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Esophageal Third Space Endoscopy: Recent Advances

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Abstract

Purpose of the review The novel concept of third space endoscopy was first applied to humans in 2008 for the management of achalasia through peroral endoscopic myotomy (POEM) procedure. Over the ensuing 10 years, this revolutionary procedure, which started in Japan, has been adopted and mastered by surgeons and gastroenterologists across the globe. In this article, we review the recent innovations and applications of third space endoscopy in the management of esophageal disorders.
Recent findings With experience and innovation, the application of third-space endoscopy has extended beyond achalasia, and currently, it is used in the management of other esophageal disorders including, spastic esophageal disorders, subepithelial tumors, complete esophageal obstruction, and esophageal diverticula.
Summary The recent advances in third space endoscopic procedures have not only permitted endoscopic access to places, previously thought impossible, but also enabled the precision of surgery along with reduced peri-operative morbidity due to its minimally invasive nature. While short- and mid-term outcome studies have shown excellent results, we eagerly await the long-term outcome studies before these procedures could be established as the procedures of choice.

Introduction

"First space" represents the natural lumen of the gastrointestinal (GI) tract. In 2004, Kalloo et al. described the natural orifice transluminal endoscopic surgery (NOTES) technique, which permitted entry into the "second space," the peritoneal cavity for surgical interventions and thereby avoiding abdominal wall incisions [1]. Major concerns with NOTES were lack of endoscopic devices that enable secure closure of the entry point into the peritoneal cavity. To resolve this technical difficulty, Sumiyama et al. introduced the concept of submucosal endoscopy or "third space" endoscopy, with mucosal flap safety valve in an animal model in 2007 [2]. Submucosal space or third space is a potential space located between the mucosa and muscularis propria (MP) layer of the gut wall. Using submucosal dissection, this space can be opened up and used as a working channel. While the intact mucosal flap prevents any peritoneal leakage, the endoscopist can use the submucosal tunnel to perform interventions in the MP layer or breech it to enter the mediastinum or peritoneal cavity without causing full thickness perforation. Pasricha et al. adapted this technique to replicate surgical Heller's myotomy in an animal model [3]. Subsequently, Inoue et al. perfected this technique and reported the first human application of peroral endoscopic myotomy (POEM) in the treatment of achalasia [4]. This started the era of clinical third space endoscopy. With widespread dissemination and success of POEM, the third space endoscopy has opened up new horizons for endoscopic interventions. Apart from achalasia, it is also applied in the treatment of spastic esophageal disorders, subepithelial tumors (SETs), complete esophageal obstruction (CEO), and esophageal diverticula (Table 1).

Peroral endoscopic myotomy

Since its first description in 2010, POEM has rapidly gained traction worldwide due to its minimally invasive nature and low risk of complications. Currently, there are more than 6000 reported cases of POEM with over 8 years of worldwide experience [5] and more than 500 peer-reviewed publications (Fig. 1). Although the long-term outcomes are evolving, POEM is swiftly replacing pneumatic dilatation (PD) and laparoscopic Heller's myotomy (LHM) as the preferred choice for treatment of achalasia.

POEM technique

POEM is performed under general anesthesia in an operating room or an endoscopy suite using standard steps as described by Inoue et al. [4]. The steps

Table 1. Third space endoscopy techniques in the esophagus

Third space endoscopy techniques in esophagus	Indications
1) Peroral endoscopic myotomy (POEM)	-Achalasia -Spastic disorders of the esophagus
2) Submucosal tunneling endoscopic resection (STER)	-Resection of subepithelial tumors
3) Peroral endoscopic tunneling for restoration of the esophagus (POETRE)	-Complete esophageal obstruction
4) Submucosal tunneling endoscopic septum division (STESD)	-Zenker's diverticulum -Mid-thoracic diverticulum -Epiphrenic diverticulum

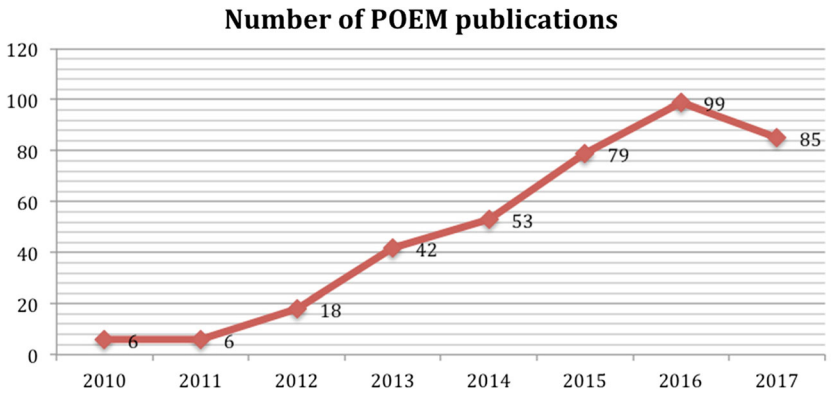

Fig. 1. Number of peer-reviewed publications about POEM from 2010 to 2017 (source: PubMed).

are (1) raising a submucosal bleb followed by a mucosotomy; (2) creation of a submucosal tunnel starting approximately 10–12 cm proximal to the lower esophaghageal sphincter (LES) and extending distally to about 2–4 cm into the gastric side; (3) myotomy of the circular muscle fibers starting 3–4 cm distally from the first incision and 2–4 cm into the gastric side; and (4) closure of the mucosotomy or entry site of the submucosal tunnel by using endoscopic clips (Fig. 2). The submucosal tunnel is either created on anterior or posterior esophageal wall based on the preference of endoscopist and if the patient had

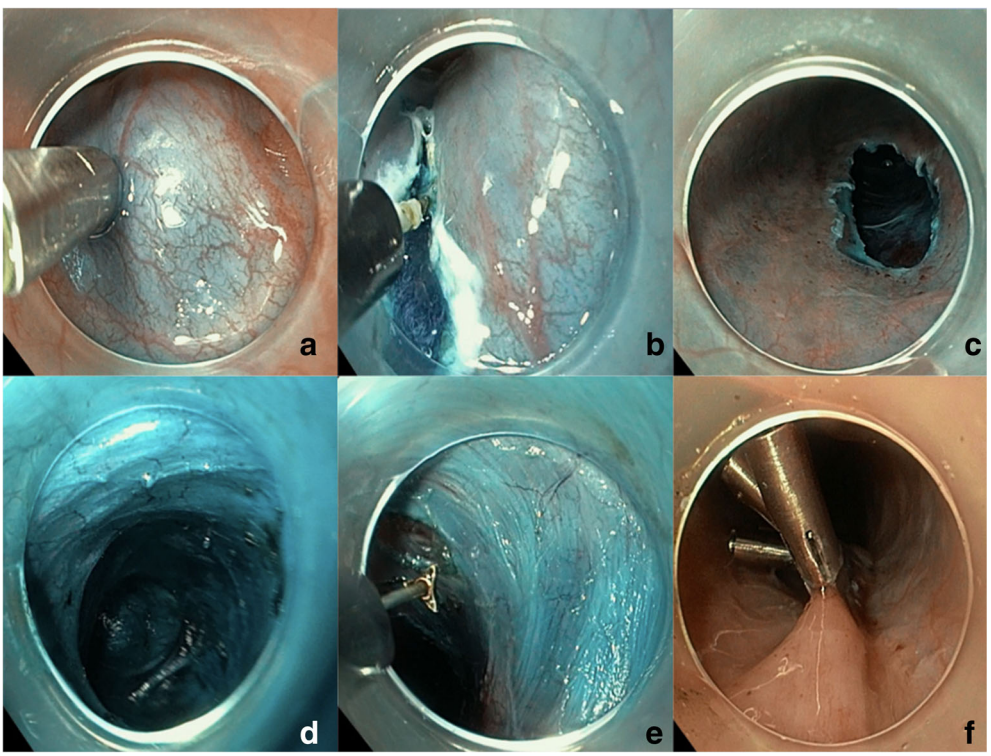

Fig. 2. Steps in peroral endoscopic myotomy are **a** raising a submucosal bleb by injecting saline solution mixed with indigo carmine, **b** and **c** creating a mucosotomy, **d** creating a submucosal tunnel by submucosal endoscopic dissection, **e** myotomy of the circular muscle fibers, and finally **f** closure of the mucosal incision with endoscopic clips.

previous surgical myotomy [6]. No significant difference in POEM outcomes was noted in a study comparing anterior vs. posterior myotomy [7•]. Grimes et al. described the utility of double scope POEM for ensuring a complete gastric myotomy, which may be useful in cases of sigmoid esophagus or other instances of altered anatomy, in which identification of gastro-esophageal junction in the tunnel is difficult [8].

Overall POEM outcomes

Inoue et al. reported a series of 500 patients, in which significant improvement in Eckardt scores and LES pressures were noted at 2 months post-procedure and these persisted at 3-year follow-up period [9]. Similarly, Nabi et al. reported a series of 408 patients, in which the POEM procedure was successfully completed in 396 (97%) patients and clinical success rates at 1, 2, and 3 years were 94, 91, and 90%, respectively [10]. Further, Akintoye et al. described a meta-analysis of 36 studies, involving 2373 POEM patients. Here, the clinical success (Eckardt score ≤ 3) was achieved in 98% of patients, and the mean Eckardt scores decreased from 6.9 ± 0.15 preoperatively to 0.77 ± 0.10, 1.0 ± 0.10, and 1.0 ± 0.08 within 1, 6, and 12 months of treatment, respectively [11]. Apart from technical and clinical success, POEM also improved all dimensions of health-related quality of life at both short-term and long-term follow-ups [12]. POEM is associated with good outcomes not only in adults but also in pediatric [13, 14] as well as geriatric populations [15•]. Poem is associated with > 90% success rate in all three manometric subtypes of achalasia [16, 17]. It is equally efficacious in obese and non-obese patients [18•], and severity of obesity does not seem to impact the clinical outcomes of POEM [19]. Achalasia is usually associated with an elevated lower esophageal sphincter-integrated relaxation pressure (LES-IRP) ≥ 15 mmHg; however, a proportion of patients with clinical and radiologic features of achalasia have normal IRP. POEM was noted to be equally effective for palliation of symptoms in patients with either normal or elevated LES-IRP [20, 21] (first study comparing outcomes of POEM in obese and non-obese patients). Hence, based on a large body of evidence, POEM appears to be an effective treatment modality with durable clinical response and is rapidly gaining acceptance as the procedure of choice for management of achalasia [9–12, 22, 23].

POEM in spastic and end-stage esophageal disorders

Recently, POEM has been used in the management of spastic disorders of the esophagus, which include diffuse esophageal spasm (DES) and nutcracker/jackhammer esophagus (JH). Chest pain and dysphagia are challenging symptoms to treat in these patients and they may benefit from an extended myotomy. POEM represents an ideal treatment option for these complex motility disorders, as it offers the flexibility of performing a longer myotomy by initiating the submucosal tunnel in the proximal esophagus [5, 24]. Further, the length of myotomy can be guided by manometry, esophageal wall thickening on endoscopic ultrasound (EUS), or intraoperative functional luminal imaging probe [25]. A recent meta-analysis involving 179 POEM patients from eight studies reported pooled success rates of 92, 88, and 72% in type III, DES, and JH, respectively, with similar safety profile [26]. POEM is also shown to be useful in end stage achalasia (sigmoidization of esophagus) where a success rate of 97% was demonstrated at 2-year follow-up period [27].

Comparison of peroral endoscopic myotomy with laparoscopic Heller's myotomy

Bhayani et al. reported comparable outcomes between POEM and LHM at 6-month follow-up period [28]. Recently, Schlottmann et al. reported a meta-analysis comparing 5834 LHM cases and 1958 POEM cases from 53 studies. In that study, the predicted probability for dysphagia improvement at 12 (93.5% for POEM and 91.0% for LHM ($P = 0.01$)) and 24 months (92.7% for POEM and 90.0% for LHM ($P = 0.01$)) was significantly higher with POEM. Of note, patients undergoing POEM had a longer length of stay and higher incidence of gastroesophageal reflux disease (GERD) [29•]. Another meta-analysis (LHM = 250, POEM = 233) comparing peri-operative outcomes showed no significant difference in the operative time, post-operative pain score, or overall complication rate between the two treatment modalities [30]. Recent studies have also shown excellent POEM outcomes in patients with failed LHM [31, 32], and it is reported to be more cost effective than LHM [33•]. Hence, at short- and medium-term follow-up, POEM outcomes are comparable and in certain aspects, even superior to LHM.

Comparison of peroral endoscopic myotomy and pneumatic dilatation

POEM and PD are noted to be equally efficacious at short-term (2 months) follow-up [6]. However, on mid-term follow-up (36 months), POEM appears to be a more durable treatment option. In a study of treatment naïve patients, Meng et al. reported a success rate of 96, 93, and 93% for POEM as compared to 75, 72, and 60% with PD at 1-, 2-, and 3-year follow-up periods, respectively ($P = 0.013$) [34]. Similar results were noted in a recent randomized control trial, in which treatment naïve achalasia patients undergoing POEM had significantly higher success rates as compared to PD (92.2% vs. 70%; $P < 0.01$), at 1-year follow-up period [35]. Of note, the incidence of reflux esophagitis was higher with POEM than after PD (40% vs.13.1%; $P = 0.02$). POEM also appears to be a safe and effective treatment modality in achalasia patients with prior PD. Prior PD does not seem to have any obvious influence on the efficacy of POEM, and it may emerge as the preferred approach for myotomy in patients with failed PD [36].

Persistent or recurrent symptoms after POEM

Van Hoeij et al. reported a study involving 441 patients who underwent POEM, among them 9.8% of patients failed POEM, of which 8% underwent one or more retreatments. Repeat LHM and repeat POEM were associated with a success rate of 63 and 45%, respectively, whereas repeat PD showed a poor efficacy of only 0 to 20% depending on the size of the balloon used. Males were more likely to have failure of retreatment compared to females, although it did not reach statistical significance ($P = 0.38$) [37]. Hence, despite its overall efficacy, a subset of patients may have persistent or recurrent symptoms after POEM. Repeat POEM or LHM can be considered for palliation of symptoms in this subgroup of patients.

Post-POEM GERD

One of the major drawbacks of POEM is that it is not combined with an anti-reflux procedure. POEM is associated with a significantly higher incidence of pathologic reflux by symptomatic, endoscopic, and esophageal pH study parameters as compared to LHM with fundoplication [29•, 38, 39]. In a meta-analysis by Repici et al., POEM was noted to have a pooled post procedural

symptom rate, pooled rate estimate of abnormal acid exposure at pH monitoring, and rate of esophagitis on upper endoscopy of 19, 39, and 29.4% for POEM and 8.8, 16.8, and 7.6% for LHM, respectively. In our practice, we prescribe proton pump inhibitors (PPIs) to all patients for 2 months after POEM. Following this, we perform a 24-h esophageal pH study off PPIs in all patients. In patients with abnormal esophageal pH study, PPIs are continued long-term. Patients are periodically monitored during clinic visits to determine the need for upper endoscopy based on clinical symptoms.

Adverse events of POEM

In general, POEM appears to be a safe procedure, and major adverse events (AEs) are rare. In a systemic review of 1680 patients who underwent POEM between 2010 and 2015, the rate of major peri-operative AEs was 3.3%. Pneumothorax, hydrothorax, and delayed mucosal barrier failure were the most common AE. Institution experience of < 1 year, air insufflation, and mucosal edema were identified as risk factors. After using CO_2 for insufflation, the rate of AEs declined and plateaued to ~ 1% [40].

Submucosal tunneling endoscopic resection (STER)

Endoscopic mucosal resection (EMR) [41, 42] and endoscopic submucosal dissection (ESD) [43–45] are well-established methods for resection of the mucosal and SETs from submucosal layer in the upper GI tract. However, they are of limited utility for SETs originating from the MP layer. Most upper GI SETs < 3 cm in size are considered as benign; however, some of these tumors, especially gastrointestinal stromal tumors (GIST), may harbor malignant potential. Conservative management/surveillance by endoscopy/EUS may lead to inaccurate diagnosis, increased health care utilization, and diagnostic uncertainty and resultant anxiety in some patients. Alternatively, if tumor resection was warranted, an invasive surgical approach would be required [46]. In 2012, Xu et al. described a novel, minimally invasive STER technique, which was applied for resection of tumors originating from the MP layer [47]. The tunnel was created by ESD, and overall, the procedure was inspired from the NOTES and POEM technique. A total of 15 patients with SETs were included, and STER was successfully performed in all the patients with a 100% en-bloc and R0 resection rates.

STER technique

Before considering STER, origin and depth of the tumor and its relationship to the surrounding structures should be determined with an EUS and/or computerized tomography scan. Lesions < 3.5 cm in size are generally amenable to STER. En-bloc removal of lesions > 3.5 cm, although technically feasible, should be avoided as it is associated with high rates of AEs and low rates of complete resection [46, 48, 49]. In this procedure, a submucosal bleb is raised, 3–5 cm proximal to the lesion by injecting saline mixed with indigo carmine dye. This is followed by creation of a 2-cm mucosotomy. Next, a submucosal tunnel is created with submucosal dissection, and an endoscope with a distal attachment cap is introduced into the tunnel. The tumor is carefully dissected

from the overlying mucosal flap and the underlying MP, while remaining close to the muscular layer to avoid any injury to the mucosa. A partial or a full thickness resection of the muscular layer may be required based on the degree of attachment of the lesion (Fig. 3). For lesions arising from the deep muscular layer or adventitia, a full thickness resection of the muscle layer along with underlying serosa is performed. En-bloc resection is completed, the tumor is retrieved using retrieval net, and mucosotomy is closed with endoscopic clips. This new method permitted accurate histopathologic evaluation due to en-bloc resection and might reduce the rate of secondary infection due to maintenance of mucosal integrity [50, 51].

STER outcomes

Reports on the efficacy and safety of STER are mostly retrospective in nature with relatively short-term follow-up [48, 52–55]. Chen et al. described the largest case series till date, in which STER was performed in 290 patients for upper GI tract SMTs. Authors reported an overall en-bloc resection rate of 89.3% and STER-related AEs in 23.4% of patients; however, only 10% of patients required intervention [48]. A recent meta-analysis involving 1041 patients from 28 studies reported similar results, a pooled complete resection and en-bloc resection rates of 97.5 and 94.6%, respectively. The pooled estimates for gas-insufflation-related AEs were 14.8%, and the pooled prevalence of perforation was 5.6% [56]. In studies comparing STER to video-assisted thoracoscopic

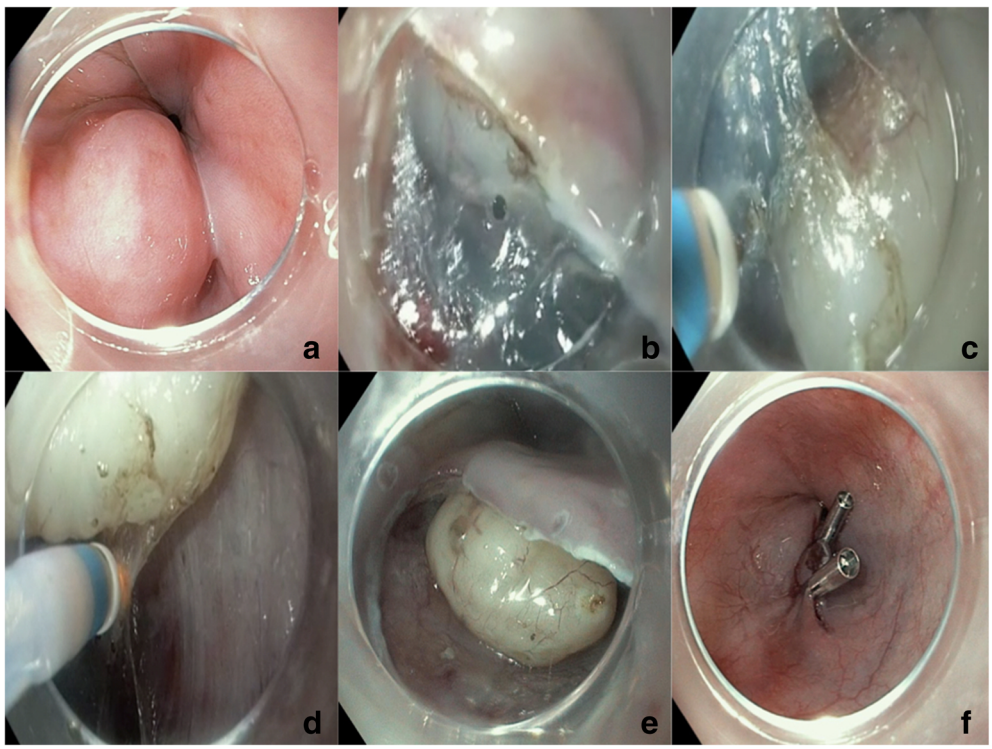

Fig. 3. Steps in submucosal tunneling endoscopic resection are **a** raising a submucosal bleb, **b** vertical mucosotomy, **c** creation of submucosal tunnel, **d** dissection of the tumor from underlying muscular layer, **e** en-bloc removal of the tumor, and **f** closure of the mucosotomy with endoscopic clips.

surgery, both modalities were found to be equally effective with similar en-bloc resection rates and AEs. However, STER was associated with lower blood loss, less post-operative pain, shorter procedure time, and shorter hospital stay [57, 58]. According to the recent national comprehensive cancer network (NCCN) guidelines, all the GI stromal tumors have malignant potential and tumors > 2 cm should be resected, whereas tumors < 2 cm in size can be surveyed or resected. STER should be considered for resection of tumors up to 3.5 cm in size, whereas surgical resection is preferred for those > 3.5 cm in size [49, 59].

Peroral endoscopic tunneling for restoration of the esophagus (POETRE)

Patients with head, neck, and upper thoracic malignancies receiving chemotherapy and radiation therapy can develop fibrosis and rarely CEO [60]. This results in poor quality of life, since patients are unable to swallow and are at increased risk of aspiration pneumonia. Several endoscopic procedures for restoration of the esophageal lumen have been described, including antegrade (via mouth), retrograde (via gastrostomy tube), combined antegrade and retrograde [61], and EUS-guided techniques [62]. These methods are useful in cases in which the length of obstructed esophageal segment is less than 3 cm. However, in cases where the length of the obstructed segment is > 3 cm, there is a higher risk of perforation and injury to important structures due to the relatively blind nature of the procedure.

Recently, Wagh et al. described a novel technique of peroral endoscopic tunneling for restoration of esophagus (POETRE), which is useful in patients with longer length of CEO (> 3 cm) [63]. In this procedure, an antegrade endoscope is inserted into the submucosal space, approximately 5 cm proximal to the blind end of the esophagus. Based on the principle of POEM, a submucosal tunnel is created and extended till the fibrotic segment is encountered. Further, the fibrotic tissue is dissected using simultaneous fluoroscopic and retrograde endoscopic guidance. When both the antegrade and retrograde endoscopes are in close proximity, the fibrotic tissue is incised and antegrade endoscope emerges into the distal unobstructed esophageal lumen. A guide wire is passed through the antegrade endoscope, and a fully covered metal stent is passed over this guide wire to establish a neo-lumen. Another potential advantage of POETRE is that, depending upon the location of the CEO, antegrade or retrograde tunneling and dissection can be accomplished; for example, cases of proximal esophageal obstruction can be treated with retrograde endoscopic tunneling. Authors reported 100% technical success rate and significant improvement in the mean dysphagia scores. However, this was a single center case series, involving only four patients. All patients required serial endoscopic dilatation after POETRE. Hence, prospective studies with larger sample size would be required before POETRE can be recommended as a definitive treatment approach for CEO.

Esophageal diverticula

An esophageal diverticulum is a pouch that protrudes outward from the weakened portion of the esophageal lining. Esophageal diverticula are classified according to their location within the esophagus: (1) Zenker's diverticula (ZD) is the most

common type of diverticula, located at the pharyngo-esophageal junction; (2) mid-thoracic diverticula, in the mid-chest; and (3) epiphrenic diverticula, just above the diaphragm [64]. Traditionally, the esophageal diverticula are treated by surgical approach. Recent advances in submucosal tunneling endoscopic septum division (STESD) technique (based on POEM principles) have permitted complete muscular septum dissection while maintaining the mucosal integrity. The initial steps of this technique, including mucosal incision and submucosal tunneling, are similar to those of the POEM procedure. The tunnel is created on both sides of the septum and extended 1 to 2 cm distal to the base of the diverticulum. Total myotomy of the septum is performed followed by mucosal closure at the tunnel entry site with endoscopic clips. Isolated case reports and small cases series have reported the use of this technique in treatment of all three types of esophageal diverticula [65–67]. STESD has the potential to reduce the rate of recurrence, risk of perforation, and mediastinitis; however, prospective studies with longer follow up duration are required prior to wider clinical application.

Zenker's diverticulum

ZD is a rare disease with a prevalence of 0.01 to 0.11% in the general population [68]. Treatment of ZD can be accomplished with open surgery, a rigid endoscope, or with a flexible endoscope (FE). With FE, ZD is treated by diving the septum between the esophageal lumen and diverticulum, and it is preferred over surgery due to its less invasive nature and fewer peri-operative complications [69]. However with FE, there is incomplete division of the septum, and hence, the recurrence rates are higher. Also, it involves the incision of both the mucosa and muscular fibers, which together form the septum of the diverticulum. FE was associated with perforation rates in up to 6.5% of the patients [69]. STESD technique offers a unique solution to the shortcomings of the FE while retaining its non-invasive nature. It uses the submucosal tunnel as an operating space, which provides a clear orientation of the septal wall and full access to myotomy. Further, submucosal tunneling method maintains mucosal integrity and prevents secondary infection [65, 70].

Mid-esophageal diverticulum

Traditionally, surgery is considered as the preferred treatment for this rare condition. Cai et al. recently reported successful treatment of two patients with giant mid-esophageal diverticula with STESD technique [67]. They concluded that this can be a safe, effective, and a less invasive treatment option for mid-esophageal diverticula in appropriately selected patients.

Epiphrenic diverticulum

Recently, a Chinese study reported successful treatment of four cases of epiphrenic diverticula by STESD technique. In this report, technical success rate was 100%, all patients had symptom relief on short-term follow up, and there were no peri-operative AEs [67].

Conclusion

Evolution of third space endoscopy has opened up new horizons for non-invasive management of a variety of esophageal disorders. Even though short-

term and mid-term studies have yielded excellent results, larger studies with long-term clinical data are needed prior to recommending these procedures as first line treatment options. Since a large number of centers across the world are performing these advanced endoscopic procedures, formal guidelines and structured training programs are required to ensure safe and effective outcomes.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that there is no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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