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2007–2019: a "Third"-Space Odyssey in the Endoscopic Management of Gastrointestinal Tract Diseases

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Abstract

Purpose of review The main scope of this review article is to introduce readers to the innovative field of third-space endoscopy and offer a closer look at its history, milestones, and procedure spectrum while discussing ongoing and future challenges arising from its increasing adoption worldwide.
Recent findings Over the past few years, third-space endoscopy has been utilized in various diagnostic and interventional procedures performed throughout the gastrointestinal tract: obliteration of Zenker's diverticulum, myotomy for achalasia, gastroparesis or Hirschsprung's disease, biopsy or removal of subepithelial tumors, stricture management, post-per-oral endoscopic myotomy endoscopic fundoplication, and mediastino-, thoraco-, and peritoneoscopy.
Summary Third-space endoscopic interventions have revolutionized the management of esophageal motility disorders, gastroparesis, and gastrointestinal tract subepithelial tumors. Despite the high efficacy and safety of such interventions, some common (e.g., the high level of necessary endoscopic skill) and unique for each procedure (e.g., post-procedure gastroesophageal reflux or poor outcomes in patient subgroups) challenges still

remain. Through a dedicated endoscopic training, a rigorous pre-procedure patient evaluation and selection, and the application of modified or new techniques, challenges can be overcome thus establishing existing procedures and paving the way for additional breakthroughs in the field of third-space endoscopy.

Introduction

Within each medical specialty, one can find key landmark moments and events that redefine and revolutionize this field. For gastrointestinal (GI) endoscopy, the shift toward flexible endoscopes and the introduction of interventional endoscopy, at the time when GI endoscopy was considered purely diagnostic, are examples of such breakthroughs [1, 2]. In more recent years, a series of events had a similar impact, gradually transforming GI endoscopy from an endoluminal to an intramural and transluminal procedure as well [2]. With the initial description and application in animals of submucosal tunneling techniques by Sumiyama et al. [3] and Pasricha et al. [4] in 2007 and the first human case of per-oral endoscopic myotomy (POEM) for treatment of achalasia, performed by Inoue in 2008 [5], the intraluminal frontier was pushed back and the field of "third-space GI endoscopy" (TSGIE) [6] was established.

With the lumen being the first and the peritoneum the second, the term third space refers to the space, cavity, or tunnel that is intentionally created within the GI wall, between the muscularis mucosa and the muscularis propria, through intrasubmucosal dissection [7]. Over the past few years, mainly fueled by the success and wide acceptance of POEM, TSGIE has been utilized in various procedures performed throughout the GI tract: obliteration of Zenker's diverticulum [8], myotomy for achalasia [5], gastroparesis [9] or Hirschsprung's disease [10], removal of tumors arising from the muscularis propria or beyond [11], stricture management [12•], and post-POEM fundoplication [13•]. The main scope of this review article is to introduce readers to the innovative field of TSGIE and to offer a closer look at TSGIE's history, milestones, and procedure spectrum as well as discuss ongoing and future challenges arising from its increasing adoption worldwide.

Principles of TSGIE interventions

Despite the fact that various TSGIE procedures have been described (Fig. 1), they all share basic features and steps. The advancement of the endoscope to the entry site can be performed per os, per anum, or through a gastrostomy port. Following the creation of a mucosal/submucosal bleb through injection of a solution, a single entry/exit site from/to the lumen is opened by means of a mucosal incision. After access to the submucosa is gained, a tunnel is being created through dissection of submucosal tissue, while keeping the mucosa intact, thus forming a mucosal flap. Depending on the type of the procedure, different outer GI or abdominal wall components (adventitia, serosa, peritoneum +/− muscular components) can be preserved. After the therapeutic part of each procedure (myotomy, tumor removal, etc.) has been completed, a closure of the initial incision takes place [5, 7–11, 12•, 13•]. Despite utilizing the third space as a working plane, endoscopic submucosal dissection (ESD) procedures cannot be considered as components of "true" TSGIE because the third space is gradually "unroofed" and "merges" with the lumen.

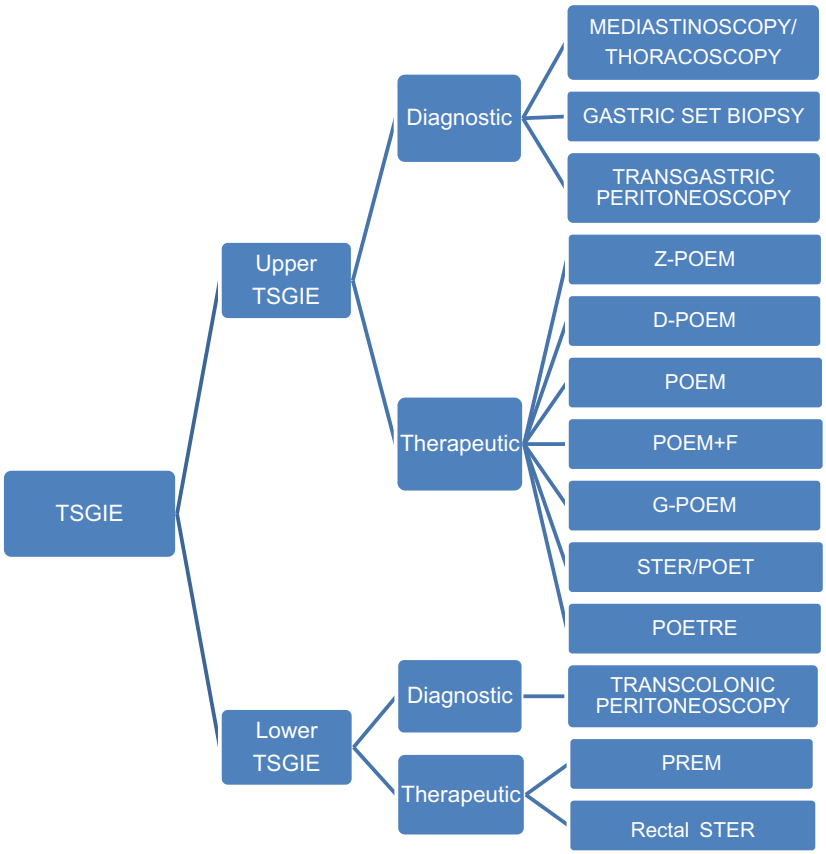

Fig. 1. Schematic overview of available third-space gastrointestinal endoscopy (TSGIE) procedures. SET, subepithelial tumor; POEM, per-oral endoscopic myotomy; Z-POEM, POEM for Zenker's diverticulum; D-POEM, POEM for esophageal diverticulum; POEM+F, POEM with endoscopic fundoplication; G-POEM, gastric POEM; STER, submucosal tunneling endoscopic resection; POET, per-oral endoscopic tunneling resection; POETRE, per-oral endoscopic tunneling for restoration of the esophagus; PREM, per-rectal endoscopic myotomy.

Apart from mastering the skills required to perform TSGIE, the use of cutting edge instruments is also mandatory. In several cases, the development of sophisticated tools or equipment for new TSGIE procedures is deemed a sine qua non for their establishment and evolution. Endoscopes with working channels large enough to accommodate tools and apply effective suction as well as water jet function, when combined with water flushing pumps, are commonly used for TSGIE. An electrosurgical unit, generating and controlling the amount of energy, duration, and pattern of electric current delivered to the tissue, is indispensable for TSGIE. The use of distal transparent caps or hoods attached to the tip of the endoscope offers advantages, e.g., optimal visibility within the third space, and a safer, less traumatic means for passage or bougienage. The use of carbon dioxide (CO_2), instead of air for insufflation at a low or very low flow state through a dedicated CO_2 insufflator and tubes, helps minimize the risk of gas-related complications such as pneumothorax or pneumoperitoneum. Injection needles and electrosurgical knives of different types with or without jet function are usually utilized for incision and dissection. The

injected solutions comprise of saline or occasionally a more viscous compound, such as glycerol or hyaluronic acid, and a dye, predominantly indigo carmine (or methylene blue), providing adequate submucosal tissue contrast [7, 14–16]. Compared to indigo, methylene blue solutions carry theoretically the additional risk of DNA methylation [17]. Coagulation forceps for hemostasis and endoclips or endostitching devices for entry site closure are also used. A major driver for endoscope and knife selection remains the endoscopist's personal preference [7, 14–16]. In a quite similar manner, the electrosurgical generator settings, meant to tailor energy delivery to each knife's properties so as to ensure its optimal performance, can be customized to meet an individual operator's requirements [7, 14–16].

TSGIE in the upper GI tract

STESD or Z-POEM

Zenker's diverticulum (ZD) represents a rarely occurring true diverticulum, arising from an area delineated by cricopharyngeus muscle fibers (Killian's triangle). The armamentarium for ZD management includes open surgery and rigid or flexible endoscopic techniques [8]. Irrespective of the differences between modalities, the final goal remains the division of the septum between the diverticular and esophageal lumen and subsequently the abolishment of the diverticulum itself [8]. Although flexible endoscopic techniques offer the advantage of being less time-consuming, exhibiting a better safety profile, and requiring a shorter inhospital stay, they are accompanied by a relatively high rate of symptom recurrence due to incomplete septum division [8, 18]. Despite the fact that the needle-knife technique [19] became the flexible-endoscopy–based treatment of choice in many centers around the world, another technique named submucosal tunneling endoscopic septum division (STESD) has gained noticeable popularity over the past few years [20•, 21, 22]. STESD bears striking similarities with POEM for achalasia, a fact also depicted in its alternate name, POEM for ZD or Z-POEM [21–24]. Unlike its rival technique where the mucosa, submucosa, and muscle layers are dissected and exposed, during Z-POEM, a submucosal tunnel is created while maintaining an intact mucosal flap. With Z-POEM, direct visualization followed by selective, but complete, dissection of the muscular septum becomes possible. Moreover, the use of an overtube is not necessary and closure of the entry site, at the end of the procedure, minimizes the risk of further complications. This combination of favorable characteristics seems to have encouraged its use for ZD treatment and results on STESD or Z-POEM have already appeared in international literature [21–24].

POEM

In April 2018, the 10th year anniversary of POEM was celebrated during the opening ceremony of Tokyo Live. Ten years after the first human POEM case [5], this procedure remains the most widely adopted and popular TSGIE intervention [16, 25–27]. POEM was launched in an era when natural orifice translumenal endoscopic surgery (NOTES) had already made a pompous entrance and had drawn the attention of the international surgical and gastroenterology community as the new "scarless," minimally invasive surgical technique [28].

Being a novel NOTES technique, POEM was introduced to an audience that was eager to witness the next step in the evolution of interventional endoscopy, that of leaving the endoluminal "safety" and advancing intra- or transmurally. POEM, through a step-by-step approach taking advantage of sophisticated equipment, has proven to be a reproducible and, most importantly, safe technique [14, 29–32]. POEM procedures have been safely performed throughout the world in all age groups, ranging from infants to octogenarians [33, 34]. Adding to this almost ideal profile, excellent efficacies of more than 90% (92–97%) in treatment-naive patients and >83% at 5-year follow-up have been reported. As this is higher than pneumatic dilatation (PD, 70%) and similar to the more invasive and time-consuming Heller's myotomy, it is not a surprise that POEM is considered the "flagship" of TSGIE [14, 33–42]. Those assets, along with the fact that the length of myotomy can be "tailored" to include spastic segments, encouraged its use in other esophageal motility disorders such as jackhammer esophagus (JE) and distal esophageal spasm (DES), with reported success rates of 70–72% and 88–100%, respectively [43, 44]. Another advantage of POEM is that it can be applied in cases where prior treatment has failed, thus also serving as a "rescue" therapy with success rates exceeding 75% [45–49]. Indeed, POEM has been successfully performed in patients after botulinum toxin injection, PD, and Heller myotomy, even in cases with Roux-en-Y gastric bypass [45–50].

Pre-POEM diagnostic assessment should include upper GI endoscopy and high-resolution manometry (HRM) as the gold standard for the diagnosis and classification of the motility disorder, as well as an esophagram [14, 36, 51, 52]. The latter has proven beneficial for detection of spastic contractions in cases where HRM falls short, e.g., spasm being either "masked" by a panpressurization intrabolus pressure pattern in type II achalasia or absent during the 5-ml water swallows of HRM, but detected with the higher volume and viscosity barium swallow on an esophagram. Upper GI endoscopy is an essential part of the patient's workup and plays a role in differential diagnostic investigation, but is also useful for food removal, HRM catheter placement, or pre-procedural strategic planning [14, 36, 51, 52]. In selected cases, additional workup, e.g., computed tomography (CT), may be required to exclude pseudo-achalasia [52].

Since POEM served as a model procedure for other TSGIE interventions, its basic steps are the ones described above. POEM, however, as it was described in the 2010 contribution by Inoue et al., bears differences from other studies and reports [5, 14, 52–54]. In terms of equipment, new instruments such as knives with jet functions are favored due to the lack of need for knife/needle exchange and thus reduction in the duration of tunnel creation [14, 16]. Initially, the anterior esophageal wall was preferentially selected for POEM, in an effort to endoscopically mimic a Heller procedure [5, 14, 52]. Although anterior POEM is still used, its posterior counterpart has been gaining increasing popularity [53, 55]. Likewise, some centers do not favor selective circular or proximal to distal myotomy and apply a full-thickness and retrograde dissection instead. The overall length of the myotomy or its extent on the gastric side is also not consistent, with various groups favoring longer or shorter lengths [14, 52, 54].

Based on available data, anterior and posterior POEM seem to be equally effective while having a similar safety profile with the exception of mucosal injuries (higher with anterior) and perhaps gastroesophageal acid exposure

(higher with posterior) [53, 55]. It seems that the choice of one approach over the other relies on the operator's preference, prior treatment, e.g., Heller myotomy, and previous POEM or "laterality" of fibrosis dictating the use of the opposite "virgin" or the less affected side of the esophageal wall. The length of the myotomy itself may be variable due to disease phenotype and between-center differences, with the reported length ranging from 5 to almost 20 cm [14, 43, 44, 52]. Shorter myotomies of 5 cm have been applied in some studies, without reducing efficacy [54]. A critical parameter affecting the length of myotomy is the presence, or not, of irregular spastic contractions. In the presence of such contractions, the myotomy should be long enough to include the entire abnormally contracting segment [43, 44, 52]. On the contrary, in cases of type I achalasia, where no scorable contractions are present, a myotomy that is short yet inclusive of the LES and the first 2–3 cm of circular muscle fibers on the gastric side will suffice [14, 52]. The three main characteristics of myotomy during POEM including orientation or axis, length, and selectivity or thickness (circular versus full-thickness) are considered important as they can affect the efficacy of POEM as well as the occurrence of post-POEM gastroesophageal reflux disease (GERD) [52–57].

Despite the high efficacy rates and advantageous safety profile, the POEM success story has been challenged, over the past few years, by concerns about the onset of GERD after POEM. The rates of GERD after POEM, reported in single- and multi-center studies and meta-analyses, range from 8.5 to 58% [29, 58, 59]. Without doubt, the width or span of this range seems inexplicable, at first glance. Further analysis of individual studies, however, shows that the differences in reported rates reflect the different methodology used to identify and determine GERD, e.g., symptoms, esophagitis on endoscopy, or pH monitoring [29, 58, 59]. The highest rates are reported from studies using pH monitoring, followed by those utilizing endoscopic criteria and symptoms [29, 59]. Ethnicity-related differences conferring increased risk to susceptible, i.e., Western, populations could also play a role [29]. Technical differences such as favoring a full-thickness myotomy or dissecting the sling fibers (oblique muscle) could have augmented the occurrence of GERD after POEM in some studies. Finally, issues related to heterogeneity of studies, patient dropout/missed at follow-up, and the presence of selection bias could have contributed to the recorded differences. Although esophagitis and symptoms can be treated successfully using proton pump inhibitors (PPIs), concerns about silent reflux, Barrett's esophagus, and malignant transformation risk have also been raised [29, 59].

In our opinion, there are three ways to look into the problem of GERD after POEM. One option is to wait for robust studies, controlling for all possible confounders, to address this issue so as to have a clear picture about short-, mid-, and long-term GERD risk in POEM-treated patients. Another option is to try to identify subgroups of patients at higher risk for GERD after POEM, weigh pros and cons, and perhaps suggest an alternative treatment, if necessary. The third and final option is to avoid practices during POEM that could increase GERD risk, and if GERD manifests anyway, then treat the patient accordingly.

The latter option of reducing GERD risk is currently performed at our institution where two major interventions are offered to patients with achalasia: (a) a modified posterior POEM preserving the sling fibers and (b) an endoscopic fundoplication, as an adjunct to an anterior POEM (POEM+F).

Modified posterior POEM

For this variation of POEM, the mucosal incision and submucosal tunnel creation maintain a posterior 5 o'clock orientation until the posterior sling muscle is encountered at the esophagogastric junction (EGJ) (Fig. 2). If not readily visible, the sling muscle is uncovered through spray coagulation of the overlying submucosa. After exposure, the scope slightly deviates to the right anterolateral side so that the subsequent myotomy will not dissect this muscle. During this modified procedure, usually the two perforating or penetrating vessels—the left gastric artery branches—can be identified [60]. Once identified, the gastroscope will pass on the right of the first penetrating and will stop advancing at the level of the second penetrating vessel. In most cases, this will establish an adequate tunnel and myotomy length. The double-scope technique during which two endoscopes are used, one inside the tunnel providing transillumination and the other inside the stomach in retroflexion for observation, is used to verify that a safe distance from the sling muscle and an adequate length are ensured during myotomy [52, 61–63]. The myotomy is selective, dissecting only circular muscle bundles, as full-thickness myotomy is associated with higher rates of GERD after POEM [57]. This modified posterior POEM ensures the integrity of the sling muscle, also known as the oblique muscle, forming with its anterior counterpart the collar of Helvetius, a natural anti-reflux barrier supporting the angle of His. Although its merit as a POEM variation with anti-reflux potency has not been proven yet, it provides the obvious advantage of not disrupting an intrinsic, inherent anti-reflux barrier.

POEM+F

The POEM+F procedure consists of two major steps: POEM and endoscopic fundoplication [13•]. In brief, a submucosal tunnel in the anterior wall of the esophagus at the 12 o'clock position, also extending 3 cm into the gastric wall, is created, followed by a full-thickness myotomy. The fundoplication "arm" of this procedure consists of three steps. First, the peritoneal cavity is entered from a distal site to the diaphragmatic crus. The endoscope is advanced into the peritoneum and the anterior gastric wall is grasped and pulled toward the EGJ (Fig. 3), while a second pediatric scope in retroflexion within the stomach helps identify the best wrap and optically pinpoint the ideal anchoring site. Then, a 2-

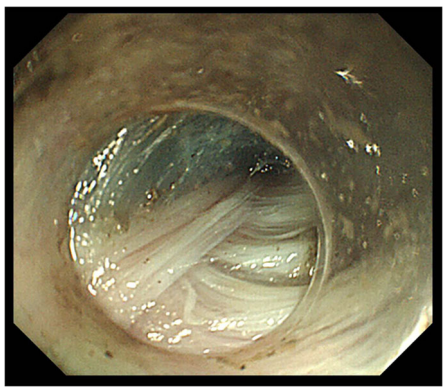

Fig. 2. Endoscopic image of the posterior sling (oblique) muscle appearing as a sinistrolateral bundle of longitudinal fibers.

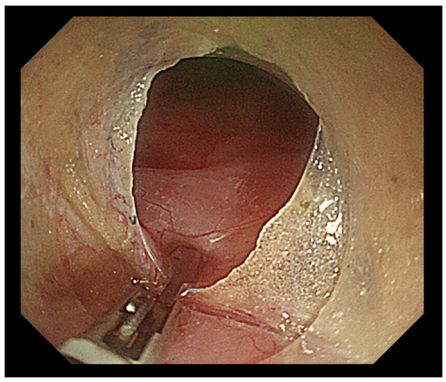

Fig. 3. Endoscopic image of the entry site to the peritoneal cavity. The anterior gastric wall is grasped and pulled toward the scope that lies inside the submucosal tunnel.

cm endoloop is introduced through the submucosal tunnel into the peritoneal cavity where it is fixed onto the anterior gastric wall. The other end of the endoloop is fixed to the dissected esophageal muscle, at the level of the EGJ. The endoloop is gradually tightened and fully closed. This partially rotates and pulls the relatively mobile anterior gastric wall (distal anchoring site) toward the fixed proximal esophageal myotomy site (proximal anchor), creating a mechanical barrier that narrows the EGJ hiatus. The final result, confirmed by the retroflexed pediatric gastroscope, is the creation of a partial anterior gastric wrap around the cardiac opening resembling the one created through a Dor fundoplication (Fig. 4) [13•].

The POEM+F technique has so far been successfully performed in 21 patients with achalasia. For the endoscopic fundoplication arm of the procedure, an extra time of 51 min on average was necessary. The fundoplication wrap could still be identified in 20 patients after 2 months. Patient recovery after POEM+F was uneventful [13•]. Although the procedure could be further refined with the use of endoscopic suturing devices instead of foreign objects (clips, endoloop), the addition of an endoscopic fundoplication to a standard POEM procedure in a single session (POEM+F) or perhaps later on, due to the onset of GERD after POEM, seems a rather appealing and promising strategy.

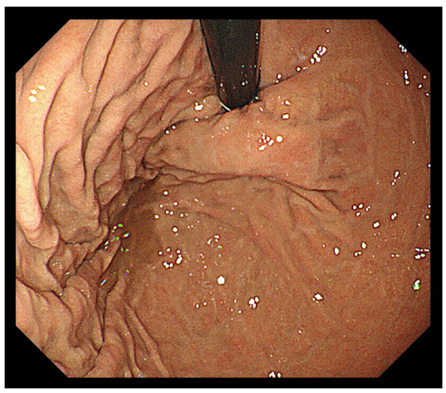

Fig. 4. Endoscopic intraluminal view of the partial fundoplication wrap, from a retroflexed gastroscope inside the stomach.

D-POEM

So far, POEM has been successfully performed in patients with achalasia and concomitant esophageal diverticula. In addition, single case or case series reports on the management of esophageal diverticula, alone, have been published [24, 64, 65]. Recently, the experience of three centers with the use of POEM principles for the treatment of ZD and non-ZD (mid-esophagus and epiphrenic diverticula) has been reported [66]. Using this POEM for esophageal diverticula (D-POEM) technique, diverticula with an average size of 3.5 cm were treated [66]. Procedure and clinical outcome success rates and acceptable procedure duration of 1 h, as well as the safety profile, make D-POEM an attractive option for future management of esophageal diverticula [64–66].

STER/POET

The management of GI tract subepithelial tumors (SETs) traditionally comprised of two strategies: (a) either leaving the SET intact, provided that the size of the lesion is small, or (b) proceeding to surgical enucleation, especially when >3 cm and arising from the muscularis propria [67, 68]. Stimulated by the success of POEM, a new similar TSGIE procedure was introduced: submucosal tunneling endoscopic resection (STER) or per-oral endoscopic tunneling resection (POET) [7, 11, 69–71]. The STER/-POET technique has been increasingly applied ever since for the removal of esophageal and gastric submucosal tumors (SMTs) [7, 11, 69–73]. For STER/POET, through a mucosal incision, an entry site is opened 3–5 cm proximal to the lesion and a short submucosal tunnel extending up to 2 cm distal to the SMT is created. The next step is the "detachment" of the tumor, using different types of electrosurgical knives, e.g., triangle tip or dual or insulated ceramic tip types, from surrounding tissue until only a smaller part of the lesion remains attached. Finally, the tumor is resected with the use of a polypectomy snare and removed, and the entry point is closed with clips [69–71]. Although this approach seems quite simple, it can become really challenging in cases of a "technically demanding" location (e.g., the fundus or lesser curvature of the stomach), a large lesion (usually >3.5 cm for safe resection and >4 cm for per os removal), or a multi-lobular lesion that is firmly attached to deep layers and exhibiting proximity to "noble" or delicate structures [16, 69–71]. The only way to prepare for these difficult procedures and avoid technical pitfalls is a rigorous pre-STER diagnostic evaluation consisting of CT and endoscopic ultrasound [7, 11, 70, 74].

According to the available literature, en bloc resection rates with STER/POET vary from 89 to 95% [7, 11, 69–73]. Application of this technique has resulted in safe removal of SMTs from the esophagus, EGJ, fundus, and proximal lesser curvature [7, 11, 69–73]. Interestingly, a variation of this technique named STER for extraluminal tumors (STER-ET) allowed resection of SETs with a predominant extraluminal growth pattern or extra-GI tumors located at the level of the cardia and the proximal part of the gastric lesser curvature [75]. Compared to the rival thoracoscopic enucleation, STER/POET is equally effective and less time-consuming while exhibiting promising post-operative (less pain, shorter inhospital stay) as well as long-term outcomes (low recurrence rates) [72, 76].

Stricture management

The TSGIE principle has also been used to provide a new means of managing patients with esophageal strictures. The technique termed per-oral endoscopic tunneling for restoration of the esophagus (POETRE) can be used for restoring GI tract patency and oral feeding in patients with post-radiation and post-surgical long-segment (>3 cm) occlusive esophageal stenosis. POETRE relies on the use of two endoscopes, one introduced per os and one through a gastrostomy port, with one of the endoscopes entering the submucosal plane allowing tunneling and dissection through the fibrosis until transillumination and indentation from the opposite endoscope is encountered. Fluoroscopy is also used to verify correct orientation and proximity of the two scopes. At the two scopes' "rendezvous" point, the tunnel wall is incised so that an exit to the lumen distal to the stenosis is opened. The restoration of continuity is further secured by placement of a fully covered metallic stent that will be removed at a later stage. Despite an improvement in dysphagia score after POETRE, removal of metallic stents after a few weeks has been reported to be associated with the need for further dilatations [12•, 77].

TSGIE mediastinoscopy and thoracoscopy

In a series of animal studies, the feasibility, reproducibility, and safety profile of a transesophageal endoscopic technique for mediastinal lymph node dissection and en bloc resection have been evaluated [78–84]. Through mucosal incision or band and snare mucosectomy, the submucosa was accessed and a tunnel was created with blunt dissection or biopsy forceps. Using tube penetration or incision with endoscopic knives and/or scissors, the muscle layer and pleura were breached allowing the endoscope to be advanced into the mediastinum and thoracic cavity, respectively. With this approach, both para-aortic and para-tracheal lymph nodes could be evaluated and removed. Due to high mortality and complication rates, this approach has remained experimental [78–84].

G-POEM

The application of TSGIE and POEM principles at the pylorus has resulted in a distinct procedure termed gastric POEM (G-POEM) or per-oral pyloromyotomy (POP). Following initial description in animal models [85] and a report of the first human case [86•], the experience has increased due to various single- and multi-center studies applying G-POEM/POP for management of refractory gastroparesis [87–92]. The technique consists of a mucosal incision; 4–6 cm proximal to the pylorus at a 5, 6, or 7 o'clock position along the greater curvature; submucosal tunnel creation; myotomy of the pylorus and the proximal 2–3 cm of the antrum adjacent to the pyloric ring; and entry closure with endoclips [86•, 87–92]. In some cases, fluoroscopy was used to facilitate orientation and pyloric ring identification, ultimately also leading to a shorter operation time [91, 92]. Short-, mid-, and longer-term results of G-POEM/POP for management of gastroparesis are promising, showing rates of symptom reduction of >80%. These results have stimulated its broader use as a salvage treatment after medication or other interventional techniques, e.g., botulinum injection, stent placement, and gastric electric stimulation, have failed [9]. Despite its success in cases of post-operative and idiopathic gastroparesis, this is not the case for diabetic gastroparesis where the results are less promising [90,

93]. This observation brings to the surface another important issue, that of careful pre-procedure evaluation and patient selection. Symptom scores and indices are useful for identifying cases with refractory gastroparesis and to document post-G-POEM/POP patient satisfaction and success, with the obvious disadvantage of subjectivity [9, 93]. "Functional" studies such as breath tests and scintigraphic and probe-based (antroduodenal manometry or distensibility studies), wireless capsule-based, or magnetic resonance imaging (MRI)-based techniques can aid in the diagnosis and patient stratification [88, 93–97]. If selected for an appropriate indication, G-POEM/POP may indeed become an attractive alternative to procedures of lower efficacy, provided that an important concern of the procedure is addressed, e.g., that of duodenal-gastric reflux.

As opposed to the acidic component of GERD after POEM, an alkaline component consisting of bile and pancreatic enzymes characterizes duodenal-gastric reflux after G-POEM. Repeated, chronic gastric exposure to this alkaline component could lead to the onset of the condition commonly referred to as "red-green stomach," alkaline or bile-reflux gastritis, or to GERD characterized by bile acid exposure [98, 99]. Since no definite answers exist so far regarding this controversial issue, the efficacy and safety of G-POEM, in experienced hands, seem to outweigh the "hypothetical" risk of bile reflux.

TSGIE for biopsy of gastric lesions

The creation of a short submucosal tunnel, while maintaining the mucosal flap, has been used to provide endoscopic visualization and biopsy of submucosal tumors. Kobara et al. used this approach to obtain a definite diagnosis on gastric SETs. Additional benefits from the use of this technique include the recognition of SETs' layer of origin and better management of bleeding due to clear identification of vascular structures [100, 101].

Submucosal transgastric endoscopic peritoneoscopy

Submucosal tunneling techniques have been applied in experimental and clinical settings to provide access to the peritoneum [102, 103]. This transgastric submucosal tunnel peritoneoscopy has been shown to allow intraperitoneal exploration and biopsy in cases of intra-abdominal lesions of obscure "nature." Peri- and post-procedural course was uneventful, with a mean inhospital stay of 3.8 days [103]. Despite its initial success, this technique has not been popularized due to the use of alternative modalities that facilitate correct diagnosis [104].

TSGIE in the lower GI tract

PREM

Following the establishment of TSGIE in the esophagus and stomach, a POEM-based procedure has been developed for the treatment of Hirschsprung's disease. Initially, the feasibility of this technique, termed per-anal endoscopic myotomy (PAEM), was demonstrated in an animal model [105]. According to the study group that tested this procedure, it could be used for the treatment of internal anal sphincter achalasia [105]. Encouraged by the success of POEM and G-POEM/POP, and the PAEM report, Bapaye et al. performed a per-rectal endoscopic myotomy (PREM) for short-segment Hirschsprung's disease [10].

In brief, following injection on the posterior rectal wall, at 1 cm proximal to the anorectal junction, a mucosal incision was made. Dissection in the submucosal plane led to the creation of a tunnel that extended beyond the spastic segment into the dilated sigmoid colon. A full-thickness myotomy was performed, and in the case of the distal rectum, internal sphincter fibers were also included. The entry site was closed with endoclips. Patient improvement was recorded post-operatively and this effect persisted throughout the follow-up period of 24 weeks [10].

Rectal STER

The feasibility of STER technique in the colon has been demonstrated by Hu et al. in 12 patients with rectal SMTs. Rectal STER resulted in an en bloc resection of tumors up to 3 cm, in all cases. No serious adverse events or recurrences at follow-up were reported [106].

Submucosal tunnel transcolonic peritoneoscopy

Taking advantage of the third space, intraperitoneal access for peritoneoscopy has been gained through the colon in an animal study. This transcolonic approach was selected due to the theoretical advantages of easier and safer access to upper abdominal structures, especially in cases where a transgastric approach may be impossible or unsafe. After povidone iodine lavage 13–15 cm from the anus, a cushion was created via injection and a mucosal incision was performed. A 5-cm-long submucosal tunnel was created, with the use of a balloon, through which, after incision of muscle fibers and serosa, the endoscope could be advanced into the peritoneum. The procedure was successful in all animals without any adverse events or infectious complications, such as peritonitis [107].

Current and future challenges

The groundbreaking field of third-space endoscopy has been expanded over the years with various GI tract-related interventions. Apart from POEM and the increasing use of STER/POET and G-POEM, the other TSGIE techniques have not been embraced with the same enthusiasm, at least not yet. The rather "experimental" character of some TSGIE procedures, tested only in animal studies and small case series, along with their interventional nature may have contributed to this phenomenon. Even for the commonly used TSGIE procedures, some technical issues may make the procedure not always easy. The performance of such interventions requires a high level of skill that for the vast majority of endoscopists cannot be obtained during a core GI training. Therefore, a separate, dedicated training seems to be a prerequisite. Ideally, TSGIE interventions should be performed by operators with optimal expertise and able to handle even the complicated cases, provide the best possible outcomes at a minimum risk, and exhibit favorable, durable effects in the absence of post-procedure side or counter-effects. Undeniably, this combination is really hard to establish and a major "headache" for endoscopists undertaking the challenge to become experienced in performing TSGIE interventions.

A major challenge, even for highly skilled and experienced endoscopists performing TSGIE, is the presence of fibrosis. Intramural fibrosis causing dense

attachment and "fusion" of GI tract wall layers (the mucosa, submucosa, and muscularis propria) makes the entry and submucosal tunnel creation a complicated task while at the same time increasing the risk for mucosal injury, unintentional transversion to deeper layers (e.g., intramuscular space, adventitia, serosa), and true perforation [14, 108, 109]. TSGIE procedures performed in patients that received prior treatment carry the additional risk that fibrosis is present [14, 108, 110]. POETRE candidates with strictures after surgery, caustic injury, or radiotherapy with or without chemotherapy, or patients with achalasia undergoing POEM after failed botulinum injection, PD, Heller myotomy, or prior POEM treatment, are such examples [14, 77, 110]. The use of two scopes, tapered attachments with smaller tips, hyaluronic acid injections, and knives with high-pressure jet functions and of course operator's experience are valuable and key components during intraoperative management of difficult "fibrotic" cases. A pre-operative identification of a fibrotic operational field may also prove helpful and endoscopic classification systems have been formulated to this end [109].

As for adverse events, TSGIE interventions share an almost identical spectrum consisting of insufflation-related events, bleeding, and wall-related injuries. Although the use of CO_2 helps reduce the risk, the occurrence of pneumo- or capnomediastinum, pneumo- or capnothorax, pneumo- or capnoperitoneum, and subcutaneous emphysema is not negligible. In the majority of cases, however, no action is needed and only in a limited number of cases is "tapping" with a needle attached to a saline-filled syringe necessary yet adequate to induce full resolution [111]. The occurrence of bleeding is rather low in POEM where it remains under 1% while it is somewhat higher for STER/POET procedures (1.7%) [7, 14, 16, 32, 112, 113]. Similarly, the overall adverse event burden is higher for STER/POET (23.4% overall, <10% requiring intervention) and G-POEM/POP (0–28.6% overall) compared to POEM (7.5% overall and 0.5% severe) [32, 113, 114]. True perforations are infrequent although the risk tends to increase with certain techniques (anterior POEM, STER for large tumors), the presence of fibrosis, and difficult anatomic location (gastric STER) [11, 14, 32, 53]. Other rare TSGIE adverse events are cardiac arrhythmias perhaps triggered by electric stimulation through the electrosurgical knife, respiratory infections (e.g., aspiration pneumonia), pleural/abdominal effusions, and fistula and diverticulum formation [11, 32, 112].

Apart from the challenges pertaining to TSGIE techniques, another critical issue is the identification of patient groups/subgroups that can benefit most from the use of these techniques. It seems that the limits of TSGIE were further stretched to include more disorders, more patients, and more problematic cases, in an attempt to prove that they can universally take over other, more "traditional" competitor techniques. Now that the feasibility and reproducibility of those procedures have been proven, it is time to look carefully at the outcomes and decide which patients are most suitable for TSGIE interventions.

For STER/POET, it is perhaps advisable to use this technique for tumors <3.5 cm, not arising from deeper layers [11, 16, 70]. In the case of G-POEM, clinicians should bear in mind that patients with diabetic gastroparesis are not a uniform group and therefore patient selection should rely more on a thorough investigation through different types of tests as discussed above [9, 87, 88, 90,

94–96, 115]. As for POEM, available results favor the notion that it is more effective in treatment-naive patients, offering the additional advantage of a more reliable management of spastic phenotypes (type III achalasia, DES, and JE), while addressing the symptom of chest pain [35, 36, 38, 43–45, 51, 52, 116]. These data imply that it is perhaps better to offer the procedure at an early stage, as a first-line therapy, thus maximizing efficacy and possibly favorable esophageal functional restoration [117•]. To date, this idea is not favored by all practitioners mainly due to the GERD after POEM discussions [36, 51]. From the authors' perspective, a way to approach this issue would be to apply a sling and longitudinal muscle preservation strategy. The identification of high-risk patients, for GERD after POEM, on the basis of, e.g., planimetric (fair distensibility) or HRM findings (marginally abnormal or relatively low integrated relaxation pressure (IRP)) prior to treatment, may also prove important. This subset of potentially high-risk patients should be offered an alternative yet effective intervention either with a lower risk for GERD (PD) or with a built-in anti-reflux component (Heller-Dor, POEM+F). As for those patients presenting with GERD after POEM despite initial GERD risk assessment, PPIs and novel endoscopic interventions, e.g., endoscopic fundoplication, after POEM could be considered.

A final challenge that needs to be addressed is who is considered "eligible" to perform TSGIE. As TSGIE procedures require a high level of skill, the obvious answer to this question would be an endoscopist granted "expert" status. Based on the available literature, this kind of expertise can be gained through a dedicated training program. Candidates for such a program are gastroenterologists and surgeons involved and exposed to interventional endoscopy. A step-up process starting from swine organ or whole-animal models, paralleled with observation of experts and extending to human cases of increasing difficulty, is recommended. TSGIE training should be undertaken in specialized centers with the necessary infrastructure, expert trainers, and patient volume to ensure optimal exposure to instruments and equipment, techniques, and number of cases. A rotation program involving different institutions can also be considered if adequate exposure to the full spectrum of TSGIE is the final goal [6, 52, 118–120].

Overall, it seems that TSGIE has proved to be an "Amalthea horn" for GI endoscopy, offering diverse, novel diagnostic and therapeutic options for patients suffering from a wide variety of disorders. The initial skepticism and overenthusiasm of the early days seem to have settled down, thus allowing the quest for further applications while at the same time accepting the limitations and merit of currently available techniques. According to Eleftheriadis et al., future applications of TSGIE could be endoscopic vagotomy, thoracoscopy, retroperitoneoscopy, peritoneoscopy, and sympathectomy [120], whereas for Chiu et al., inspection and tissue sampling of the muscularis propria, submucosal (Meissner) nerve plexus, myenteric (Auerbach) nerve plexus, or lung could be additional options [70]. Perhaps an even bigger challenge and desire for TSGIE experts is to see that this third-space endoscopic odyssey eventually leads to novel treatments for the management of the two modern-day epidemics, GERD and obesity. With the feasibility and safety of endoscopic fundoplication now demonstrated through the POEM+F procedure, this goal may be closer than previously imagined.

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Compliance with Ethical Standards

Conflict of Interest
Haruhiro Inoue reports grants from Olympus Corporation and other funds from Takeda Pharmaceutical Company and Top Corporation. Manolakis AC is a Hellenic Society of Gastroenterology grant holder. Yuto Shimamura declares that he has no conflict of interest. Akiko Ueno declares that she has 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.

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