

Research article

Beyond the Boundaries of Gi Tract: Astronauts Land in Submucosal Space

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Abstract

Beyond all the expectations, in the last few decades, pioneers of endoscopy brought us to undiscovered lands, across gut's lumen limits. That is the case of third-space endoscopy. Its purpose is to exploit the submucosal layer as a safe working place where it is now possible to carry out multiple target therapies. Paramount tools for such an adventure are the deep knowledge of anatomy and high endoscopic skills. Since 2010, when Inoue et al. published the first report of per-oral endoscopic myotomy (POEM) on human, many progresses are being made. Therefore, the aim of this review is to summarize the past literature and to give a glimpse to future's perspectives on the field.

Keywords: submucosal endoscopy, per-oral endoscopic myotomy, third-space endoscopy

Introduction

Since POEM procedure was introduced in endoscopy's world, a new landscape began to unfold. In fact, the promising results opened many therapeutic perspectives, hence multiple applications of submucosal endoscopy were found. Let us go back to the beginning.

Before the man

Natural Orifice Transluminal Endoscopic Surgery (NOTES) was first described in 2004 when Kalloo et al. accessed the peritoneal cavity (second-space) from the gastric lumen (first-space), avoiding any abdominal incision [2]. It was the lack of devices able to ensure the closure, the *primum movens* that ended up in submucosal endoscopy, so called third-space endoscopy. In fact, in 2007 Sumiyama et al. described the technical feasibility and safety of submucosal endoscopy with mucosal flap (SEMF) in accessing the peritoneal cavity through a large full-thickness gastric-muscle-wall resection [3]. The same year, thanks to Pasricha et al. and the sacrifice of 4 pigs, the first series of peroral endoscopic myotomy was successfully attempted. In a mean time of 15 minutes, submucosal tunneling, myotomy and closure of the mucosal flap were made. As a result, LES pressure went down from 16.4 mmHg to 6.7 mmHg, without any evidence of complications at necropsy [4]. Until that moment, all NOTES procedures ever attempted were made on animal

models. It was the 8th September 2008, in Japan, that Inoue performed the first cardiomyotomy on a human, [1] opening the gates of a new dimension once and for all. Since then, different clinical scenarios and therapeutic perspectives arose from all over the world.

Overview

Applications of third-space endoscopy include the upper and lower gastrointestinal tract and can be subdivided in therapeutic and diagnostic procedures. Regarding therapeutics (Table 1), we summarized three major groups:

Myotomies

POEM, Z-POEM (Zenker- POEM), D-POEM (Diverticula-POEM) and G-POEM (Gastric-POEM).

Tumor enucleation

POET (per-oral endoscopic tumor) resection also called STER (submucosal endoscopic resection) and rectal STER

Lumen recanalization

POETRE (per-oral endoscopic tunneling for restoration of the esophagus) and PREM (per-rectal endoscopic myotomy). Furthermore, there are two additional procedures:

POEF (per-oral endoscopic fundoplication) and POEM-F (per-oral endoscopic myotomy + fundoplication) which cannot fit into this classification.

As well as therapeutics, diagnostic procedures such as peritoneoscopy and gastric SETs biopsies have been carried out on humans. (Table 2) Kobara et al. used a tunneling technique to take biopsies of gastric submucosal-tumors and study their vascularization and layer of origin [5,6]. Peritoneoscopy [7-9] is not widespread, perhaps because there are simpler ways to obtain the same information. Mediastinoscopy and thoracoscopy were attempted on animals, but due to the low safety profile, this approach remained experimental [10-14].

Table 1. Therapeutic procedures are summarized in: myotomies such as POEM (Per-Oral Endoscopic Myotomy), Z-POEM (Zenker Diverticulum Per-Oral Endoscopic Myotomy), G-POEM (Gastric Per-Oral Endoscopic Myotomy) and D-POEM (Diverticulum Per-Oral Endoscopic Myotomy); Tumors' enucleation such as POET (Per-Oral Endoscopic Tumor resection) and rectal STER (Submucosal Tumor Endoscopic Resection); and Recanalization such as POETRE (per-oral endoscopic tunneling for restoration of the esophagus) and PREM (per-rectal endoscopic myotomy). Under the name "out-of-the-box" there are POEM+F (Per-Oral Endoscopic Myotomy+fundoplication) and POEF (Per-Oral Endoscopic fundoplication).

Therapeutic Procedures	
Myotomies	POEM Z-POEM G-POEM D-POEM
Tumors' enucleation	POET Rectal STER
Recanalizations	POETRE PREM
Out-of-the-box	POEM+F POEF

Technical issues

All the procedures that require access to the submucosal layer share some common steps: mucosotomy, tunneling, and closure of the flap. First of all, to navigate and to ensure the right location of the submucosal tunnel, the careful examination and identification of landmarks is needed. After that, a solution is injected in the submucosa/mucosa to create a bleb. The incision is then made so that the endoscope has a space into which it can be insinu-

ated to enter the submucosa. The third space, located between the muscularis mucosae and the muscularis propria layers, contains only flimsy areolar tissue and blood vessels; here a stepwise dissection with additional injection of solution can be performed to create the tunnel. It is important to dissect just above the muscular layer, to avoid overlying mucosal injury and full-thickness perforation. Once the target is achieved and the intervention in the muscularis propria or beyond it (into the mediastinum or peritoneum) has been performed, the mucosal flap must be carefully closed. Devices used for this purpose differ depending on the expertise and the opportunity of each single centre [15-19].

Table 2. Diagnostic procedures carried out on human are: Peritoneoscopy and Gastric SET's biopsies. Procedures such as Mediastinoscopy and Thoracoscopy were attempted only on animal models.

Diagnostic Procedures	
On human	Peritoneoscopy Gastric SET's biopsies
On animals	Mediastinoscopy Thoracoscopy

Therapeutic: myotomies

POEM

The POEM procedure is the first widely adopted NOTES technique [20-22]. As already mentioned, in 2010, Inoue et al. published the first series of POEM in 17 patients showing promising clinical results for the treatment of esophageal achalasia [1]. Since then, POEM rapidly gained traction worldwide due to its minimally invasive nature, effectiveness, and safety. The indications for this procedure have expanded from achalasia type I, II, and III (according to Modified Chicago Classification) to non-achalasia motility disorders such as jackhammer esophagus and distal esophageal spasm. It has been safely performed in all age groups [23,24], those with straight and sigmoid type esophagus [25], failed surgical patients, [26-28] or cases who had multiple failed endoscopic treatments [15]. The success rate of the POEM procedure can be easily evaluated through clinical scores such as the Eckardt [29] or Vaezi Scores [30]. In treatment-naive achalasia patients, the success range of POEM ranges from 92 to 97% with a median surveillance period of 6 months, and >90% at 2-year follow-up [19,24,31-33]. The efficacy for type III achalasia, distal esophageal spasm and jackhammer esophagus was 93%,100%, and 70% respectively [34]. Good results have also been achieved in patients after pneumatic balloon dilatation (PBD), Heller myotomy (HM) and Roux-en-Y gastric by-pass [35,36].

Technique

POEM technique is performed with general anaesthesia with endotracheal intubation, with the use of a single-channel gastroscope, transparent hood, and knife with jet function. The use of carbon dioxide (CO₂) insufflation is mandatory because of the increase number of adverse events when air insufflation is used [37].

First of all, the esophagus is suctioned and cleared of any residual fluid or debris. Once the main landmarks (the spine, trachea, left main bronchus, aortic arch, and GEJ) have been identified to ensure the right orientation of the scope, abnormal contractions must be recognized to be able to choose the appropriate strategy. Anterior (11–1 o'clock) and posterior (5–7 o'clock) approaches are most commonly used, but the lateral greater curve (8 o'clock), or lateral lesser curve (3 o'clock) approaches can be also performed. Recently, the posterior approach has gradually increased in popularity, because of the easier position (5 o'clock) and equal effectiveness [38,39]. It also appears that the anterior approach leads to a higher number of mucosal injuries, and the posterior approach has a stronger correlation with post-POEM gastro-esophageal reflux disease (GERD). To avoid these problems, Inoue et al. proposed a posterior approach avoiding myotomy of sling fibres. These fibres ensure the angle of His, an important anti-reflux anatomical barrier, remain intact [15]. Once the best approaches for the patient is decided and the entry point has been selected, an injection of a few ml of saline solution tinted with methylene blue or indigo carmine is made in the submucosal space. A longitudinal incision of 1-2 cm is then made using an electrosurgical knife and the scope is gently slid between the layers. To create the third-space, additional solution is injected (without epinephrine) to facilitate the dissection. Dissection should be directed perpendicularly to the circular muscle fibres and must be as close as possible to the muscular layer to avoid mucosal injury. On the way, vessels may be encountered and can be managed with the needle knife or coagulation forceps for more substantial bleeding or prophylactic coagulation of larger vessels. When the lower esophageal sphincter (LES) is reached, the tunnel gets narrow and vascularity tends to increase. Once the high pressure zone is crossed, the tunnel should be extended for a few centimetres on the gastric side. Many strategies have been proposed to ensure the right position of the scope. Anatomical landmarks such as penetrating vessels are accurate indicators of the appropriate distal end of the gastric myotomy [40]. Normally, in the posterior approach, after the LES, it is possible to appreciate the first penetrating vessel and on its left the sling fibres. These landmarks should be preserved, and the second penetrating vessel should be reached. An alternative option is the double scope technique. In fact, thanks to the introduction of a "baby" scope in the stomach, it is possible to see, by transillumination, the edge of the tunnel [41]. Regarding the myotomy extension on the gastric side, whether selective circular, full-thickness, antero-

grade, or retrograde, has not yet been standardized [17,42-44]. The length of the myotomy depends on the centre and, of course, on the disease's phenotype [19]. For example, in the presence of irregular spastic contractions, a myotomy of the entire abnormal contraction zone is mandatory [34,45,46]. However, type I and II achalasia can be treated with short myotomies (5 cm), with good response to therapy [47]. The length of the myotomy, its thickness, and preservation or sacrifice of sling fibres can affect the efficacy of the procedure and the occurrence of post-POEM GERD, the greatest adversary of POEM procedure [39,46-49]. The risk of developing reflux after POEM appears to be variable depending on how GERD is defined. Many studies have reported ranges from 15% to 39% [50,51]. All of the strategies just described must be considered before treating the patients depending on the disease characteristics and operator skills.

Z-POEM

Zenker's diverticulum is prolapse of the mucosal and submucosal layers located dorsally at the pharyngoesophageal junction through Killian's triangle. The most severe complication of this condition is the aspiration of food that can lead to recurrent pneumonia, other complications are cancer, bleeding, and perforation [52-55]. Therefore, treatment can be indicated regardless of the size, and consists of myotomy of the cricopharyngeal muscle [56]. Historically, Zenker's diverticulum had been treated by head and neck surgeons. Since 1917, the endoscopic approach has evolved from rigid endoscopy to flexible endoscopy, with the development of different tools ranging from staplers to laser knives. Many efforts have been expended in this field because of its multiple advantages, such as reduced procedure time, earlier diet introduction, shorter hospitalization time, and lower complication rates. Despite that, patients treated endoscopically reported higher rate of recurrence, probably due to incomplete myotomy [57-62]. The evolution of the previous endoscopic technique is Z-POEM. Of course, it took inspiration from the POEM procedure. In this case, the endoscopists, by the creation of the third-space, can directly visualize the septum and achieve a deeper and more complete myotomy. In fact, until now, some reports showed good correlation between longer septotomy and clinical success. The tunnel is created on both sides of the septum and extended for 1 or 2 cm, and after the full myotomy, the flap is closed by the use of clips [63]. Thus, the complete dissection can be performed due to the mucosal integrity. Moreover, the accurate closure of the entry seems to prevent secondary infection [64-66].

D-POEM

Epiphrenic and mid-esophagus diverticula have never been a contraindication to POEM procedure. Recently, some centers have reported successful treatment of such diverticula using the same principles of the POEM technique. Tunneling, septal myotomy, and closure of the

flap are carried out at least in 1 hour. Good success and safety make D-POEM an attractive option for future management of esophageal diverticula [67-70].

G-POEM

Gastroparesis (GP) is a chronic syndrome characterized by sluggish emptying of solid food from the stomach. This motility disorder has very limited medical therapeutic options. Interventional options include pyloric dilatation, botulinum toxin injection, electrical stimulation, surgical pylorotomy or pyloroplasty and finally, partial or total gastrectomy. Gastric-POEM, also known as per-oral pylorotomy (POP), is an emerging novel endoscopic technique [71]. POEM sub-mucosal tunneling technique have been adapted to perform pyloromyotomy. It consists of a mucosal incision, which is generally performed on the greater curve, 4-6 cm before the pylorus. Tunneling continues until the duodenal mucosa is visualized. However, because of long-standing chronic disease, the stomach can lose its J shape, and the manoeuvrability of the scope becomes difficult on the greater curve. For this reason, some centres prefer the approach along the lesser curve [72]. In both cases, after the tunneling, selective-circular myotomy [73] for 2-3 cm in the antrum is made and extended to the pyloric ring, and finally, the entry is closed with endoclips. In same series, fluoroscopy was used to ensure the orientation and to identify pylorus [74,75]. G-POEM is used as a salvage therapy in patients refractory to medical therapies [73] showing symptom reduction in more than 80% cases [76-80]. Unfortunately, not all patients with refractory gastroparesis can benefit from the G-POEM procedure. For example, results in diabetic gastroparesis are less promising [80]. Previous studies reported gastric stimulators as the best option for diabetic gastroparesis, but direct intervention on pylorus seems to be more effective in idiopathic or post-surgical disease [81-84].

Therapeutic: tumor enucleation

POET

In 2012, almost simultaneously, Inoue et al., Xu et al. and Gong et al. reported, in 3 different venues, the same procedure (POET, STER and ESDT (endoscopic submucosal tunnel dissection)). It consists of the submucosal tunneling and endoscopic resection of subepithelial-tumours (SETs) involving/arising from the muscularis propria or the adventitia [43, 5-87]. It is known that the management of SETs depends on dimension, location, and histology. Among them, gastrointestinal stromal tumours (GISTs) are considered to have malignant potential [88]. Leiomyomas, neurogenic tumours, and fibrous tumours of the upper gastrointestinal (GI) tract are rare tumours and we do not have enough data about their malignancy risk [89]. Until the advent of POET procedure, endoscopic resection could not guarantee a complete resection and prevention of recurrence. Moreover, when the lesions originated from the muscular layer, the

risk of perforation became relevant. For this reason, before every procedure, it was, and still is, mandatory to carefully study the tumour. CT scan or endoscopic ultrasound should characterize position, attachment to deeper layers, and tissue features. However, their ability to evaluate tumour size, fibrosis, and muscularis propria invasion is limited [90-93]. As already mentioned, two years after the advent of POEM, its direct offshoot POET/STER/ESDT was successfully attempted in three different centres, and it is increasingly performed to remove upper GI SETs [85,86,91,94-98]. The entry is about 3-5 cm proximal to the lesion, a short tunnel is made and extended 2 cm over the SET. The tumour can be dissected from the mucosal layer until just a small part of the lesion is still attached. Finally, it is taken with a snare, cut and removed [17,85,86,97]. The last step can be blind because of the bulk of the tumour which impedes the visualization of the distal end. Double-opening (DO-STER) technique has been developed to overcome this difficulty, it can be applied for tumours located at the distal esophagus, EGJ, and in the fundus [99]. According to the literature, en-bloc resection is achieved in 89-95% of cases [85,86,94-96,100]. Despite that, depending on the SET's features, the procedure can become very challenging, especially in those with delicate tissue, multiple lobes, or when the lesion is larger than 4 cm [94,95,101]. Moreover, some locations seem to be very challenging such as the proximal esophagus and deep gastric fundus [102]. For lesions located in the fundus, a novel transgastric endoscopic technique (TCTT) may facilitate access [103]. Moreover, areas which are more difficult to reach laparoscopically are the most suitable for an endoscopic approach and vice versa. One last theoretical concern about POET was the microscopic margins. The enucleation cannot achieve negative microscopic margin R0. Therefore, large series and prospective trials suggest the equivalence of R0 and R1 in endoscopic resection of small upper gastrointestinal GISTs [104,105]. Some additional advantages of this technique, compared to ESD or resection, are more rapid wound healing, preserving an intact mucosal layer, and prevention of leakage, especially in the esophagus [85,106].

RECTAL STER

The same procedure as POET/STER/ESDT was reported by Hu et al. in 12 patients with rectal SMTs. The median size of the lesion was 1.4 cm, ranged 1 cm to 3 cm. All the tumours were resected en bloc without major adverse events [107].

Therapeutic: lumen recanalization

POETRE

In patients treated with chemotherapy and radiation for lung and neck cancers, complete esophageal obstruction can occur. The inability to swallow and the high risk of aspiration lead to a poor quality of life. The aim of per-oral endoscopic tunneling for restoration of the

esophagus (POETRE) is to restore the esophageal lumen and feeding, through endoscopic rendezvous. One endoscope is inserted from the mouth and the second scope is inserted from the gastrotomy (G-tube) in a retrograde direction. This technique can be performed even in long stenosis (<3 cm) [108]. One of the two endoscopes enters the submucosal space, so tunneling and dissection is performed safely thanks to the transillumination of the second scope which directs the route. To ensure the direction, fluoroscopy can also be used. When the rendezvous point is reached, the esophageal wall is incised, and a fully covered metal stent is placed. Unfortunately, frequently after the removal of metal stent further dilatation is needed [108,109].

PREM

Hirschsprung's disease is an inherited disease, characterized by dysplasia of the enteric nervous system presents with constipation, megacolon, and stenosis or complete intestinal obstruction [110]. Frequently, the recto-sigmoid area is involved. Pre-rectal endoscopic myotomy seems to be a promising treatment for adults and children with Hirschsprung's. The procedure was first demonstrated on animal models [111], then Bapaye et al. performed successfully the first case on a human. The technique follows the steps of POEM procedure: 1 cm proximal to the anorectal junction a bleb and incision is made, then, tunneling and myotomy of the spastic segment is done following oral direction, the entry is finally closed with endoclips [112].

Future perspective

Recently Inoue proposed two new different NOTES procedures which cannot be summarized as the previous: POEM+F and POEF.

POEM+F

As is well known, the greatest enemy of the POEM procedure is GERD. Someone asked if reflux will kill POEM [113], but the spirit of reinvention led POEM over its limits on the back of its older sister Heller myotomy. The surgical myotomy was performed with different funduplications in order to prevent reflux disease: Nissen, Dor and Toupet. POEM+F consist of 2 major steps: myotomy (POEM) and fundoplication (F). It is indicated in patients who have major risks to develop GERD, such as sliding hiatal hernia. When POEM+F is planned, the anterior approach is preferred. After the completion of the selective myotomy, a few centimetres distal to the diaphragmatic crus a full thickness myotomy is performed. The defect is enlarged so that the endoscope can reach the peritoneal cavity. In this position, it is possible to see the left hepatic lobe, angulating the scope up and left, it is possible to see and reach the anterior wall of the stomach. To identify the right position for the anchoring process, a paediatric scope is introduced in the gastric lumen, so that trans-illumination can be seen from the

peritoneal cavity and vice versa. Once that point is defined, an endoloop is grasped with one endoclip and fixed on the designated point of the gastric wall with further clips. The other side of the loop is fixed to the dissected esophageal muscle, at the EGJ, and the endoloop is closed. This way a fundoplication (>90°) is achieved, like in the Dor technique. POEM+F was finally refined though the use of endoscopic suturing device (curved needle) which ensures the suture of all of the gastric wall (Figures 1 and 2) without too many devices (clips and endoloop) [114].



Figure 1

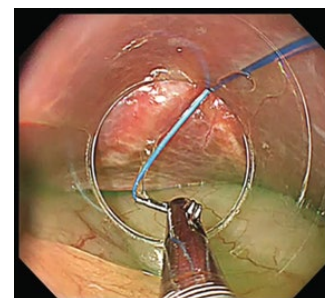


Figure 2

POEF

Per-oral endoscopic fundoplication, presented in Tokyo Live 2019 by Prof Inoue et al. can become a therapeutic option for patients affected by reflux disease resistant to medical treatment or for patients who develop GERD after POEM. For this reason, in POEM procedures, the posterior approach should be used instead so that the anterior approach can be preserved for endoscopic fundoplication. This technique is the same as explained for POEM+F, but without any myotomy.

Conclusion

In conclusion, submucosal space endoscopy is becoming more and more popular among interventional endoscopists, and represents the starting point for multiple paths to tread. However, it is important to underline that these procedures need a strong background of interventional GI to minimize and manage potential complications. A deep knowledge of anatomy is also required. Last but not least, the biggest challenge is to understand the most appropriate indications for each procedure in order to obtain the maximum benefits and, at the same time, lower risk for patients.

Abbreviations

POEM: per oral endoscopic myotomy; NOTES: natural orifice transluminal endoscopic surgery; LES: low esophageal sphincter; Z-POEM: zencker per oral endoscopic myotomy; D-POEM: diverticulum per oral endoscopic myotomy; G-POEM: gastric per oral endoscopic myotomy; POET resection: per oral endoscopic tumour resection; STER: submucosal endoscopic resection; POETRE: per-oral endoscopic tunneling for restoration of the esophagus; PREM: per-rectal endoscopic myotomy;

POEF: per-oral endoscopic fundoplication; POEM-F: per-oral endoscopic myotomy + fundoplication; GERD: gastro-esophageal reflux disease; ESDT: endoscopic submucosal tunnel dissection; SETs: subepithelial-tumours; GISTs: gastrointestinal stromal tumours

Conflict of Interest

H. Inoue is an advisor for Olympus and TOP Corporation. He has also received educational grants from Olympus Corporation and Takeda Pharmaceutical.

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