International Journal of Gastrointestinal Intervention

journal homepage: www.ijgii.org

Review Article

Adverse events associated with third space endoscopy: Diagnosis and management

Radhika Chavan*, Zaheer Nabi, and Duvuur Nageshwar Reddy

A B S T R A C T

Third space endoscopy (TSE) is a ‘magnum opus’ in the field of therapeutic gastrointestinal (GI) endoscopy that has led to a paradigm shift in the management of various GI disorders. TSE or submucosal endoscopy is based on the concept of mucosal flap safety valve technique. Since, the basic principle is more or less similar for all the TSE procedures, the nature of major adverse events (AE) also shares some similarity across the spectrum of TSE procedures. These AE include insufflation related AE, bleeding, perforation, and infection. Insufflation related events are among the most commonly encountered AEs. However, majority of the insufflation related AE do not require a specific intervention and not regarded as AE in true sense. Identification of risk factors and adaptation of preventative strategies may help in reducing the incidence of AE. At the same time, early recognition and expeditious management is paramount to reduce morbidities associated with these AE. Due to heterogeneity in the reporting of AE, it is difficult to estimate the actual incidence of AE and compare the results between different studies. Therefore, universal adaptation of a standard reporting system is required to quantify the true incidence of AE for each procedure.

Copyright © 2020, Society of Gastrointestinal Intervention.

Keywords: Endoscopy; Esophageal achalasia; Intraoperative complications, Myotomy; Natural orifice endoscopic surgery

Introduction

Third space endoscopy (TSE) is a major leap in the arena of therapeutic gastrointestinal (GI) endoscopy.¹ Besides peroral endoscopic myotomy (POEM), other procedures which are being performed under the umbrella of TSE include submucosal tunneling endoscopic resection (STER) for subepithelial tumors, peroral endoscopic pyloromyotomy or gastric POEM (G-POEM) for gastroparesis, POEM for Zenker’s diverticulum (Z-POEM), per-rectal endoscopic myotomy (PREM) for Hirschsprung’s disease and peroral endoscopic tunnelling for restoration of esophagus (POETRE) for esophageal strictures.^{1,2}

During TSE, the endoscopist works in the submucosal space in close proximity to the mediastinum and the peritoneal cavity. Since, the vast majority of TSE procedures are performed using the same principle and utilize submucosal space to accomplish the procedures. The nature of AE bears some similarity across these procedures even when performed for different indications. Insufflation related adverse events (AE) are the most commonly reported with all the TSE procedures. Apart from insufflation re-

lated events, other commonly reported AE include bleeding and inadvertent mucosetomy or perforation.³

Overview of AE during TSE

AE during TSE can be divided into three major categories i.e., insufflation related, mucosal injuries, and bleeding. In the following section, we briefly discuss the overview of AE encountered during TSE procedures. The risk factors, strategies to prevent AE and management protocols have been discussed later.

Insufflation related events are the most common AE seen during TSE procedures and include subcutaneous emphysema, capnothorax, capnoperitoneum, retroperitoneal air, mediastinal emphysema, and capnopericardium (Fig. 1, 2).^{4,5} The varying incidences of insufflation related AE is mainly due to the routine use of intraprocedural fluoroscopy or post-procedural computed tomography (CT) in some studies. CT can detect even small amounts of extraluminal air/CO₂ which may not bear any clinical relevance.⁶

Since, mucosa is the only barrier between lumen and medias-

Department of Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, India

Received February 27, 2020; Revised April 7, 2020; Accepted April 7, 2020

* Corresponding author. Department of Gastroenterology, Asian Institute of Gastroenterology, 6-3-661 Somajiguda, Hyderabad 500082, India.

E-mail address: dradrikachavan@gmail.com (R. Chavan).pISSN 2636-0004 eISSN 2636-0012 <https://doi.org/10.18528/ijgii200010>

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Fig. 1. Fluoroscopy showing air around the kidney suggestive of retroperitoneal air.

tinum/peritoneum unattended full thickness mucosal injuries can lead to mediastinitis or peritonitis. Mucosal injuries may occur as a result of thermal injury from the knife or coagulation forceps used for hemostasis. In addition, the endoscope shaft may strain the mucosal incision and lead to an inadvertent enlargement of the mucosal incision.⁷ The overall incidence of mucosal injury during POEM ranges from 1.6% to 17.7%.⁷⁻¹³ Major mucosal injuries are those which cannot be closed endoscopically but require alternative measures such as endoscopic stenting, sponge therapy, surgery, and or drainage.¹² Others have classified mucosal injuries into two types i.e., easy to repair (type I) and difficult to repair (type II).¹¹ Examples of type I mucosal injuries include single to multiple superficial thermal injuries (small, whitish, linear/dotted). Type II mucosal injuries are deep and large (e.g., scorched, round/unevenly bordered mucosal damage). The frequency of type II injuries is usually less (1.7%).¹⁰

Bleeding can occur during or post-procedure and depending on severity it is further classified as minor or major events. Minor intraprocedural bleeding is common during TSE procedures. On the contrary, major bleeding is uncommon (0.2% [0%–1.4%]).^{9,12-15} Major or significant bleeding is considered when it is associated with hemodynamic instability or requires blood transfusion and or endoscopic reintervention, surgery or drainage.^{3,12}

Infectious complications are uncommon during TSE procedures and include mediastinitis, peritonitis, pneumonia, and empyema (0.1%–4.8%).³

Other peri-operative AE include aspiration pneumonia, post-procedure chest/abdominal pain, esophageal/gastric leaks, pleural effusion, atelectasis, cardiac arrhythmia, and pulmonary embolism. Overall incidence of these AE is 0.1% to 0.7%.³ The patients with achalasia are at high risk of aspiration. Therefore, prophylactic measures are required to prevent the risk of aspiration.¹⁶ These include instructions for clear liquids for at least 24 hours before procedure and aspirating esophageal and gastric contents before induction of anesthesia.^{17,18}

Fig. 2. Fluoroscopy showing air under diaphragm suggestive of capnoperitoneum.

AE Related to Types of Intervention

POEM

POEM has been established as a safe and efficacious modality for achalasia cardia. Due to established safety profile, the POEM procedure can be safely accomplished in an endoscopy suite.¹⁹ As with other TSE procedures, there is no established classification system specific to POEM procedure.³ Major AE are uncommon after POEM procedure and have been described in the previous sections (Table 1).^{7-9,11-14,20,21} Initial studies reported a high incidence of AE with POEM mainly due to the use of air for insufflation (instead of CO₂).³ The incidence of AE especially mucosal injuries is higher early during learning curve.²²

Long-term AE specific to POEM include gastroesophageal reflux disease (GERD).²³ Reflux esophagitis is seen in about 30% to 40% cases after POEM. The incidence of severe esophagitis (grade C and D) and symptomatic GERD after POEM is low.^{7,9,21} The risk of GERD is higher after POEM as compared pneumatic balloon dilatation (41% vs 7%) and laparoscopic Heller's myotomy with fundoplication (44% and 29%).^{24,25} Asymptomatic GERD detected on pH studies is more prevalent than symptomatic GERD after POEM.²⁶ It is generally believed that post-POEM GERD responds well to proton pump inhibitor therapy, however there is no long term data on the response to antisecretory therapy in these patients. Several novel strategies have been proposed to prevent GERD after POEM. These include limiting the gastric extent of myotomy (< 4 cm), preservation of sling fibers during posterior POEM and performing NOTES (natural orifice transoral endoscopic surgery) fundoplication along the POEM procedure.²⁶⁻³⁰ However, these techniques need to be validated in prospective trials.

STER

STER is utilized for upper GI tract sub-epithelial tumors. The most common AE associated with STER include insufflation related and mucosal injuries (Table 2).^{5,31-33} A meta-analysis involving 12 studies including 397 patients and 430 lesions showed that the pooled complication rate of STER is 21.5% (95% confidence interval [CI], 13.2–33.1).³⁴ Gas related events are most com-

Table 1 Adverse Events during POEM (Selected Large Studies)

Study	No. of patients/type of study	Adverse events*	GERD (%)
Von Renteln et al (2013) ⁸	70/multicenter prospective	Total = 10 (14.3) Clip dislocation at mucosal closure = 3 (4) Perforation into mediastinum at mucosal entry side = 1 (1) Mucosal injury through electrocautery = 3 (4) Bleeding requiring intervention = 1 (1) Cap detached in submucosal tunnel = 1 (1) Delayed bleeding leading to mediastinal hematoma = 1 (1)	At 3 mo Symptoms = 33 PPI use = 34 Erosive esophagitis = 42 At 6 mo Symptoms = 30 PPI use = 39
Inoue et al (2015) ⁹	500/prospective	Total = 16 (3.2) Pneumothorax underwent drainage = 1 (0.2) Severe bleeding = 1 (0.2) Mucosal perforation = 8 (1.6) Postoperative hematoma = 3 (0.6) Inflammation in gastric lesser omentum = 1 (0.2) Pleural effusion = 2 (0.4)	At 2 mo Symptoms = 16.8 Esophagitis = 64.7 At 1–2 yr Symptoms = 19.4 Esophagitis = 59.2 At 3 yr Symptoms = 21.3 Esophagitis = 56.3
Zhang et al (2016) ¹¹	1,680/retrospective	Major = 55 (3.3) Delayed mucosal barrier failure = 13 (0.8) Delayed bleeding = 3 (0.2) Hydrothorax = 8 (0.5) Pneumothorax = 25 (1.5) Miscellaneous = 6 (0.4) Hospital readmission = 3 (0.2) ICU admission = 2 (0.1) Vital sign instability = 1 (0.1)	Not included
Werner et al (2017) ¹²	241/retrospective	Major = 3 (1.2) Pneumothorax requiring drainage = 1 (0.4) Gastric cardia perforation underwent surgery = 1 (0.4) Hemothorax underwent surgery = 1 (0.4) Minor = 87 (31.1) Prolonged intra-procedural bleeding = 23 (9.5) Mucosal injury = 20 (8.3) (difficult to repair = 2.9) Subcutaneous emphysema = 76 (31.5) Capnoperitoneum = 86 (35.7) Submucosal hematoma = 2 (0.8) Fever = 8 (3.3) Readmission = 2 (0.8)	Not included
Haito-Chavez et al (2017) ¹³	1,826/multicentre retrospective	Total = 137 (7.5) Mild = 116 (6.4) Moderate = 31 (1.7) Severe = 9 (0.5) Esophageal leak = 2 (0.1) Bleeding = 2 (0.1) Perforation = 1 (0.05) Aspiration pneumonia = 1 (0.05) Empyema = 1 (0.05) Capnomediastinum = 1 (0.05) Cardiac arrhythmia = 1 (0.05)	Not analysed
Nabi et al (2018) ⁷	502/retrospective	Major = 8 (1.6) Capnopericardium = 2 (0.4) Capnothorax requiring drainage = 2 (0.4) Enlargement of mucosal incision = 3 (0.6) Readmission = 1 (0.2) Minor = 169 (33.7) Mucosal injury = 19 (3.7) Capnothorax = 3 (0.4) Capnoperitoneum = 62 (12.5) Retroperitoneal air = 84 (16.7) Subcutaneous emphysema = 106 (21.1) Pleural effusion = 1 (0.2)	At 3 mo Symptoms = 46 Erosive esophagitis = 32 High De Meester score = 28.8 At 1 yr Symptoms = 17 Erosive esophagitis = 21.5

monly observed during STER. In a systematic review, the pooled prevalence of gas-related events was 14.8% (95% CI, 10.5–20.5) for subcutaneous emphysema and pneumomediastinum, 6.1% (95% CI, 4.0–9.0) for pneumothorax, and 6.8% (95% CI, 4.7–9.6) for pneumoperitoneum.³⁵ Gas related complications occur more frequently in esophageal tumors and mucosal injuries were seen

in cardia tumor.^{33,34} The main reason for differences in the complications between esophageal and cardia tumor is the absence of serosa in esophagus and a thicker muscularis propria (MP) in cardia which reduces the likelihood of gas related complication. In addition, the complex anatomy of cardia increases the risk of mucosal injury. Majority of the gas related events do not require an

Table 1 Continued

Study	No. of patients/type of study	Adverse events*	GERD (%)
Li et al (2018) ¹⁴	564/prospective	Major = 36 (6.4) Delayed mucosal barrier failure = 3 (0.5) Delayed bleeding requiring admission = 3 (0.5) Hydrothorax requiring drainage = 6 (1.1) Pneumothorax requiring drainage = 21 (3.7) Other = 3 (0.5) (1-postoperative epilepsy, 1-pharyngeal edema, 1-transient hypoxia) Minor = 5 (0.9) Intraoperative bleeding = 3 (0.5) Subcutaneous emphysema = 1 (0.2) Pneumoperitoneum = 1 (0.2)	Symptoms = 36.5 Erosive esophagitis = 17 Clinical reflux = 37.3 (combining symptom + reflux esophagitis)
Shiwaku et al (2019) ²⁰	233/multicenter prospective	Total = 24 (10.3) Deep mucosal injury (perforation) = 11 (4.7) Mucosal injury without perforation = 9 (3.9) Submucosal hematoma = 3 (1.3) Pleurisy = 1 (0.43) Peritonitis = 1 (0.43)	At 1 yr Symptoms = 14.7 PPI use = 21.1 Erosive esophagitis = 54.2
Shiwaku et al (2020) ²¹	1,346/multicentre retrospective	Total = 50 (3.7) Mucosal perforation = 5 (0.4) Mucosal injury without perforation = 24 (1.8) Submucosal hematoma = 9 (0.7) Major bleeding = 2 (0.1)	At 6 mo Symptoms = 14.8 Erosive esophagitis = 63

POEM, peroral endoscopic myotomy; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; ICU, intensive care unit.

*Values are presented as number (%).

Table 2 Adverse Events during Submucosal Tunneling Endoscopic Resection (Selected Studies)

Study	No. of patients/type of study	Location of SET (n)	Size, range (cm)	Adverse events*
Ye et al (2014) ³¹	85/prospective	Esophagus = 60 Cardia = 16 Stomach = 9	1.9 (1.0–3.0)	Total = 8 (9.4) Pneumothorax = 6 (7.1) Subcutaneous emphysema = 8 (9.4) Pneumoperitoneum = 4 (4.7)
Chen et al (2016) ⁵	290/retrospective	Esophagus = 199 Esophagogastric junction = 68 Stomach = 23	2.1 (1.0–7.0)	Total = 68 (23.4) Subcutaneous emphysema = 61 (21) Pneumothorax = 22 (7.6) (drainage = 3.1) Pneumoperitoneum = 15 (5.2) Mucosal injury = 3 (1) (clipping) Major bleeding = 5 (1.7) (endoscopic coagulation) Thoracic effusion = 49 (16.9) (drainage = 3.8) Esophageal pleural fistula = 1 (0.3) (clipping)
Mao et al (2017) ³²	56/prospective	Location of cardia tumor Above GE junction = 18 Below GE junction = 38	1.8 (1.0–3.2)	Total = 9 (15.3) Subcutaneous emphysema = 9 (15.3) Pneumoperitoneum = 9 (15.3) Pneumothorax = 8 (14.3) Pleural effusion = 5 (8.9)
Du et al (2019) ³³	165/retrospective	Upper esophagus = 49 Middle esophagus = 46 Cardia = 59	2 (0.5–8)	Total = 35 (21) Esophageal tumor = 21 (19.8) Cardia tumor = 14 (23.7) Gas related complication = 16 (9.7) Fever = 10 (6) Mucosal injury = 10 (6) Chest/abdominal pain = 4 (2.4) Pleural effusion = 1 (0.6) Perforation = 1 (0.6)

SET, subepithelial tumor; GE, gastroesophageal.

*Values are presented as number (%). More than one events patients.

intervention and therefore, are not AE in true sense. Chen et al⁵ retrospectively analysed 290 patients who underwent STER and reported total 23.4% complications. Only 10.0% out of 23.4% of AE required a special intervention. Other complications reported with STER include pleural and abdominal effusion (8.4% [95% CI, 5.6–12.3]), fever (6%–17%), subphrenic abscess, and perforation requiring thoracotomy.^{33–38}

AE during STER also significantly depends on the origin of

tumor (deeper MP layer 46.7% vs superficial muscularis layer 4.9%; $P < 0.05$), tumor histology (gastrointestinal stromal tumor 26.3% vs leiomyoma 4.6%), size of tumor (5.4% for tumors < 2.0 cm vs 36.8% for tumors ≥ 2.0 cm; $P < 0.05$), irregular shape of the tumor, resection of synchronous lesions, use of air for insufflation, long operative time, and tumor growth pattern (4.1% for the intraluminal growth vs 100% for the extraluminal growth; $P < 0.001$).^{31,32}

Several modifications have been utilized to ease the removal of subepithelial tumor using STER. Repeated withdrawal of the endoscope from the submucosal tunnel may help in rectifying the direction of submucosal tunnel and avoiding overshooting. In addition, repeated injections of around the tumor during the dissection of tumor from MP layer may reduce the risk of mucosal injuries.³² Double-opening method has also been proposed to reduce the difficulties in removing cardia tumors.^{39,40}

G-POEM

G-POEM or peroral pyloromyotomy is gaining acceptance for the management of refractory gastroparesis. AE reported with G-POEM include pain, bleeding, perforation, and capnoperitoneum (Table 3).^{41–47} In different studies, the rate of AE varies from 3.3% to 42.8%.^{41,44,48–50} In a meta-analysis of 10 studies involving 292 patients, the pooled rate of AE was 6.8% (95% CI, 2.4–11.2; $I^2 = 60.8\%$, $P = 0.006$).⁵⁰ In a large study including 100 patients, Rodriguez et al⁴³ reported an AE rate of 10% along with 1 mortality (cardiac reason) within 30 days. Jacques et al,⁴⁶ reported a cumulative of 28 AE in his series of 20 patients. Of these, one patient underwent exploratory laparoscopy for perforation. Pyloric stricture and peri-gastric abscess have also been reported after G-POEM.^{42,51}

A wide variation in the reported incidences of AE is mainly due to heterogeneity in the definitions used in different studies. Patients with gastroparesis are at high risk for post-procedure dehydration (2.2%).⁴³ Therefore, adequate hydration is important in these patients. Injury to duodenal mucosa is also a potential concern and can be prevented by careful dissection near the pyloric

ring and avoiding excess tunnelling (> 1 cm) into the duodenum. Some experts recommend the use of an insulated tip knife to prevent inadvertent mucosal injury.² In addition, selective use of fluoroscopy for identification of pylorus has also been shown to reduce the risk of AE.⁵²

Other submucosal endoscopy procedures

Submucosal endoscopy has been recently introduced for the management of Z-POEM. Most of the published literature regarding Z-POEM is in the form of case reports and small case series. In a recent multicenter study including 75 patients with Zenker's diverticulum, the overall incidence of AE was 6.7% including 1 bleed (managed conservatively) and 4 perforations (1 = severe, 3 = moderate).⁵³

POEM for diverticula (POEM-D) is performed for mid esophageal and epiphrenic diverticula. In case series of 4 patients 2 pneumoperitoneum, 1 with subcutaneous emphysema and 1 patient with aspiration pneumonia is reported.⁵⁴ In a study of 25 patients (20 = Zenker's diverticula, 5 = epiphrenic diverticula) who underwent POEM-D reported 100% technical success with no intra or peri-operative AE.⁵⁵ Compared to other TSE, POEM-D is more technically challenging procedure. High success rate with no AE could be because of highly experienced endoscopist performed the procedure.

Other TSE procedures like POETRE, POEM with fundoplication and PREM have been described in small case series. These procedures are largely experimental, and the technique has not been standardized. Therefore, the safety profile of these procedures re-

Table 3 Adverse Events during Gastric Peroral Endoscopic Myotomy (Selected Studies)

Study	No. of patients/type of study	Adverse events*	Follow-up (mo)
Shlomovitz et al (2015) ⁴¹	7/retrospective	Total = 3 (42.8) Bleeding within 2 wk-pyloric ulcer-clipping done = 1 (14.2) Dysphagia = 1 (14.2) Hospital acquired pneumonia = 1 (14.2)	6.5
Gonzalez et al (2017) ⁴²	29/retrospective	Total = 11 (37.9) Pneumoperitoneum-needle decompression = 5 (17) Moderate abdominal pain-analgesics = 3 (10) Bleeding-spontaneously stopped = 1 (3) Abscess with bleeding (clipping) = 1 (3) Stricture-endoscopic radial incision (insulated tip knife) = 1 (3)	10
Rodriguez et al (2018) ⁴³	100/prospective	Total = 10 (10) Capnoperitoneum and subcutaneous emphysema requiring diagnostic laparoscopy = 1 (1) GI bleeding (2 mucosal ulcer, 2 source not identified) = 4 (4) Severe dehydration = 2 (2) Upper GI endoscopy within 30 days = 3 (3) Death within 30 days-cardiac cause = 1 (1)	3
Kahaleh et al (2018) ⁴⁴	33/multicentre retrospective	Total = 2 (6.1) Ulcer (mucosal defect)-clip placement = 1 (3) Procedural bleeding-managed with coagrasper = 1 (3)	11.5
Mekaroonkamol et al (2019) ⁴⁵	40/retrospective	Total = 3 (7.5) Capnoperitoneum = 1 (2.5) Chronic obstructive pulmonary disease exacerbation = 1 (2.5) Mucosectomy closure site disruption = 1 (2.5)	18
Jacques et al (2019) ⁴⁶	20/prospective	Total 28 adverse events in 16 patients (80%) 20 Related events, 8 Unrelated events 5 Major events Perforation with severe pain requiring laparoscopy = 1 (5)	3
Abdelfatah et al (2020) ⁴⁷	90/retrospective Single myotomy = 55 Double myotomy = 35	Total = 2 (2.2) Tension pneumoperitoneum-needle decompression = 1 (1.1) Mucosectomy site ulcer bleed-endoscopic intervention = 1 (1.1)	3–6

GI, gastrointestinal.

*Values are presented as number (%).

mains to be established in future studies.¹

Safety of Submucosal Endoscopy in Special Population

The literature is limited regarding the safety of TSE procedures in special population like children, elderly, and those with co-morbidities. Few small studies have concluded that POEM is a safe procedure in pediatric population.^{56–59} A recent multicentre study including 117 children reported the outcomes of POEM in children with achalasia. AE in this study included bleeding (1%), aspiration pneumonia (2%), mucosotomies (4%), subcutaneous emphysema (2%), esophageal fistula (1%; required endoscopic fistulotomy with surgical drainage), and GER (15%).⁶⁰

Elderly people may be at high risk of AE because of associated co-morbidities and relatively poor tolerance to general anaesthesia in general. Limited data suggests that POEM can be safely performed in elderly patients as well. In one study including 76 octogenarians, AE were reported in 14.6% patients.⁶¹ Of note, one patient suffered from cardiac arrhythmia which was regarded as severe AE according to ASGE (American Society for Gastrointestinal Endoscopy) lexicon.⁶² In a propensity score matched comparative study (≥ 65 and < 65 years), the rate of AE (2.88% vs 2.18%, $P = 0.663$) and clinical reflux (23.5% vs 21.59%, $P = 0.724$) were similar in both the groups.⁶³

In a study (abstract form) including 61 patients who underwent POEM, 18 patients had severe systemic illnesses with American Society of Anesthesiologists classification grade 3–4. POEM could be safely accomplished in all the patients with no major AE.⁶⁴ The data on the safety of TSE procedures in this special cohort of patients should be interpreted with caution. Large, prospective trials are required before concluding the safety of TSE in children, elderly, and those with severe co-morbidities.

Prediction, Prevention, and Management of AE

The prediction or the risk factors predisposing to AE is important as it alerts the endoscopist and allows for better management strategies. In this section, we will discuss the risk factors predisposing to AE, strategies to prevent them and appropriate management in case AE occur (Table 4).

Insufflation related events

All the TSE procedures are performed in third space or submucosal space. Therefore, insufflation related events are far more frequent than other therapeutic endoscopic procedures performed in GI lumen. Since, the diffusion capacity of air is much lower than CO₂, the use of air for insufflation is the most important determinant of insufflation related AE. The impact of the type of mucosal incision on the incidence of insufflation related AE is not well known. In a study from China, gas related complications were significantly fewer in the transverse incision group as compared to longitudinal incision (9.8% vs 41.7%) during POEM procedure.⁶⁵ Barring this study, there is not enough data to support transverse incision during POEM. The use of knives equipped with water jet has been shown to reduce the procedure duration. This in turn can potentially reduce the incidence of insufflation related AE.^{66,67}

The decision to intervene in cases with insufflation related AE is made after a combined assessment by the endoscopist and the accompanying anaesthetist. Subcutaneous emphysema is common during TSE procedures performed in esophageus. However, it usually gets resolved within 24–48 hours and does not require

any specific intervention. The decision to intervene in other insufflation related AE (capnoperitoneum, retroperitoneal CO₂) is based on the ventilatory parameters (e.g., end-tidal CO₂ > 50, high peak airway pressure) and the presence of clinically significant abdominal distension. When an intervention is required, a stepwise approach can be utilized to deal with these events. These include temporary stopping the procedure for 10–15 minutes, modifying the ventilator settings to augment washout of CO₂ (increasing positive end-expiratory pressure, increasing respiratory rate and giving 100% oxygen in the fresh gas flow), and needle drainage of air/CO₂ in that order.¹⁸

When available, fluoroscopy may aid in differentiating retroperitoneal CO₂ from capnoperitoneum (Fig. 1, 2). The latter can be readily managed using needle drainage using a 18 G intravenous cannula in right subchondral region along the anterior axillary line.¹⁸ On the other hand, accumulation of significant retroperitoneal CO₂ requires temporary pausing of the procedure and modification of ventilatory settings.¹⁸ In our experience, accumulation of retroperitoneal CO₂ during POEM is as common as capnoperitoneum (air under diaphragm) (16.7% vs 12.4%).⁷ Capnothorax is uncommon as compared to capnoperitoneum and identified by reduced chest wall excursion on the affected side and increased

Table 4 Risk Factors for Adverse Events during TSE

Patient related
Elderly patient with co-morbidities
American Society of Anesthesiologist classification grade 3–4
Patients on antithrombotics
Disease related
Achalasia cardia
Unhealthy mucosa (stasis esophagitis) during POEM
Sigmoid esophagus
Prior treatment (Heller's myotomy, balloon dilatation)
Lots of food residue in esophagus (risk of aspiration)
Esophageal candidiasis
Subepithelial tumor
Large size of tumor (> 3 cm), irregular shape
Tumor originating from muscularis propria
Cardia tumor
Extraluminal tumor
Gastroparesis
Scarring or ulceration in antrum
Diverticula
Large size of diverticula
Diverticula associated with motility disorder
Procedure related
Use of air for insufflation
Incorrect electrosurgical settings (other than spray coagulation)
Continuous large/heavy burst of current during tunneling or myotomy
Knife (without water jet facility)
STER of two synchronous lesions
Unable to localize the lesion during STER and pyloric sphincter during G-POEM
Operator related
Long operative time
During learning curve

TSE, third space endoscopy; POEM, peroral endoscopic myotomy; STER, submucosal tunnelling endoscopic resection; G-POEM, gastric POEM.

airway pressure. The management options include temporary pausing the procedure in small capnothoraces and drainage in cases with a large capnothorax. Drainage of capnothorax is accomplished by puncturing the intercostal space in infra-scapular region along the posterior axillary line. Capnopericardium is rare and usually goes undetected (2.4%).⁶⁸ However, tension capnopericardium is life threatening and early detection is paramount.^{69–71} We have previously described capnopericardium during POEM procedure successfully managed by simply withholding the procedure for few minutes.⁷²

Mucosal injuries

Mucosal injuries are the most common clinically relevant AE. Several factors found to increase the risk of mucosal injuries during POEM include previous myotomy (Heller's or POEM), submucosal fibrosis, presence of diverticula, and during learning curve.¹⁰ Anterior approach in POEM may be associated with a higher incidence of mucosal injuries as compared to posterior approach because of acute angulation of knife during anterior POEM.³ Similarly, STER for cardia tumor is more prone for mucosal injury because of complex anatomy and difficulty in creating tunnel when compared to esophageal STER.³³

All the TSE are based on the principle of mucosal flap safety valve technique where preservation of muscle fibers is essen-

tial along the incision site. Therefore, it is important to avoid deep thermal injuries at the site of mucosal incision. This can be achieved by ensuring adequate bulge at the incision site. Minor bleeding is common at incision site and stops spontaneously in majority of the cases. Therefore, application of excess coagulation along incision site is not only unwarranted but may lead to delayed thermal injury as well. Other steps to reduce the risk of mucosal injuries include liberal use of submucosal injections to separate mucosa from the muscle layer, dissecting close to the muscle layer, checking the direction of tunnelling at regular intervals, and avoiding prolonged bursts of spray coagulation. The endoscopist should exercise caution while using spray coagulation in circumstances where mucosa and muscle layer are close to each other like tight gastroesophageal junction, cases with severe submucosal fibrosis. In some cases, meticulous fiber by fiber dissection using endocut mode can be rewarding. It is crucial to carefully inspect the mucosa at the end of the procedure.³ The utility of routine second look endoscopy before initiating oral diet is debatable. In selected cases, where the mucosa is thick and friable especially in cases with achalasia and where the closure of incision was thought to be sub-optimal, second look endoscopy may be performed. The use of novel bipolar devices may reduce the incidence of mucosal injuries. In this regard, the utility of a new bipolar device for performing POEM and STER procedures was shown by our group. This knife uses a bipolar radiofrequency energy for cutting which produces less charring. In addition, this device has insulated upper surface and a protective hull at bottom which prevents inadvertent injury to mucosa or muscle.⁷³

Majority of the mucosal injuries can be dealt with through the scope clips. In special circumstances, over the scope clips, endoscopic sutures, endoloop and self-expandable metal stents, endoloop and clips and fibrin glue have also been used to close the defect.¹⁰ Surgery has been reported, but is rarely used to repair the mucosal injuries (0.4%).^{12,13}

Bleeding

Intra-procedural bleeding can occur at any of the steps during TSE i.e., mucosal incision, submucosal tunnelling, and myotomy or tumor excision (Fig. 3).³ Submucosal space is enriched with small to medium sized vessels especially along lower esophagus and gastric cardia which is also the site of significant bleeding in most of the cases (Fig. 4). In our experience, bleeding is more frequent in cases with long standing achalasia with changes of stasis esophagitis. In these cases, it is important to choose an appropriate and relatively avascular site for mucosal incision to avoid bleeding at incision site. The utility of optical coherence tomography (OCT) to assess vascularity prior to POEM has been evaluated

Fig. 3. Bleeding from the site of mucosal incision during peroral endoscopic myotomy.

Fig. 4. (A) Active spurting seen during tunnelling from inadvertent injury to vessels. (B) Control of bleeding using coagulation forceps.

in a multicentre, observational study. Bleeding was significantly less frequent in the OCT arm as compared to control group (8% vs 43%).⁷⁴ However, routine use of OCT may not be justified as intraprocedural bleeding is almost never a major concern and can be easily managed.

Minor bleeds and small vessels can be managed with the knife itself in spray coagulation (Effect 2, 50 W) or soft coagulation mode (Effect 4, 80 W). Whereas, larger vessels should be prophylactically coagulated using a hemostatic forceps (Fig. 5). Whenever in doubt, the beginner should err on the side of using a hemostatic forceps for prophylactic coagulation. The steps for effective hemostasis during TSE are as follows: transient tamponade using the cap attached to the scope to minimize the contamination of dissection field, accurate localization of the bleeding site using water jet, closure of hemostatic forceps over the presumed bleeding point, use water jet to confirm that the correct site has been grasped and finally, coagulation till the vessel gets blanched. After completion of the procedure, the tunnel should be inspected for any actively bleeding site or partially coagulated vessels.

In contrast to intraprocedural bleeding, delayed bleeding is exceedingly rare (0.2%–0.8%).^{4,11,14} In a large series of POEM (1,680 patients), delayed bleeding was reported in 3 patients (0.2%).¹¹ Significant delayed bleeding may present with chest pain, hematemesis and melena. The management of delayed bleeding is challenging and depends on the hemodynamic status of patients.

In one series, the authors achieved hemostasis by endoscopic vessel coagulation and Sengstaken–Blakemore tube compression.¹¹ However, caution is advised while using Sengstaken–Blakemore tube due to the risk of pressure necrosis especially when the underlying muscular layer has been severed.

Infections

Dehiscence of the mucosal barrier is one of the major factors predisposing to infection (Fig. 6). In our opinion, pre-POEM status of esophageal mucosa is one of the major factors responsible for delayed mucosal barrier failure.

Zhang et al¹¹ reported 13 cases (0.8%) of delayed mucosal barrier failure leading to infection.

The prevention of infections during TSE procedures is usually achieved by administering antibiotic prophylaxis before and after the procedure for a variable duration. However, this practice is not evidence based and the dose/duration of antibiotic prophylaxis is variable in different studies. Contrary to the popular belief, the use of gentamycin (40–80 mg) spray into the submucosal tunnel is probably not useful in reducing the risk of infectious complications.⁷⁵

Mild post-operative infections can usually be managed with antibiotics alone. Whereas, significant infections are those which require an active intervention (drainage/surgery), prolonged

Fig. 5. (A) Penetrating vessels encountered beyond the gastroesophageal junction. (B) Prophylactic coagulation of the same vessels with coagrasper.

Fig. 6. Delayed mucosal barrier failure after peroral endoscopic myotomy.

Fig. 7. Computed tomography showed right pleural effusion in post-peroral endoscopic myotomy patient who was complaining of right infra-scapular pain and fever on day 2.

course of antibiotics, prolonged hospital stay.¹² The management of delayed mucosal barrier failure includes withholding oral feeds, nasogastric/naso-jejunal feedings and intravenous antibiotics. Endoscopic closure is usually not successful under such circumstances. Empyema should be promptly drained along with administration of broad-spectrum antibiotics (Fig. 7).

Classification/Grading of AE

In majority of the published studies, no standard classification system has been used to define the severity of AE. Other studies have utilized ASGE lexicon and Clavien–Dindo classification systems. The latter was established for surgical procedures. A large study (abstract form) including 1,829 POEM procedures, compared ASGE lexicon to Clavien–Dindo classification system. The authors concluded that Clavien–Dindo is more appropriate for POEM procedures.⁷⁶ Our group has previously proposed a new classification system for AE encountered during POEM procedure.³ There is no

consensus over which classification system to use for TSE procedures.

We propose the following strategy for classifying AE during TSE procedures. AE can be defined according to the time of onset and the severity of AE. Accordingly, the AE can occur during the procedure, early post-procedure period (up to 14 days) and late (any time after 14 days).⁷² The severity of AE can be classified into major and minor AE.^{11,12,14} Major perioperative AE are those which result in vital-sign instability, intensive care unit stay, hospital readmission, conversion to open surgery, invasive postoperative procedures, blood transfusion, or hospitalization > 5 days because of functional impairment of the patient. Minor require interventions but do not qualify for major AE as mentioned above. These include pneumoperitoneum requiring needle decompression only, prolonged intraoperative bleeding (> 200 mL) not demanding transfusion, and small mucosal injuries amenable to closure with standard endoclippping (Table 5).^{3,12,62,76}

Table 5 Classification of AE during Third Space Endoscopy^{3,12,62,76}

Category	Type of AE
Severe	Any events requiring prolongation of hospital for > 10 days and ICU admission > 1 night Insufflation related events - Causing hemodynamic instability - Requiring premature termination of procedure ± drainage Mucosal injury (during or after) - Requiring special closure techniques (stenting/sponge/surgery/drainage) Bleeding (during or after) - Requiring blood transfusion - Causing hemodynamic instability - Endoscopic reintervention or surgery Post procedure leak - Requiring endoscopic reintervention, drainage or surgery Cardiopulmonary events - Causing hemodynamic instability - Requiring premature termination of procedure Infection - Causing hemodynamic instability requiring antibiotics ± drainage or surgery
Moderate	Any events requiring prolongation of hospital for 4–10 days and ICU admission for 1 day Insufflation related events with high probability of hemodynamic compromise requiring prolonged withholding of procedure (15 min) ± immediate drainage - Capno-pericardium - Mediastinal emphysema - Tension pneumothorax Pleural effusion (during or after) - Requiring drainage ± antibiotics
Mild	Insufflation related events requiring temporary withholding of procedure ± drainage - Retroperitoneum - Pneumothorax - Capno-peritoneum Mucosal injury (during or after) which can closed endoscopically Bleeding (during or after) not requiring blood transfusion or additional endoscopic intervention Infection requiring prolonged antibiotics
Not an AE	Insufflation related events not requiring any measures and accidently detected during fluoroscopy - Small pneumothorax - Small pneumoperitoneum - Retroperitoneum - Mild mediastinal emphysema - Subcutaneous emphysema

AE, adverse event; ICU, intensive care unit.

Fig. 8. Approach to prevent adverse events during third space endoscopy. POEM, peroral endoscopic myotomy; G-POEM, gastric POEM.

Summary

TSE has emerged as an effective treatment modality for various GI diseases. The understanding of the nuances associated with submucosal space has allowed the endoscopists to expand the indications for TSE procedures. Although TSE is technically challenging and complex procedure, major AE are uncommon. POEM and STER have been the mainstay of TSE procedures. Other procedures like Z-POEM, G-POEM, and PREM are relatively new. For the same reason, the nature and frequency of AE associated with the latter procedures is not well known. Learning curve is one of the factors for high incidences of AE; however, it can be minimised by extensive preclinical training and training on animal models. Systematic approach towards AE and adapting important preventive strategy helps in reducing the incidence of AE (Fig. 8). In addition, a uniform reporting of AE should be adapted to allow for comparison among different studies.

Conflicts of Interest

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

ORCID

Radhika Chavan, <https://orcid.org/0000-0002-5363-597X>
 Zaheer Nabi, <https://orcid.org/0000-0003-2713-4781>
 Duvuur Nageshwar Reddy, <https://orcid.org/0000-0002-5992-1678>

References

- Nabi Z, Nageshwar Reddy D, Ramchandani M. Recent advances in third-space endoscopy. *Gastroenterol Hepatol (N Y)*. 2018;14:224-32.
- Bapaye A, Korrapati SK, Dharamsi S, Dubale N. Third space endoscopy: lessons learnt from a decade of submucosal endoscopy. *J Clin Gastroenterol*. 2020;54:114-29.
- Nabi Z, Reddy DN, Ramchandani M. Adverse events during and after per-oral endoscopic myotomy: prevention, diagnosis, and management. *Gastrointest Endosc*. 2018;87:4-17.
- Ren Z, Zhong Y, Zhou P, Xu M, Cai M, Li L, et al. Perioperative management and treatment for complications during and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA) (data from 119 cases). *Surg Endosc*. 2012;26:3267-72.
- Chen T, Zhang C, Yao LQ, Zhou PH, Zhong YS, Zhang YQ, et al. Management of the complications of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors. *Endoscopy*. 2016;48:149-55.
- Cai MY, Zhou PH, Yao LQ, Zhu BQ, Liang L, Li QL. Thoracic CT after peroral endoscopic myotomy for the treatment of achalasia. *Gastrointest Endosc*. 2014;80:1046-55.
- Nabi Z, Ramchandani M, Chavan R, Tandan M, Kalapala R, Darisetty S, et al. Peroral endoscopic myotomy in treatment-naïve achalasia patients versus prior treatment failure cases. *Endoscopy*. 2018;50:358-70.
- Von Renteln D, Fuchs KH, Fockens P, Bauerfeind P, Vassiliou MC, Werner YB, et al. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology*. 2013;145:309-11.e1-3.
- Inoue H, Sato H, Ikeda H, Onimaru M, Sato C, Minami H, et al. Per-oral endoscopic myotomy: a series of 500 patients. *J Am Coll Surg*. 2015;221:256-64.
- Wang Y, Liu ZQ, Xu MD, Chen SY, Zhong YS, Zhang YQ, et al. Clinical and endoscopic predictors for intraoperative mucosal injury during per-oral endoscopic myotomy. *Gastrointest Endosc*. 2019;89:769-78.
- Zhang XC, Li QL, Xu MD, Chen SY, Zhong YS, Zhang YQ, et al. Major perioperative adverse events of peroral endoscopic myotomy: a systematic 5-year analysis. *Endoscopy*. 2016;48:967-78.
- Werner YB, von Renteln D, Noder T, Schachschal G, Denzer UW, Groth S, et al. Early adverse events of per-oral endoscopic myotomy. *Gastrointest Endosc*. 2017;85:708-18.e2.
- Haito-Chavez Y, Inoue H, Beard KW, Draganov PV, Ujiki M, Rahden BHA, et al. Comprehensive analysis of adverse events associated with per oral endoscopic myotomy in 1826 patients: an international multicenter study. *Am J Gastroenterol*. 2017;112:1267-76.
- Li QL, Wu QN, Zhang XC, Xu MD, Zhang W, Chen SY, et al. Outcomes of per-oral endoscopic myotomy for treatment of esophageal achalasia with a median follow-up of 49 months. *Gastrointest Endosc*. 2018;87:1405-12.e3.
- Akintoye E, Kumar N, Obaitan I, Alayo QA, Thompson CC. Peroral endoscopic myotomy: a meta-analysis. *Endoscopy*. 2016;48:1059-68.
- Saxena P, Pippenger R, Khashab MA. Preventing aspiration during peroral endoscopic myotomy. *J Anesth*. 2014;28:959.
- Yang D, Pannu D, Zhang Q, White JD, Draganov PV. Evaluation of anesthesia management, feasibility and efficacy of peroral endoscopic myotomy (POEM) for achalasia performed in the endoscopy unit. *Endosc Int Open*. 2015;3:E289-95.
- Darisetty S, Nabi Z, Ramchandani M, Chavan R, Kotla R, Nageshwar Reddy D. Anesthesia in per-oral endoscopic myotomy: a large tertiary care centre experience. *Indian J Gastroenterol*. 2017;36:305-12.
- Khashab MA, El Zein M, Kumbhari V, Besharati S, Ngamruengphong S, Messallam A, et al. Comprehensive analysis of efficacy and safety of peroral endoscopic myotomy performed by a gastroenterologist in the endoscopy unit: a single-center

- experience. *Gastrointest Endosc.* 2016;83:117–25.
20. Shiwaiku H, Inoue H, Sato H, Onimaru M, Minami H, Tanaka S, et al. Peroral endoscopic myotomy for achalasia: a prospective multicenter study in Japan. *Gastrointest Endosc.* 2019. doi: 10.1016/j.gie.2019.11.020. [Epub ahead of print]
 21. Shiwaiku H, Inoue H, Onimaru M, Minami H, Sato H, Sato C, et al. Multicenter collaborative retrospective evaluation of peroral endoscopic myotomy for esophageal achalasia: analysis of data from more than 1300 patients at eight facilities in Japan. *Surg Endosc.* 2020;34:464–8.
 22. Liu Z, Zhang X, Zhang W, Zhang Y, Chen W, Qin W, et al. Comprehensive evaluation of the learning curve for peroral endoscopic myotomy. *Clin Gastroenterol Hepatol.* 2018;16:1420–6.e2.
 23. Kumbhari V, Familiari P, Bjerregaard NC, Pioche M, Jones E, Ko WJ, et al. Gastroesophageal reflux after peroral endoscopic myotomy: a multicenter case-control study. *Endoscopy.* 2017;49:634–42.
 24. Ponds FA, Fockens P, Lei A, Neuhaus H, Beyna T, Kandler J, et al. Effect of peroral endoscopic myotomy vs pneumatic dilation on symptom severity and treatment outcomes among treatment-naïve patients with achalasia: a randomized clinical trial. *JAMA.* 2019;322:134–44.
 25. Werner YB, Hakanson B, Martinek J, Repici A, von Rahden BHA, Bredenoord AJ, et al. Endoscopic or surgical myotomy in patients with idiopathic achalasia. *N Engl J Med.* 2019;381:2219–29.
 26. Nabi Z, Ramchandani M, Reddy DN. Per-oral endoscopic myotomy and gastroesophageal reflux: where do we stand after a decade of “POETRY”? *Indian J Gastroenterol.* 2019;38:287–94.
 27. Inoue H, Shiwaiku H, Kobayashi Y, Chiu PWY, Hawes RH, Neuhaus H, et al. Statement for gastroesophageal reflux disease after peroral endoscopic myotomy from an international multicenter experience. *Esophagus.* 2020;17:3–10.
 28. Inoue H, Ueno A, Shimamura Y, Manolakis A, Sharma A, Kono S, et al. Peroral endoscopic myotomy and fundoplication: a novel NOTES procedure. *Endoscopy.* 2019;51:161–4.
 29. Tanaka S, Toyonaga T, Kawara F, Watanabe D, Hoshi N, Abe H, et al. Novel peroral endoscopic myotomy method preserving oblique muscle using two penetrating vessels as anatomic landmarks reduces postoperative gastroesophageal reflux. *J Gastroenterol Hepatol.* 2019;34:2158–63.
 30. Nabi Z, Ramchandani M, Darisetty S, Kotla R, Reddy DN. Peroral endoscopic myotomy with endoscopic fundoplication in a patient with idiopathic achalasia. *Endoscopy.* 2020;52:74–5.
 31. Ye LP, Zhang Y, Mao XL, Zhu LH, Zhou X, Chen JY. Submucosal tunneling endoscopic resection for small upper gastrointestinal subepithelial tumors originating from the muscularis propria layer. *Surg Endosc.* 2014;28:524–30.
 32. Mao XL, Ye LP, Zheng HH, Zhou XB, Zhu LH, Zhang Y. Submucosal tunneling endoscopic resection using methylene-blue guidance for cardiac subepithelial tumors originating from the muscularis propria layer. *Dis Esophagus.* 2017;30:1–7.
 33. Du C, Chai NL, Ling-Hu EQ, Li ZJ, Li LS, Zou JL, et al. Submucosal tunneling endoscopic resection: an effective and safe therapy for upper gastrointestinal submucosal tumors originating from the muscularis propria layer. *World J Gastroenterol.* 2019;25:245–57.
 34. Song S, Wang X, Zhang S, Li Y, Zhang X, Chu X. Efficacy and complications of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors and exploration for influencing factors. *Z Gastroenterol.* 2018;56:365–73.
 35. Lv XH, Wang CH, Xie Y. Efficacy and safety of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors: a systematic review and meta-analysis. *Surg Endosc.* 2017;31:49–63.
 36. Li Z, Gao Y, Chai N, Xiong Y, Ma L, Zhang W, et al. Effect of submucosal tunneling endoscopic resection for submucosal tumors at esophagogastric junction and risk factors for failure of en bloc resection. *Surg Endosc.* 2018;32:1326–35.
 37. Li QL, Chen WF, Zhang C, Hu JW, Zhou PH, Zhang YQ, et al. Clinical impact of submucosal tunneling endoscopic resection for the treatment of gastric submucosal tumors originating from the muscularis propria layer (with video). *Surg Endosc.* 2015;29:3640–6.
 38. Li QY, Meng Y, Xu YY, Zhang Q, Cai JQ, Zheng HX, et al. Comparison of endoscopic submucosal tunneling dissection and thoracoscopic enucleation for the treatment of esophageal submucosal tumors. *Gastrointest Endosc.* 2017;86:485–91.
 39. Nabi Z, Ramchandani M, Sayyed M, Darisetty S, Kotla R, Rao GV, et al. Outcomes of submucosal tunneling endoscopic resection in upper gastrointestinal subepithelial tumors. *Indian J Gastroenterol.* 2019;38:509–17.
 40. Zhang Q, Cai JQ, Xiang L, Wang Z, de Liu S, Bai Y. Modified submucosal tunneling endoscopic resection for submucosal tumors in the esophagus and gastric fundus near the cardia. *Endoscopy.* 2017;49:784–91.
 41. Shlomovitz E, Pescarus R, Cassera MA, Sharata AM, Reavis KM, Dunst CM, et al. Early human experience with per-oral endoscopic pyloromyotomy (POP). *Surg Endosc.* 2015;29:543–51.
 42. Gonzalez JM, Benezzech A, Vitton V, Barthet M. G-POEM with antro-pyloromyotomy for the treatment of refractory gastroparesis: mid-term follow-up and factors predicting outcome. *Aliment Pharmacol Ther.* 2017;46:364–70.
 43. Rodriguez J, Strong AT, Haskins IN, Landreneau JP, Allemang MT, El-Hayek K, et al. Per-oral pyloromyotomy (POP) for medically refractory gastroparesis: short term results from the first 100 patients at a high volume center. *Ann Surg.* 2018; 268:421–30.
 44. Kahaleh M, Gonzalez JM, Xu MM, Andalib I, Gaidhane M, Tyberg A, et al. Gastric peroral endoscopic myotomy for the treatment of refractory gastroparesis: a multicenter international experience. *Endoscopy.* 2018;50:1053–8.
 45. Mekaroonkamol P, Patel V, Shah R, Li B, Luo H, Shen S, et al. Association between duration or etiology of gastroparesis and clinical response after gastric peroral endoscopic pyloromyotomy. *Gastrointest Endosc.* 2019;89:969–76.
 46. Jacques J, Pagnon L, Hure F, Legros R, Crepin S, Fauchais AL, et al. Peroral endoscopic pyloromyotomy is efficacious and safe for refractory gastroparesis: prospective trial with assessment of pyloric function. *Endoscopy.* 2019;51:40–9.
 47. Abdelfatah MM, Li B, Kapil N, Noll A, Li L, Luo H, et al. Short-term outcomes of double pyloromyotomy versus single pyloromyotomy at peroral endoscopic pyloromyotomy in treatment of gastroparesis (with video). *Gastrointest Endosc.* 2020. doi: 10.1016/j.gie.2020.01.016. [Epub ahead of print]
 48. Mekaroonkamol P, Dacha S, Wang L, Li X, Jiang Y, Li L, et al. Gastric peroral endoscopic pyloromyotomy reduces symptoms, increases quality of life, and reduces health care use for patients with gastroparesis. *Clin Gastroenterol Hepatol.* 2019; 17:82–9.
 49. Khashab MA, Ngamruengphong S, Carr-Locke D, Bapaye A, Benias PC, Serouya S, et al. Gastric per-oral endoscopic myotomy for refractory gastroparesis: results from the first multicenter study on endoscopic pyloromyotomy (with video). *Gastrointest Endosc.* 2017;85:123–8.
 50. Spadaccini M, Maselli R, Chandrasekar VT, Anderloni A, Carrara S, Galtieri PA, et al. Gastric peroral endoscopic pyloromyotomy for refractory gastroparesis: a systematic review of early outcomes with pooled analysis. *Gastrointest Endosc.* 2020; 91:746–52.e5.
 51. Xu J, Chen T, Elkholy S, Xu M, Zhong Y, Zhang Y, et al. Gastric peroral endoscopic myotomy (G-POEM) as a treatment for refractory gastroparesis: long-term outcomes. *Can J Gastroenterol Hepatol.* 2018;2018:6409698.
 52. Xue HB, Fan HZ, Meng XM, Cristofaro S, Mekaroonkamol P, Dacha S, et al. Fluoroscopy-guided gastric peroral endoscopic pyloromyotomy (G-POEM): a more reliable and efficient method for treatment of refractory gastroparesis. *Surg Endosc.* 2017;31:4617–24.
 53. Yang J, Novak S, Ujiki M, Hernández Ó, Desai P, Benias P, et al. An international study on the use of peroral endoscopic myotomy in the management of Zenker’s diverticulum. *Gastrointest Endosc.* 2020;91:163–8.
 54. Orlandini B, Barret M, Guillaumot MA, Léandri C, Leblanc S, Prat F, et al. Per-oral endoscopic myotomy for esophageal diverticula with or without esophageal motility disorders. *Clin Res Hepatol Gastroenterol.* 2020;44:82–9.
 55. Maydeo A, Patil GK, Dalal A. Operative technical tricks and 12-month outcomes of diverticular peroral endoscopic myotomy (D-POEM) in patients with symptomatic esophageal diverticula. *Endoscopy.* 2019;51:1136–40.
 56. Nabi Z, Ramchandani M, Darisetty S, Kotla R, Reddy DN. Impact of prior treatment on long-term outcome of peroral endoscopic myotomy in pediatric achalasia. *J Pediatr Surg.* 2019. doi: 10.1016/j.jpedsurg.2019.07.010. [Epub ahead of print]
 57. Nabi Z, Ramchandani M, Chavan R, Darisetty S, Kalapala R, Shava U, et al. Outcome of peroral endoscopic myotomy in children with achalasia. *Surg Endosc.* 2019;33:3656–64.
 58. Liu Z, Wang Y, Fang Y, Huang Y, Yang H, Ren X, et al. Short-term safety and efficacy of peroral endoscopic myotomy for the treatment of achalasia in children. *J Gastroenterol.* 2020;55:159–68.
 59. Lee Y, Brar K, Doumouras AG, Hong D. Peroral endoscopic myotomy (POEM) for the treatment of pediatric achalasia: a systematic review and meta-analysis. *Surg Endosc.* 2019;33:1710–20.
 60. Choné A, Familiari P, von Rahden B, Desai P, Inoue H, Shimamura Y, et al. Multicenter evaluation of clinical efficacy and safety of per-oral endoscopic myotomy in children. *J Pediatr Gastroenterol Nutr.* 2019;69:523–7.
 61. Chen YI, Inoue H, Ujiki M, Draganov PV, Colavita P, Mion F, et al. An international multicenter study evaluating the clinical efficacy and safety of per-oral endoscopic myotomy in octogenarians. *Gastrointest Endosc.* 2018;87:956–61.
 62. Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc.* 2010;71:446–54.
 63. Liu XY, Cheng J, Chen WF, Xu MD, Liu ZQ, Wang Y, et al. Effect of peroral endoscopic myotomy in geriatric patients: a propensity score matching study. *Surg Endosc.* 2019. doi: 10.1007/s00464-019-07070-9. [Epub ahead of print]
 64. Bapaye A, Dubale N, Desai PN, Mehta N, Pujari R, Date S, et al. Tu1500 safety of per-oral endoscopic myotomy (POEM) in patients with severe co-morbidities. *Gastrointest Endosc.* 2015;81(5 Suppl 1):AB486.
 65. Zhai Y, Linghu E, Li H, Qin Z, Wang X, Du H, et al. [Comparison of peroral endoscopic myotomy with transverse entry incision versus longitudinal entry incision for achalasia]. *Nan Fang Yi Ke Da Xue Xue Bao.* 2013;33:1399–402. Chinese.
 66. Cai MY, Zhou PH, Yao LQ, Xu MD, Zhong YS, Li QL, et al. Peroral endoscopic myotomy for idiopathic achalasia: randomized comparison of water-jet assisted versus conventional dissection technique. *Surg Endosc.* 2014;28:1158–65.
 67. Nabi Z, Ramchandani M, Chavan R, Kalapala R, Darisetty S, Reddy DN. Outcome of peroral endoscopic myotomy in achalasia cardia: experience with a new triangular knife. *Saudi J Gastroenterol.* 2018;24:18–24.
 68. Pannu D, Yang D, Abbott PL, Draganov PV. Prospective evaluation of CT esophagram findings after peroral endoscopic myotomy. *Gastrointest Endosc.* 2016;84: 408–15.
 69. Banks-Venegoni AL, Desilets DJ, Romanelli JR, Earle DB. Tension capnopericardium and cardiac arrest as an unexpected adverse event of peroral endoscopic myotomy (with video). *Gastrointest Endosc.* 2015;82:1137–9.
 70. Kim D, Haouzi P. Tension pneumopericardium during peroral endoscopic myotomy: a case report and review of literature. *Chest.* 2016;150(4 Suppl 1):265A.
 71. Louridasamy D, Patel S, Thyagarajan B, Anthony JS, Gorcey S, Kramer V, et al. Pneumopericardium due to delayed esophageal leak after per oral endoscopic myotomy (POEM). *Chest.* 2016;150(4 Suppl 1):671A.

72. Nabi Z, Ramchandani M, Chavan R, Kalapala R, Darisetty S, Rao GV, et al. Peroral endoscopic myotomy for achalasia cardia: outcomes in over 400 consecutive patients. *Endosc Int Open*. 2017;5:E331-9.
73. Nabi Z, Chavan R, Ramchandani M, Darisetty S, Reddy DN. Peroral endoscopic myotomy in a patient with failed Heller's myotomy by use of a novel bipolar radiofrequency device. *VideoGIE*. 2020;5:138-40.
74. Desai AP, Tyberg A, Kedia P, Smith MS, Martinez G, Zamarripa F, et al. Optical coherence tomography (OCT) prior to peroral endoscopic myotomy (POEM) reduces procedural time and bleeding: a multicenter international collaborative study. *Surg Endosc*. 2016;30:5126-33.
75. Familiari P, Gigante G, Marchese M, Boskoski I, Tringali A, Perri V, et al. Peroral endoscopic myotomy for esophageal achalasia: outcomes of the first 100 patients with short-term follow-up. *Ann Surg*. 2016;263:82-7.
76. Parsa N, Chavez YH, Gutierrez OIB, Paiji C, Inoue H, Beard KW, et al. Sa1907 classification and grading of adverse events related to peroral endoscopic myotomy (poem): a comparison between the American Society of Gastrointestinal Endoscopy lexicon and the Clavien-Dindo classification. *Gastrointest Endosc*. 2018;87(6 Suppl 1):AB244-5.