection at the septum between the diverticulum and muscularis propria. The common types of esophageal diverticulum included Zenker's diverticulum, mid esophageal diverticulum and epiphrenic diverticulum. Treatment of esophageal diverticulum focused on relief of symptoms caused by both the pulsion diverticulum and the underlying motility disorder. Zenker's diverticulum is an acquired pulsion type diverticulum at the Killian triangle over pharyngo-esophagus.⁶⁶ Conventional treatment for Zenker's diverticulum included diverticulectomy, diverticulopexy, diverticular inversion with or without myotomy, cricopharyngeal myotomy as well as endoscopic septotomy.⁶⁷ Recently, third space endoscopy was reported as a novel approach to achieve septotomy through a submucosal tunnel. The approach was named as submucosal tunneling for endoscopic septum division (STESD) or otherwise Z-POEM.^{68–72} This approach avoided direct incision into the septum, and theoretically allowed endoscopists to achieve a higher rate of complete septotomy. The submucosal tunnel enabled non-exposure of the cut-edge of the septotomy and preventing leakage or perforation after the procedure. The same principles and techniques of Z-POEM can be applied for treatment of diverticulum in mid-esophagus and epiphrenic area, the procedure named as diverticular POEM (D-POEM). D-POEM achieved complete septal dissection without risk of perforation and achieved high symptomatic relief.⁷⁰ The largest reported multi-center retrospective study involves 75 patients who received Z-POEM for Zenker's diverticulum⁷³ with high clinical success rate of 92% in relieving dysphagia, and a low adverse event rates of 6.7% (1 bleeding, 4 perforations). A separate cohort of patients with mid-esophageal diverticula and epiphrenic diverticula by the

Table 3 Summary of Cohort Studies on Clinical Outcomes of Endoscopic Full-Thickness Resection (EFTR) of Treatment of Gastric Subepithelial Tumors

Author	Study period	No. of patients	Closure method	Mean tumor size (cm)	Mean operative time (min)	Complete resection rate (%)	Follow-up duration (mo)	Tumor recurrence rate	Complication
Zhou et al (2011) ⁴⁷	July 2007 to January 2009	26	Metallic clips	2.8 (1.2–4.5)	105 (60–145)	100	8 (6–24)	No lesion residual or recurrence	None of the studied patients had peritonitis or abdominal abscess.
Ye et al (2014) ⁴⁸	January 2009 to December 2012	51	Clips with endoloop	2.4 (1.3–3.5)*	52 (30–125)*	98.0	22.4 (1–48)*	No residual tumor or tumor recurrence	No patients had severe complications, such as massive bleeding, delayed bleeding, peritonitis, or gastrointestinal tract leakage.
Feng et al (2014) ⁴⁹	November 2009 to October 2012	48	Metallic clips	1.59 (0.50–4.80)	59.72 (30–270)	100	11.8 (2–48)	No recurrence	No post-EFR complication, such as bleeding and peritonitis, was observed.
Huang et al (2014) ⁵⁰	January 2010 to September 2013	35	Metallic clips	2.8 (2.0–4.5)	90 (60–155)	100	6 mo for all patients	No residual lesion, no recurrence	No gastric bleeding, peritonitis or abdominal abscess occurred
Yang et al (2015) ⁵¹	June 2012 to April 2014	41	–35 patients with metallic clips –6 patients with the over-the-scope clip, i.e., OTSC system	1.63 ± 0.59	78.82 ± 46.44	100	Not applicable	Not assessed	No severe complications such as peritonitis, digestive tract hemorrhage, or local infection
Guo et al (2015) ⁵²	October 2013 to March 2014	23	OTSC system	1.21 (0.6–2.0)	40.5 (16–104)	100	3 (1–6)	No residual lesion, no recurrence	No postoperative bleeding or perforation
Schmidt et al (2015) ⁵³	January 2007 to February 2014	31	–29 patients, with the Plicator suturing device –2 patients with the GERDX suturing device	2.05 (0.8–4.8)	60.0 (39–229)	90.3	7.1 (0–58)	No recurrence	–12 (38.7%) bleeding –3 (9.6%) perforations
Lu et al (2016) ⁵⁴	January 2013 to March 2015	62	Metallic clips	0.6–6.0	25–180	98.4	1–24	No recurrence	No peritonitis
Shi et al (2017) ⁵⁵	April 2014 to February 2015	68	Metallic clips with endoloops	2.6 (2.0–3.5)	41 (23–118)	100	7 (3–13)	No residual tumor, no recurrence	–1 (1.5%) Mallory–Weiss syndrome –1 (1.5%) delayed bleeding
Duan et al (2018) ⁵⁶	April 2011 to May 2016	28	Metallic clips	1.53 ± 0.7	63.3 ± 24.4	100	22.8 ± 18.4	No recurrence	–1 (3.6%) delayed bleeding
Shichijo et al (2019) ⁵⁷	January 2016 to December 2018	8	–3 clip-and-endoloop purse-string suturing –2 simple endoclipping –1 OTSC system	2.0 (1.0–3.5)*	67.5 (50–166)*	100% En-bloc resection, but 5/8 (62.5%) had indeterminate resection margins histologically	Not applicable	Not assessed	No ≥ CTCAF grade 2 adverse events

Values are presented as mean (range) or mean ± standard deviation.

EFR, endoscopic full-thickness resection; OTSC, over-the-scope clip; CTCAF, Common Terminology Criteria for Adverse Events (ver. 5.0; released on 2017).

*Median (range).

same group⁷⁴ also demonstrated good efficacy and safety for D-POEM. There was no long term adverse events reported for the 25 patients after D-POEM in a 12-month follow-up study.⁷⁵

G-POEM for Gastroparesis

The principles of POEM and third space endoscopy were applied to treatment of gastroparesis, which is caused by inco-ordinate peristalsis of antrum and relaxation of pylorus.⁷⁶ The etiology of gastroparesis can be divided into iatrogenic (usually caused by surgical trauma to vagal nerve), diabetes and idiopathic. For gastroparesis caused by uncoordinated relaxation of pylorus, therapeutic options mostly targeted at pyloric myotomy and release the spastic contraction. In 2013, Khashab et al⁷⁷ performed the first human case of gastric POEM (G-POEM), also known as peroral endoscopic pyloromyotomy (POEP or POP). The technique of G-POEM is very similar to POEM with the myotomy focused on the muscular ring of pylorus. Numerous small-scale case series subsequently reported the safety and efficacy of G-POEM for treatment of gastroparesis.^{78–83} The first meta-analysis⁸⁴ pooled 196 cases of G-POEM from seven observational studies. These patients included those with refractory gastroparesis not responsive to medical therapy or with persistent symptoms of more than 6 months. It was found that the clinical success rate was 82%, with statistically significantly improved gastric emptying 2 to 3 months postoperatively. Twelve adverse events (6.1%) were reported, with capnoperitoneum being the most common one. It was interesting to note that the underlying etiology of gastroparesis does not affect the clinical success of G-POEM. A more recent meta-analysis⁸⁵ comparing G-POEM (332 patients pooled from 11 studies) with surgical pyloroplasty (375 patients from 7 studies) also demonstrated comparable rate of clinical success (75.8%) and low adverse event rate (11%) in the G-POEM group when compared to surgical pyloroplasty. Follow-up of 16 patients in 14.5 months shows a promising long-term clinical efficacy of 81.6%.⁸⁶

Hirschsprung's Disease: Third Space Endoscopy in the Lower GI Tract

Another exciting development in third space endoscopic myotomy is the extension of submucosal endoscopic myotomy to the lower GI tract. Hirschsprung's disease is characterized by aganglionosis of Auerbach and Meissner plexuses starting from the rectum and extending proximally, resulting in a functional obstruction.⁸⁷ After the initial description of per-anal endoscopic myotomy in a porcine model,⁸⁸ Bapaye et al⁸⁹ performed the first successful per-rectal endoscopic myotomy (PREM) in a 24-year-old adult patient with Hirschsprung's disease. The same group published case reports of successful PREM in a pediatric patient (8 years old)⁹⁰ and an infantile patient (2 years old).⁹¹ With more evidence, the same technique can perhaps be expanded to manage other lower GI motility disorders such as hypertensive anal sphincter and sphincter dyssynergia.

Other Novel Applications

Submucosal endoscopy may serve as a novel approach to treatment of GERD. Electrostimulation of the LES aimed to its functionality for treatment of refractory GERD, and clinical studies demonstrated significant improvement in symptomatic relief for GERD.³² Third space endoscopy for the implantation of stimulation leads⁹³ or even devices⁹⁴ in the LES was tested in porcine models for electrostimulation therapy. In future, further refine-

ments in the device and the techniques will lead to clinical trial on submucosal endoscopic electrostimulation therapy for treatment of GERD.

Wagh and Draganov⁹⁵ described peroral endoscopic tunneling for restoration of the esophagus (POETRE) in 4 patients with complete esophageal obstruction. In this procedure, submucosal dissection was performed in the fibrotic obstructed segment followed by guidewire-assisted insertion of esophageal stent, enabling easier traverse of longer segments of completely obstructed esophagus (> 3 cm).

While most of the procedures covered are therapeutic in nature, the technique of submucosal endoscopy also offers a safer means for natural orifice transluminal endoscopy compared to its earlier forms.⁶ The mucosal safety valve technique enables safe access into mediastinum or peritoneal cavity via the esophagus, stomach or even colons, with feasibility demonstrated in animal models as well as human case series.^{8,96,97} With further development, third space endoscopy has the potential to replace laparoscopy for staging of malignancies.

Conclusion

Third space endoscopy is an evolving field with on-going innovative development. The submucosal space allowed endoscopists to perform novel therapeutic procedures for GI tract for a variety of disease spectrum ranging from functional/motility disorders to malignancies. Nevertheless, the current clinical evidence lacks sufficient sample size and high-quality randomized trials. Given the procedures' novelty, long term efficacy and safety data is also deficient. Further research and follow-up studies is warranted to better understand third space endoscopy, and establish it as an integral part of clinical care in this new age of endoscopy.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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