Future Applications of Submucosal Surgery: NOTES, Full-Thickness Resections and Beyond

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Introduction

Navigation in the submucosal (SM) space is a common element in several emerging procedures in interventional endoscopy, including endoscopic submucosal dissection (ESD), POEM (peroral endoscopic myotomy), POP (peroral pyloromyotomy), and POET (peroral enucleation tumors). The use of a submucosal endoscopic mucosal flap (SEMF) technique as a valve in natural orifice translumenal surgery (NOTES) procedures has also proven to be useful. Submucosal endoscopy has an evolving role in diagnosis of neuromuscular disorders of the gastrointestinal tract (Fig. 16.1).

Past, present, and future perspectives of procedures in which submucosal endoscopy has a role will be discussed in this chapter. While some SM procedures are part of current medical practice, others are still in an animal testing phase (Table 16.1).

The Submucosal Space and NOTES

The ability to endoscopically create a submucosal (SM) working space within the wall of the gastrointestinal tract was first described by Sumiyama et al. in 2006 [1]. The original description included the use of pressurized CO2 injected through an

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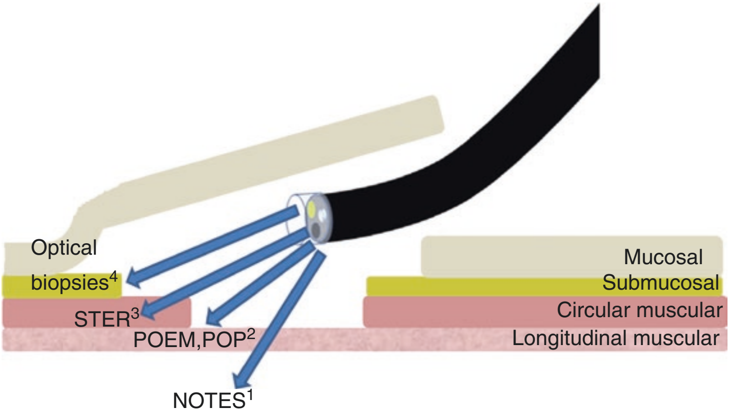

Fig. 16.1 Endoscopic interventions with submucosal navigation. (1) *NOTES* natural orifice transluminal surgery (SEMF valve approach). (2) Endoscopic myotomies—*POEM* peroral endoscopic myotomy, *POP* peroral pyloroplasty. (3) Endoscopic tumor resection—*STER* submucosal tunneling endoscopic resection. (4) Optic biopsy and tissue sampling for subepithelial lesions or neuromuscular disorders of the gastrointestinal tract

Table 16.1 Examples of procedures with submucosal navigation in different stages

Animal experiments	Early clinical adoption	Clinical adoption
		Per-oral endoscopic myotomy (POEM)
Per-oral endoscopic pyloroplasty (POP)		
	Submucosal tumor endoscopic resection (STER)	
Peritoneoscopy under conscious sedation		
Optical biopsies – OTC, endocytoscopy, CLE		
Trans-rectal NOTES		
Transesophageal thoracic NOTES		

endoscopic needle placed into the submucosa with creation of a large SM gas bubble. The next step was a mucosal incision in the edge of the bubble and further development of a tunnel with a biliary extraction balloon. This technique was developed in an effort to create a self-sealing exit site for NOTES procedures. This approach was advantageous because the incision in the mucosa and in the seromuscular layer of the gut was made several centimeters apart, thus avoiding the need for single-site full-thickness closure of the GI tract in NOTES procedures. The SEMF technique was first used to perform full-thickness muscular layer resections [1]. In 2007, the same group published the technical feasibility of transesophageal mediastinoscopy [2] and trans-gastric cholecystectomy [3] in survival animal model using the SEMF technique. During mediastinoscopy, the defect in the muscular layer was not closed and the mucosa was approximated with clips. In the trans-gastric cholecystectomy, the authors used anchors or clips to close the mucosal incision. Despite complications and mortality in the animal models, the SEMF technique was felt to be potentially feasible and effective. In the same year, Pasricha et al. published the use of a submucosal tunnel as an access route for an esophageal myotomy, which started a new era in the treatment of achalasia [4].

One caveat of the SEMF technique as proposed by Sumiyama et al. was the possibility that the creation of a wide area of separation between the mucosa and the submucosa could potentially lead to ulceration and necrosis of the overlying mucosa due to devascularization [5]. To overcome this, different authors described the creation of narrow and long tunnels using ESD techniques for trans-gastric [6] and transrectal NOTES [7] procedures. Also, narrow SM tunnels helped to correctly align the endoscope with the proposed intraperitoneal target [8]. Despite theoretical advantages, a comparison between direct incision (DI) of the gastric wall and submucosal tunnel (SMT) creation for trans-gastric access in NOTES favored the DI method in one study [9]. In this animal experiment, six pigs had intraperitoneal targets implanted in predetermined positions inside the abdominal cavity. The operative time was higher in the SMT group and more intra-abdominal targets were reached in the DI group. However, when considering closure of the initial gastrotomy, most studies have favored the SMT method as it provides a more secure and lower-risk closure of the enterotomy [9–11].

Both DI method and the SMT method reached early clinical adoption. For example, Lee et al. published a study in which ten patients had submucosal tunneling (SMT) as an access route for NOTES. Five patients had a diagnostic peritoneoscopy (four with ascites and one with a lymphadenopathy of unknown cause), while the other five had a full-thickness resection due to subepithelial tumors. Remarkably, the procedures were successfully conducted under conscious sedation. No severe postoperative complications occurred [5]. Conversely, Magdeburg et al. published a series of 43 patients that had trans-gastric NOTES procedures (36 appendectomies, six bilateral salpingo-oophorectomies, and one hysterectomy) using the direct incision method to access the peritoneal cavity. In these patients, closure of the gastric incision was done using an over-the-scope nitinol clip (OTSC 12/6a-220; Ovesco Endoscopy, Tubingen, Germany). There were three adverse events in the series: two patients had bleeding originating from the clipped closure site and one patient had a local peritonitis due to insufficient closure of the gastrotomy [12].

The trans-gastric SEMF method seems to be a reasonable way of exploring the abdominal cavity under conscious sedation. No dedicated high-cost equipment is required to perform the technique, and the closure of the gastric mucosotomy is usually accomplished with regular endoscopic clips. Therefore, one can theorize that this may become an useful method for peritoneoscopy in the future, especially in cases in which general anesthesia is undesirable, such as critically ill patients [5]. Furthermore, as new NOTES platforms develop, advanced operations may be performed under conscious sedation, with minimal invasiveness and morbidity using an incision in the gastric mucosa and a submucosal tunnel as the route to the peritoneal cavity. New wide-angle endoscopes as well as navigation systems may facilitate orientation and visualization inside the abdomen [13, 14]. A number of platforms dedicated to NOTES, both robotized and mechanical, are under development [15, 16].

In addition to trans-gastric procedures, a number of experimental studies have explored the feasibility and potential utility of transesophageal access for the mediastinum and thoracic cavity. In animal studies, it has been demonstrated that procedures such as mediastinoscopy, lymphadenectomy, truncal vagotomy, pleural biopsy under direct vision, pericardial windows, myocardial and left atrium injection, epicardial ablation, and even thoracic spine procedures can be performed through the transesophageal route [17]. The SEMF technique (mucosal incision and submucosal tunneling) has been employed more frequently than the direct incision (DI) method for transesophageal thoracic NOTES [17]. To facilitate esophagotomy closure, endoscopic clips, tissue anchors, and covered stents have been used with favorable outcomes in the animals [17, 18], but stent migration with current devices is a problem.

In order to increase safety and efficacy in submucosal explorations and NOTES, it has been advocated that image guidance could be helpful. In one study, Córdova et al. [19] assessed the utility of a navigation system based on reconstructed 3D CT images and electromagnetic tracking of the tip of the scope (3D Guidance trakSTAR; Ascension Technology Corp, Burlington, Vt). In this study, 30 pigs underwent transesophageal NOTES mediastinoscopy, with half of those having the abovementioned navigation system while the other half without guidance. A mucosal incision and submucosal tunneling (SMT) technique was used to enter the mediastinum. The number of adverse events was similar in with and without guidance, and the author was able to identify the right atrium and the vena cava in more animals in the group that had the navigation system. No complications from the SMT were reported.

Indeed, transesophageal NOTES for mediastinal or thoracic exploration until now have not reached widespread clinical adoption. Nevertheless, trans-oral esophageal procedures like the peroral endoscopic myotomy (POEM) and subepithelial tumor enucleation (POET) including endoscopic full-thickness resections (EFTR) have enjoyed clinical acceptance. With this growing experience, slower yet steady progress is been made to push forward the boundaries of transesophageal NOTES. It has now been clearly demonstrated that esophageal mucosotomy and tunnel development are safe and can reach beyond the esophageal wall. Transesophageal exploration of the mediastinum and chest remains a possible future application for the SEMF technique in humans [20].

Transrectal peritoneal access using the submucosal tunnel technique has also been described in animal studies. Despite potential bacterial burden and concerns about healing in rectal wounds, possible advantages of this route are enhanced visualization and the ability to reach of the upper abdomen, due to the fact that the endoscope is in a straight position. This approach also affords less incisional pain by use of the anus for retrieval of specimens compared to a transabdominal approach. In one study [7], six pigs had transrectal SMT access for 20 min of peritoneoscopy. The author did not observe complications and noted that the healing process was more advanced at the seromuscular level compared to the mucosal level after 7 days. In this study, the mucosal incision was closed with titanium clips. Also, transrectal incision and submucosal tunnel have been the access route for a retroperitoneoscopy and feasibility of a NOTES nephrectomy in cadaver models [21].

Trans-oral NOTES access to perform operations in the thyroid gland without visible scars had used a mucosal incision and the development of a tunnel [22]. In the trans-oral thyroidectomy vestibular approach (TOETVA) described by Anuwong, the surgeon performs three incisions in the oral vestibule and inserts conventional laparoscopic ports and instruments. Then, the subplatysmal space is dissected, from the larynx to the sternal notch distally and laterally to the anterior border of the sternocleidomastoid muscle. The space is then maintained by a CO_2 insufflation pressure of 6 mmHg. The author reported 60 procedures using this method with good outcomes. Other authors reported minimally invasive thyroidectomies from the base of the tongue. It is intuitive to imagine that the vestibular incision and subplatysmal dissection can also be used to reach the cervical esophagus. As such, treatment of pharyngoesophageal (Zenker's) diverticulum and even esophageal resections could be approached without skin incision, thus leaving no scars and potentially decreasing morbidity.

Submucosal Tunneling: Beyond POEM

POEM was the first widely accepted non-NOTES application of the SEMF access technique. It has since developed into a standard treatment for achalasia. As endoscopists became more comfortable with the technology and approach, the indications in the field of esophageal dysmotility have expanded. End-stage disease, reoperative cases, spastic motility disorders, and other non-classified disorders are now routinely treated using POEM access. Several other disease states are also being treated via tunneling access. The best described is the treatment of gastroparesis by endoscopic pyloromyotomy. Idiopathic and diabetic gastroparesis has been shown to respond well to surgical pyloroplasty [23].

Early reports, of this procedure, including one multicenter study, have shown symptom improvement or relief in around 86% of patients and normalization of radionuclide exam in between 47 and 80% of patients [24]. While long-term outcomes are unknown, it appears that the POP procedure may prove to be an important tool in the management of these difficult patients.

Another reported procedure is endoscopic cricomyotomy. Cervical dysphagia due to cricopharyngeal spasm or hypertrophy is an annoying condition, not uncommon in the elderly population. Because it is a benign condition and surgical treatments are rather invasive, treatment is seldom offered to these patients, leaving them to suffer with their decreased quality of life. Endoscopic cricomyotomy has been described using a POEM-like approach, making the mucosal incision in the posterior pharynx, tunneling to the cricopharyngeal muscle, and dividing the muscle well onto the normal proximal esophagus. Good results have been reported in small studies [25].

There are numerous other anecdotal reports of use of submucosal tunneling to treat a variety of conditions, including recalcitrant strictures, congenital cartilage rings, muscularis propria biopsies, and even rectal myotomy for adult Hirschsprung disease [26, 27]. It is clear that the success of POEM has opened the door to a whole brave new world of working in this new "third space"—neither endolumenal nor extralumenal—but providing direct access to the origins of many digestive diseases.

Submucosal Endoscopy in Tumor Resection: Full Thickness and Beyond

Endoscopic resection of gastrointestinal lesions is a rapidly evolving field. The first endoscopic polypectomies for colorectal lesions were described in 1974, and the strip biopsy technique of mucosectomies was described by Tada et al. in 1984. In 1992 cap-fitted EMR (endoscopic mucosal resection) was first described. With the development of the IT (insulated tip) knife in the late 1990s, endoscopic submucosal dissection (ESD) techniques began to thrive, and larger mucosal lesions could be resected en bloc [28]. With knowledge granted from ESD practice, new techniques [29, 30] for tumor resection based on navigation within the submucosa, such as the endoscopic submucosal excavation technique (ESE) and submucosal tunneling endoscopic resection (STER) approaches, were made possible. More recently, the full-thickness resection device (FTRD), which is a combination of a modified over-the-scope-clip (OTSC) system with an electrocautery snare, has emerged as a new method for purely endoscopic full-thickness resection [31].

The endoscopic submucosal excavation (ESE) is an ESD that goes beyond the submucosa. Briefly, the steps of the procedure are the following: normal saline is injected into the submucosa; a precutting incision at the mucosal and submucosal layers around the lesion is performed. After that, a circumferential incision as deep as necessary to isolate the tumor at the MP or serosal level is done. The final resection is usually done with a snare. If a full-thickness viscerotomy results, it can be closed with regular titanium clips, over-the-scope clips, or suturing devices with similar outcomes. This approach is less technically demanding compared with the submucosal tunneling, but there are inherent issues with a full-thickness defect, including loss of working space, peritoneal soiling, and need for an airtight closure of the incision [29].

The submucosal tunneling endoscopic resection (STER) technique is a challenging procedure with a long learning curve. However, in this technique the mucosa is not breached at the resection level, decreasing soiling, losing working space, and facilitating closure. Briefly, the steps of the procedure include: submucosal injection, mucosotomy about 5 cm proximal to the tumor, SM tunnel development, and approach of the lesion with ESD instrumentation [32]. The lesion is resected and the mucosal incision is closed with clips. Lu et al. [33] published a study comparing ESE and STER for resection of esophageal and cardial submucosal tumors less than 3 cm in diameter. Thirty-five patients had ESE and 42 patients had STER. The complete resection and perforation rates were similar for the two techniques, but air leakage symptoms (subcutaneous and mediastinal emphysema) were more frequently in the ESE group when the resected tumor was more than 1 cm of diameter. They concluded that for SMT >1 cm, the STER procedure was preferred. In one of the largest series published to date, Ye et al. [34] described the use of the STER technique in 85 patients with subepithelial tumors. Sixty were located in the esophagus, 16 in the cardia, and 9 in the stomach. All tumors were less than 3 cm in diameter. A 100% resection rate was obtained and eight patients had complications (9.4%), in all cases related to air leakage (pneumoperitoneum, subcutaneous emphysema, pneumothorax). The odds for complications was higher in tumors located in the deep muscularis propria layer.

The location of the submucosal lesion has a major role in the choice of technique for removal (Table 16.2). Tumors located in the esophagus or cardia may favor the STER approach. In the stomach, the STER technique can be performed if the lesion is in the lesser curvature of gastric body and the greater curvature of gastric antrum. In other areas, like the anterior and posterior body, the submucosal excavation technique or the full-thickness resection device (FTDR) can be the best approach. In the colon, FTDR is the most common technique. The FTDR device may be used for mucosal lesions, such as non-lifting or recurrent adenomas and early cancers. A limitation of the FTDR device is the size of the lesion, which has to be accommodated into a dedicated endoscopic cap before resection with a snare. In one study, 18 out of 24 lesions (75%) were resected en bloc [35].

In the future, we can anticipate that different techniques for full-thickness endoscopic resections will have clear indications taking into consideration anatomic site, size, and histology of tumors. It seems unlikely that the same technique and device will prove to be superior for use in removing all esophageal, gastric, or colonic tumors. Submucosal tunneling will most likely be part of the repertoire. Robotized endoscopic platforms with emphasis in surgical tasks and easier manipulation will have a pivotal role in enabling more physicians, not only highly specialized surgical endoscopists, to perform endoscopic full-thickness resections [13, 15, 16].

The Role of Submucosal Endoscopy for Diagnosis of Disorders of the Muscularis Propria and Myenteric Neurons

Comprehensive histological evaluation of motility disorders in the gastrointestinal tract, such as achalasia, gastroparesis, and Hirschsprung disease, has been limited due to difficulties in tissue acquisition in layers deeper than the mucosa. Assertive methods of tissue sampling, such as the double EMR technique and full-thickness resections, are needed [36].

Table 16.2 Comparison between STERcopic submucosal excavation (ESE), and OTSC (over-the-scope clip)

Author/year	# of patients	Location	Pathology	Mean size (mm)	Technique	% en bloc resection	Complications
Huang et al.	35	14 fundus 21 corpus	25 GISTs 7 leiomyomas 2 schwannomas	28	ESE	100	None reported
Guo et al.	23	11 fundus, 9 corpus, 3 antrum	19 GISTs 4 leiomyomas	12	OTSC	100	2 localized peritonitis
Lu et al. (2014)	83	56 esophagus, 27 cardia	74 leiomyomas 9 GISTs	12	STER-45 ESE-38	STER-97 ESE-92	STER-SE/ME-1/45 ESE-SE/ME–5/38
Feng et al.	48	40 fundus, 7 corpus, 1 antrum	43 GISTs, 4 leiomyomas, and 1 schwannoma	15, 9	ESE	100	5 PP
Li et al. (2015)	32	3 fundus close to the cardia 12 corpus close to the cardia 6 lesser curvature corpus 11 greater curvature of antrum	11 GISTs, 18 leiomyomas, 3 others	23	STER	100	1 bleeding, 6 PP, 3 PTX, and SE
Zhou et al. (2015)	21	Esophagogastric junction	6 GISTs, 15 leiomyomas	23	STER	100%	9 ME and SE
Ye et al. (2014)	85	60 esophagus, 16 cardia, 9 stomach	19 GISTs, 65 leiomyomas, 1 calcifying fibrous tumor	19.2	STER	85%	6PTX, 8SE, 4PP

Abbreviations: *GIST* gastrointestinal stromal tumor, *SE* subcutaneous emphysema, *ME* mediastinal emphysema, *PTX* pneumothorax, *PP* pneumoperitoneum

Recently, optical biopsy methods have been developed, aiming to provide analysis at a cellular level in GI endoscopy. Numerous studies on the application of technologies such as optical coherence tomography (OTC), endocytoscopy, and confocal laser endomicroscopy have been published in the evaluation of mucosal diseases [37–39]. At the submucosa, endocytoscopy and confocal laser endomicroscopy have been tested to evaluate the muscularis propria and myenteric plexus with encouraging results, thus potentially replacing the current cumbersome methods to obtain deep-layer samples in the GI tract. For example, Sato et al. [40] used endocytoscopy, a technique in which there is a ×380 magnification and methylene blue staining, to evaluate the muscular cells in seven achalasia patients undergoing POEM procedure. After submucosal tunnel creation and completion of the myotomy, the GIF-Y0002 endoscope (prototype from Olympus Co.) was used to perform the optical biopsies. No abnormalities in the muscular layer were found in endocytoscopy and similar results were found on conventional biopsy. The nerve plexuses were not visualized in this setting because of a lack of neuron-specific fluorescent stain available for safe use in humans. Neuroenteric plexus visualization remains a future perspective in submucosal endocytoscopy.

The use of probe-based confocal laser endomicroscopy (pCLE, Cellvizio technology, Mauna Kea, Paris, France) in the submucosa has been tested in the porcine model. Ohya et al. [41] studied two ex vivo and six in vivo pigs, in which a submucosal tunnel was developed and neuron-like cells were stained with a fluorescent neuronal molecular probe (available for animal use). The author then developed specific sites for inspection with pCLE and posterior histologic evaluation. The muscularis propria was visualized in all cases and neuron-like cells were identified in 41.7% of the sites with pCLE.

Conclusions

Submucosal endoscopy is the basis for a diverse set of exciting procedures and techniques, including myotomy, tumor resection, NOTES, and optical biopsy. With several indications today, the ability to work in the potential space of the submucosal plane may still be somewhat novel, but the potential is enormous and the future is bright for those willing to extend this path in advanced surgical endoscopy [42–47].

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