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Endoscopic treatments for small gastric subepithelial tumors originating from muscularis propria layer

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Abstract

Minimally invasive endoscopic resection has become an increasingly popular method for patients with small (less than 3.5 cm in diameter) gastric subepithelial tumors (SETs) originating from the muscularis propria (MP) layer. Currently, the main endoscopic therapies for patients with such tumors are endoscopic muscularis excavation, endoscopic full-thickness resection, and submucosal tunneling endoscopic resection. Although these endoscopic techniques can be used for complete resection of the tumor and provide an accurate pathological diagnosis, these techniques have been associated with several negative events, such as incomplete resection, perforation, and bleeding. This review provides detailed information on the technical details, likely treatment outcomes, and complications associated with each endoscopic method for treating/removing small gastric SETs that originate from the MP layer.

Key words: Gastric subepithelial tumors; Endoscopic treatment; Submucosal tunneling endoscopic resection; Endoscopic muscularis excavation; Endoscopic full-thickness resection

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Core tip: Minimally invasive endoscopic resection has become an increasingly popular method for small gastric subepithelial tumors (SETs) that originate from the muscularis propria (MP) layer. Currently, the main endoscopic therapies for patients with such tumors are endoscopic muscularis excavation, endoscopic full-thickness resection, and submucosal tunneling endoscopic resection. This review provides detailed information on the technical details, likely treatment

outcomes, and complications associated with each endoscopic method for treating small gastric SETs that originate from the MP layer.

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INTRODUCTION

Gastric subepithelial tumors (SETs) that originate from the muscularis propria (MP) layer are often asymptomatic and as a result are most frequently found incidentally during endoscopic procedures. A proportion of such gastric SETs are diagnosed as gastrointestinal stromal tumors (GISTs), which have the potential for malignancy^[1]. Resection of gastric SETs can both aid in diagnosis and may at the same time be curative if the entire lesion is removed. Previously, surgical resection was the principal therapeutic option for removing small gastric SETs that originate from the MP layer^[1-4]. However, surgical procedures are invasive and associated with certain complications, such as postoperative hemorrhage, gastroesophageal reflux, or late anastomotic stenosis^[3], especially in asymptomatic patients with tumors less than 2.0 cm in diameter. According to the National Comprehensive Cancer Network guideline, endoscopic surveillance is another approach for GIST < 2 cm without high-risk EUS features^[5]. However, repeated endoscopic examinations involve known issues associated with cost-effectiveness, patient compliance and risk related to delayed diagnosis of a malignancy.

Previously, endoscopic methods, such as snare polypectomy, band ligation, and endoscopic mucosal resection (EMR), were used to remove gastrointestinal SETs, but their use has generally been restricted to tumors located in the muscularis mucosae or submucosal layer^[6-8]. Recently, with improvements in endoscopic submucosal dissection (ESD) technology, ESD is not only used to successfully treat superficial gastrointestinal (GI) lesions but also GI SETs that originate from the MP layer^[9-12]. Currently, several studies have described various modalities of endoscopic resection that have been used to successfully treat gastric SETs that originate from the MP layer. Thus, this article is to review the current status of minimally invasive endoscopic treatments for such gastric SETs.

ENDOSCOPIC MUSCULARIS EXCAVATION

ESD is an effective endoscopic technique, which has made it possible to perform *en bloc* resections of

superficial gastric cancers. With the development of ESD techniques and the application of new endoscopic accessories, several studies have recently evaluated the safety and effectiveness of ESD techniques in the treatment of small gastric SETs that originate from the MP layer. Lee *et al*^[9] reported that ESD was successfully performed in 11 patients with a total of 12 gastric SETs that originate from the MP layer, with a complete resection rate of 75%, and without massive bleeding, perforation, or any other severe complications during hospitalization. In another study of 18 gastric SETs, Zhang *et al*^[12] reported that the complete resection rate was 94.4%. During the same procedure, 2 patients developed perforations, which were successfully treated by endoscopic methods. These results demonstrate that ESD can be used for successful removal of small gastric SETs that originate from the MP layer, which may ultimately replace treatment by surgical resection (at least in some cases).

Although standard ESD procedures can be used safely for the resection of gastric SETs while providing an accurate pathologic diagnosis, this procedure is associated with some complications, including perforation, bleeding, and abdominal infection^[10,11,13]. Among them, perforation is the main complication of such ESD procedures. Previous studies using ESD to treat gastric SETs have reported an incidence of perforation ranging from 0%-20%^[10,11,14-16]. In addition, if tumors presenting with a tight connection to the underlying MP have extended over a large area, complete resection by ESD often fails^[10,16]. In a recent study focusing on the use of ESD to treat gastric SETs, Bialek *et al*^[10] reported that the complete resection rate was 100% when tumors had no connection to the underlying MP; yet when tumors presented with a narrow connection to the underlying MP, the complete resection rate was only 68.2%. Therefore, ESD has some limitations for the treatment of gastric SETs with a tight connection to the underlying MP tightly.

Recently, with improved ESD technology, there have been an increasing number of reports on the use of endoscopic resection methods for gastric SETs that originate from the MP layer. During this procedure, a circumferential muscularis excavation is usually made that is as deep as the MP layer around the tumor, which is used to peel the tumor from the MP layer. Due to this critical difference in procedure, this technology has been named endoscopic muscularis excavation (EME)^[17]. Note that EME is similar to the technique of standard ESD, with the only difference in the depth of excavation.

In our center, EME is performed as follows (see Figure 1)^[17]: After marking the lesion margins with a needle-knife, several milliliters of submucosal injection solution is injected into the submucosa around the lesion. Subsequently, a cross-incision is made inside the marker dots using the electric knife, and several

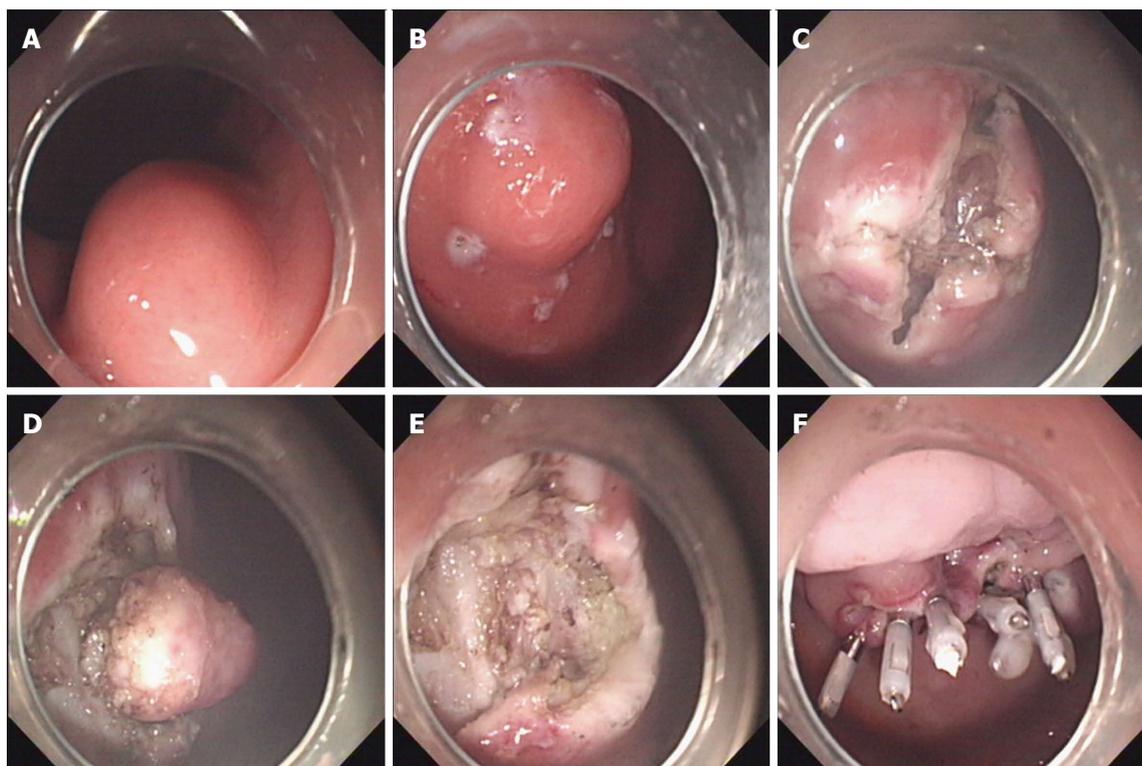


Figure 1 Endoscopic muscularis excavation. A: A subepithelial tumor was found at the posterior wall of the gastric body; B: Making several dots around the tumor; C: A cross-incision was made at the overlying mucosa of the tumor; D: Excavating the tumor from the muscularis propria layer; E: An artificial ulcer was observed after excavation; F: The artificial ulcer was closed with several clips.

milliliters of submucosal injection solution (above mentioned) is injected around the lesion to help distinguish the tumor mass from the gastric muscular layers and avoid tumor rupture during the excavation. A circumferential excavation is made along the edge of the tumor until the tumor is completely separated from the MP layer using the electric knife. After tumor removal and adequate hemostasis, the wound is closed with metallic clips.

Compared with standard ESD procedure, the primary advantage of EME is the improved complete resection rate. In our previous study using EME to remove gastric SETs that originate from the MP layer, the complete resection rate was 96.2% (204/212)^[18]. In almost all similar studies reported to date, the complete resection rate has been higher than 90%, which reaches an acceptable level^[19-21] (Table 1). In contrast, standard ESD for SETs originating from the MP layer has classically yielded a lower *en bloc* resection rate of 64%-75%^[22], suggesting that EME may be a better technique for the resection of SETs that infiltrate the MP layer.

However, as a result of deeper dissection (as compared to ESD), the risk of complications associated with EME is significantly increased^[22]. Massive bleeding is often caused by the accidental injury of the arteries that feed the tumor, which is one of the key factors that can affect procedure success or failure. Once massive bleeding is encountered, the endoscopic view may be affected, and the EME procedure might need to

be discontinued^[16]. Endoscopic hemoclips could be one effective method to control rapid bleeding. However, their use may possibly hamper subsequent endoscopic operations. It should be noted that although massive bleeding rarely happens, EME procedures should be halted and changed to open surgery or laparoscopic surgery when it cannot be managed using endoscopic methods. However, minor bleeding is not uncommon and can be treated successfully with argon plasma coagulation or coagulation forceps during the procedure.

Perforation is the considered major complication of EME treatment of gastric SETs originating from the MP layer. Some perforations can be avoided by repeated doses of submucosal injection solution and meticulous excavation. However, when the tumor is tightly attached to the MP layer or serosa, perforation is often inevitable. Several studies have reported that perforation may be associated with several factors, including histologic diagnosis, location, and origin of the tumor^[18,19]. Our recent study demonstrated that perforation was more likely to occur with tumors located in the fundus compared to any other part of the stomach, which is also common for tumors originating in the deeper MP layers as opposed to those in the superficial MP layer. In addition, the rate of perforation was significantly higher for GISTs than for leiomyomas. Therefore, an EUS examination is necessary to evaluate the tumor features and the origin of the tumor to predict the risk of perforation

Table 1 Clinical outcomes of endoscopic muscularis excavation for gastric subepithelial tumors originating from the muscularis propria layer

Ref.	No. cases (tumors)	Location (details)	Mean tumor size (mm)	Pathology	Complete resection rate, <i>n</i> (%)	Mean operating time (min) and range(min)	Complications (details)	Mean follow-up time (mo) and recurrence
Jeong <i>et al</i> ^[19]	64 (65)	23 cardia 8 fundus 30 body 4 antrum	13.8	26 GISTs 32 leiomyomas 2 schwannomas 3 others	60 (92.3)	34.7	8 perforations	10.0 No recurrence
Chu <i>et al</i> ^[21]	16 (16)	1 cardia 3 fundus 9 body 3 antrum	26.1	14 GIST 2 leiomyoma	15 (93.8)	52.0	0	14.8 No recurrence
Liu <i>et al</i> ^[20]	31 (31)	14 esophagus 7 cardia 5 fundus 5 body	22.1	16 GISTs 15 leiomyomas	30 (96.8)	76.8	4 perforations	17.7 No recurrence
Zhang <i>et al</i> ^[18]	212 (212)	93 fundus 104 body 15 antrum	16.5	97 GISTs 115 leiomyomas	204 (96.2)	46.1	32 perforations 9 massive bleeding	26.0 No recurrence

GISTs: Gastrointestinal stromal tumors.

before the procedure^[18]. Usually, perforations were relatively small and could not be directly visualized during the procedure. Therefore, the occurrence of subcutaneous emphysema during the procedure should be monitored as it may be used to denote such perforations. Fortunately, patients with perforations usually can be successfully managed by endoscopic methods and conservative treatment; few require surgical intervention^[17-21].

ENDOSCOPIC FULL-THICKNESS RESECTION

During the application of EME for gastric SETs originating from the MP layer, our center found that when the tumor had extraluminal growth or was tightly connected to the underlying MP or serosa, it was necessary to resect the underlying MP or serosa that adhered to the tumor. This technique of creating an iatrogenic perforation of the gastric wall for the subsequent removal of the tumor was named endoscopic full-thickness resection (EFTR)^[23-26] (Table 2). EFTR is performed as shown in Figure 2. Several milliliters of mixture solution are injected into the submucosa after dots are marked around the tumor with a needle-knife. Then, mucosal incision is made in the overlying mucosa to reveal the tumor. A circumferential excavation is then made as deep as the MP around the tumor with the electric knife. After the intraluminal side of the tumor is fully revealed, a small puncture is first made in the proximal seromuscular layer of the tumor with the electric knife, and then the resection is made along the puncture. Subsequently, snare resection is performed to completely remove the lesion after the electric knife resects three-quarters of the circumference of the tumor. Before performing snare resection, a dual-channel endoscope is used

while grasping the tumor in the gastric cavity to avoid it falling into the peritoneum. Clips or clips combined with an endoloop are used for closure of the gastric wall defect.

With the development of EFTR, the indications of endoscopic resection may be further expanded. However, several problems need to be noted. One key problem with the EFTR procedure involves issues with completely closing the gastric wall defect after full-thickness resection to avoid secondary surgical intervention. Incomplete closure of the gastric wall defect is a dangerous adverse event, and may lead to serious morbidity. This is a probable major safety consideration for the clinical application of EFTR. A wide range of methods and devices for closure of gastric wall defects have been studied, but most techniques require complex or specialized equipment, which represents a significant technical challenge^[25-27]. How to easily and safely close the defect is a problem that is worth further exploration. Previously, metal clips were widely used for closure of the iatrogenic perforation during the endoscopic procedure. Based on these experiences, some endoscopists elected to apply these clips as a closure technique for gastric wall defects after EFTR. In a recent study of 26 patients treated by EFTR, Zhou *et al*^[23] reported that clips are an effective and safe method for closure of the gastric wall defect. However, some endoscopists contend that the edge of the gastric wall defect might exhibit edema for a long time after the procedure, and the clip can therefore only close the gastric mucosa. Thus, there is a risk of gastric leakage when only using clip closure after EFTR, especially for some large defects (≥ 3 cm)^[28]. In a recent study, our center reported an easier to operate "clips plus endoloop" method in which the defect was closed with clips in a "side-to-center" manner using an endoloop to trap and

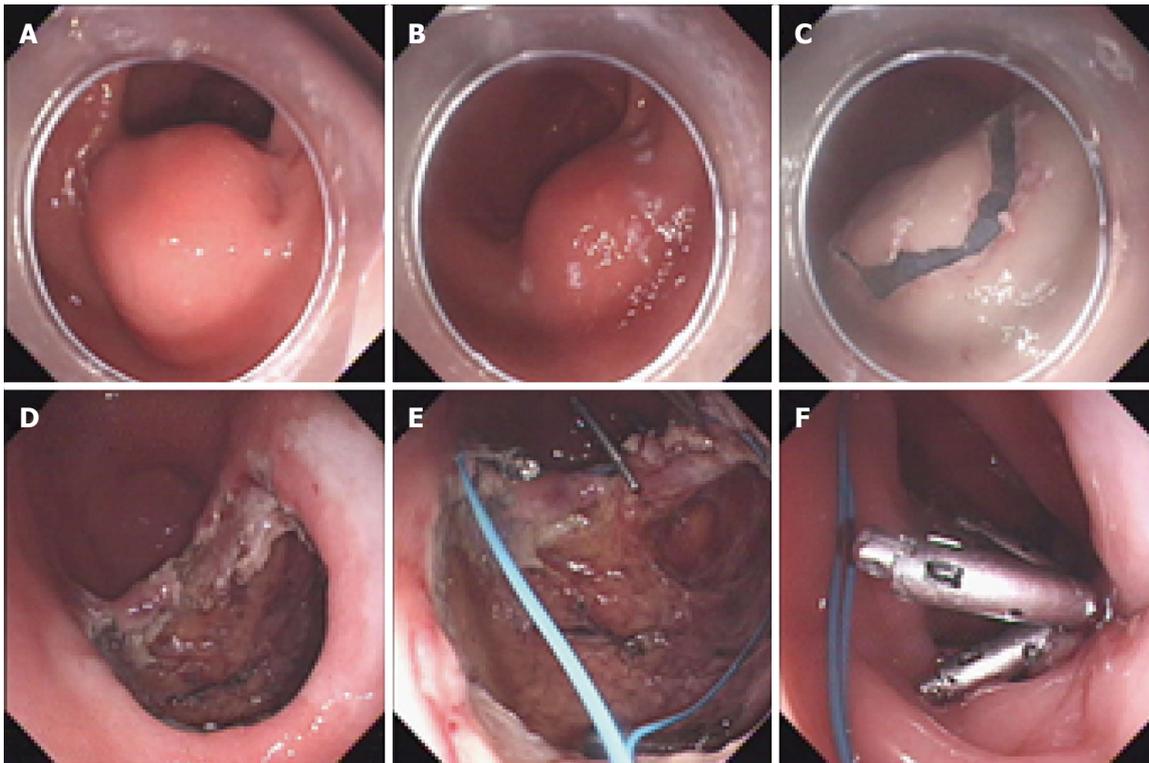


Figure 2 Endoscopic full-thickness resection. A: A subepithelial tumor was found at the greater curvature of the gastric antrum; B: Making several dots around the tumor; C: The mucosa incision was incised outside the marker dots; D: The omentum could be seen through the gastric wall defect after endoscopic full-thickness resection; E, F: Closure of the gastric wall defect using clips and an endoloop.

Table 2 Clinical outcomes of endoscopic full-thickness resection for gastric subepithelial tumors originating from the muscularis propria layer

Ref.	No. cases	Location (details)	Mean tumor size (mm)	Pathology	Complete resection rate, <i>n</i> (%)	Mean operating time (min)	Complications (details)	Mean follow-up time (mo) and recurrence
Guo <i>et al</i> ^[26]	23	11 fundus 9 body 3 antrum	12.1	19 GISTs 4 leiomyomas	23 (100)	40.5	2 localized peritonitis	3 No recurrence
Zhou <i>et al</i> ^[23]	26	12 fundus 14 body	28	16 GISTs 6 leiomyomas 3 glomus tumors 1 schwannoma	28 (100)	105	0	8 No recurrence
Schmidt <i>et al</i> ^[25]	31	3 cardia 4 fundus 13 body 11 antrum	20.5	18 GIST 2 leiomyomas 2 adenomyomas 3 ectopic pancreas 1 lipoma 1 schwannoma 4 others	28 (90.3)	60	12 bleeding	7 No recurrence
Ye <i>et al</i> ^[24]	51	22 fundus 28 body 1 antrum	24	30 GIST 21 leiomyoma	50 (98.0)	52	0	22.4 No recurrence

GISTs: Gastrointestinal stromal tumors.

tighten all clips. Compared with single clip closures, this closure method would reinforce the closure of the gastric defect and prevent postoperative gastric leaks and peritonitis^[24]. In addition, it has the advantage of being a simple manipulation that does not require complex or specialized equipment. One thing to note is that closure by clips or clips plus endoloop only

approximates the mucosal and submucosal layers, although this method appears to be safe and effective based on the present literature. However, these methods contradict accepted surgical safety principles, such that additional and more comprehensive randomized, controlled, and multicenter studies are required to confirm its safety and reliability.

Table 3 Clinical outcomes of submucosal tunneling endoscopic resection for gastric subepithelial tumors originating from the muscularis propria layer

Ref.	No. cases (tumors)	Location (details)	Mean tumor size (mm)	Pathology	Complete resection rate, n (%)	Mean operating time (min)	Complications (details)	Mean follow-up time (mo) and recurrence
Xu <i>et al</i> ^[30]	15 (15)	9 esophagus 3 cardia 2 body 1 antrum	19	5 GISTs 9 leiomyomas 1 glomus tumor	15 (100)	78.7	1 pneumoperitoneum 1 pneumothorax 1 SE	3.9 No recurrence
Liu <i>et al</i> ^[34]	12 (12)	7 esophagus 5 cardia	18.5	2 GISTs 9 leiomyomas 1 schwannoma	12 (100) ¹	78.3	2 pleural effusion 4 pneumothorax 8 SE	7.1 No recurrence
Wang <i>et al</i> ^[36]	57 (57)	57 esophago-gastric junction	21.5	7 GISTs 46 leiomyomas 1 intramuscular lipoma 1 granular cell tumor 2 schwannomas	57 (100)	47.0	8 pneumothorax 3 pneumoperitoneum 12 pneumothorax and SE 2 pleural effusion	12 No recurrence
Ye <i>et al</i> ^[32]	85 (85)	60 esophagus 16 cardia 9 stomach	19.2	19 GISTs 65 leiomyomas 1 calcifying fibrous tumor	85 (100)	57.2	6 pneumothorax 4 pneumothorax 8 SE	8 No recurrence

¹The 100% is *en-bloc* resection rates, no information on complete resection rate was given in this study. GIST: Gastrointestinal stromal tumors; SE: Subcutaneous emphysem.

Another key problem with the EFTR procedure is the potential risk of abdominal cavity infection, although the current literature reports no significant instances of peritonitis and abdominal cavity infection with EFTR. During the EFTR procedure, the abdominal cavity will be at risk of contamination by the gastric fluid, nonsterile endoscopes, and endoscopic accessories. Similarly, abdominal cavity infection is a serious problem, which is currently the subject of heated arguments in the field of natural orifice transluminal endoscopic surgery (NOTES). However, compared with NOTES, EFTR offers a shorter operation time and a lesser risk of contact with the adjacent tissue/organs. Thus, sterile endoscope/accessories and antiseptic gastric lavage are not likely required^[29]. However, optimized bowel preparation, intravenous infusion of antibiotics, and gastrointestinal decompression are warranted. In addition, it is also very important to prevent the gastric juice from flowing into the abdominal cavity to minimize the risk of contamination. Thus, before gastric wall puncture, the operative field should be separated from the gastric fluid by changing the position to obtain a satisfactory view of the tumor and then suctioning the gastric fluid completely^[23].

SUBMUCOSAL TUNNELING ENDOSCOPIC RESECTION

With the introduction of EME and EFTR, endoscopic resection techniques have evolved continuously. Recently, the emergence of NOTES marked the rise of a new branch of therapeutic endoscopy. Inspired by

NOTES and peroral endoscopic myotomy, in 2012, Xu *et al*^[30] reported a new technique, named submucosal tunneling endoscopic resection (STER), which can be implemented for upper gastrointestinal SETs originating from the MP layer. Since its introduction, there have been an increasing number of reports on the use of STER for upper gastrointestinal SETs originating from the MP layer^[31-36] (Table 3).

The STER procedure is performed as follows (Figure 3)^[31]: (1) to avoid losing the target while creating a submucosal tunnel, the space between the lesion and the mucosal incision is also located by methylene blue or indigo carmine injection, which provides guidance in creating a submucosal tunnel; (2) a 2 cm longitudinal mucosal incision is made 5 cm proximal to the tumor as the entry point with a needle-knife. Then, a submucosal tunnel to the SET is established using an electric knife between the submucosal and muscular layers. The tunnel ends 1-2 cm distal to the tumor to ensure enough working space for tumor resection. Subsequently, endoscopic resection of the tumor is then performed by ESD using the electric knife. During the tumor resection, repeated injections of saline solution help to differentiate the MP layer from the tumor mass and to avoid tumor capsule rupture during the excavation of the tumor from the MP layer; and (3) the mucosal incision site is then closed with several clips after tumor removal.

In contrast with EME or EFTR, STER has advantages in terms of preserving the integrity of the digestive tract mucosa and submucosa, while also promoting early wound healing. Moreover, a 5-cm-long submucosal tunnel has a good "leak-proofing" effect. If digestive tract leakage occurs during the procedure,

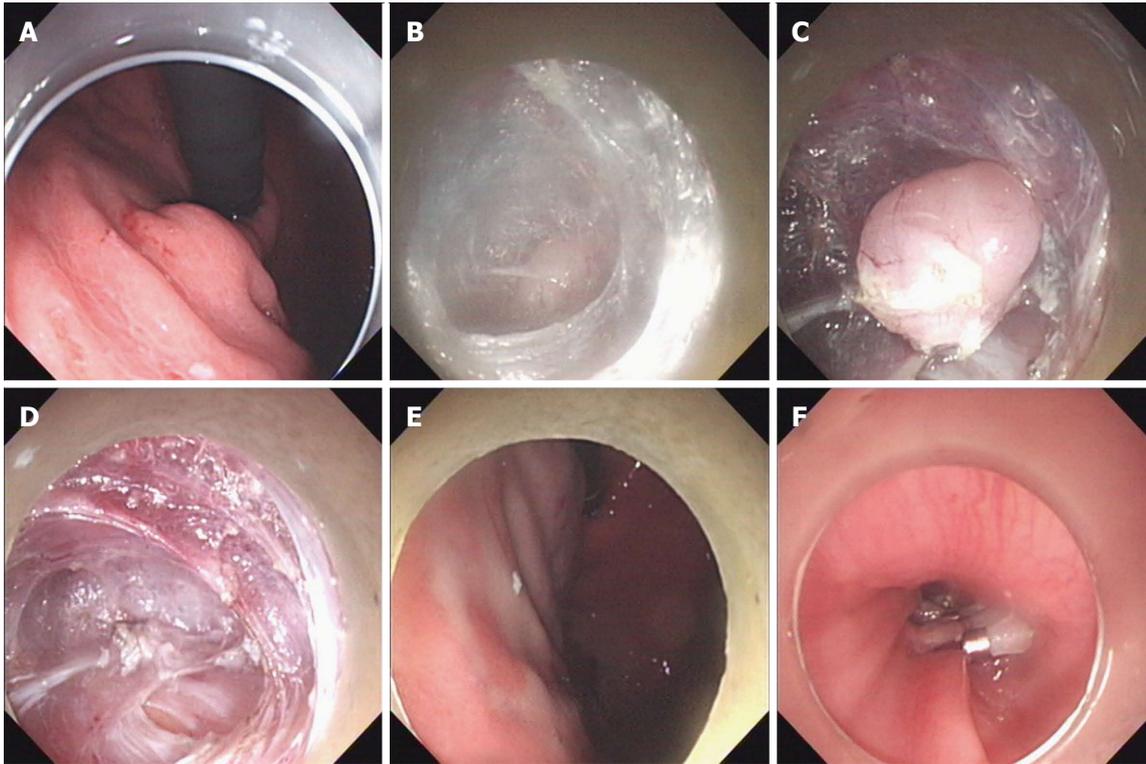


Figure 3 Submucosal tunneling endoscopic resection. A: A subepithelial tumor was found in the gastric fundus; B, C: Creating a submucosal tunnel to the tumor and then excavating the tumor from the muscularis propria layer *via* the submucosal tunnel; D: The omentum could be seen through a small gastric wall after tumor removal; E: The gastric mucosa was intact; F: The entrance of the submucosal tunnel was closed with several clips after tumor removal.

it reduces the risk of postoperative digestive tract fistula and pleural/abdominal infection^[34]. Compared with EME and EFTR, STER seems to be a safer and more effective treatment for gastric SETs originating from the MP layer. However, some complications are frequently observed. The main complications of STER are subcutaneous emphysema, pneumoperitoneum, pneumothorax, and pleural effusion^[30-36]. Previous studies using STER have reported an incidence of complications ranging from 0%-20%^[30-36]. However, these patients usually recover without any need for further endoscopic or surgical intervention. In addition, insufflation with CO₂ can significantly reduce the occurrence of post-procedural mediastinal emphysema^[36].

There are still several technical challenges with the use of STER to treat gastric SETs originating from the MP layer^[32]. First, one important challenge of this technique is the establishment of a submucosal tunnel to the lesion. General stomach features, such as a great space, extensibility, and mucosa hypertrophy, increase the difficulty in establishing a submucosal tunnel (as compared to the esophagus). Moreover, specific locations within the stomach present with varying levels of difficulty for establishing a submucosal tunnel. Compared with other parts of the stomach, in our experience, it is relatively simple to establish a submucosal tunnel in the cardia adjacent to the gastric fundus, the greater curvature of gastric antrum, and

the lesser curvature of gastric body. Second, the tunnel directions can be more difficult to identify in the stomach, which increases the difficulty of establishing a submucosal tunnel to the tumor. The route between the tumor and the mucosal incision is first oriented by injection of indigo carmine or methylene blue before establishing a submucosal tunnel, which plays a guidance role for the operator. Third, keeping the tunnel mucosa intact is more difficult in the stomach than in the esophagus. "Leak-proofing" can only work effectively when the tunnel mucosa maintains its integrity. Fourth, in some cases the lesion is more tightly connected to the underlying MP or serosal layer. It is then necessary to resect the lesion including the underlying muscularis propria and serosa. In this situation, care needs to be taken to avoid injury to the adjacent organs. However, STER is still a generally safe and effective technique for SETs that originate from the MP layer, so long as strict criteria for case selection and admittance of surgical operations are adopted.

INDICATIONS OF ENDOSCOPIC PROCEDURE

The optimal indication for endoscopic resection in gastric SETs should be less than 3.5 cm in diameter of tumor size. The reasons for this indication are as follows. First, when a tumor is > 3.5 cm in diameter, it is difficult to remove *via* an endoscopic approach

after *en bloc* resection because of the limitations of the cardia and esophageal cavity space. Second, for the STER procedure, it is also difficult to excavate a large tumor during the narrow submucosal tunnel, which is often associated with an obscured endoscopic view and a high risk of tunnel mucosa perforation. Third, for the EFTR procedure, resecting a large tumor will create a large gastric wall defect, which is extremely difficult to close by clips and associated with a potential risk of postoperative gastric leaks. Thus, at present, very few cases of SETs > 3.5 cm were reported in published literature and some of them resulted in partial or piecemeal resection^[10,20]. However, partial or piecemeal resections, not an *en-bloc* resection, make the histologic evaluation very difficult. In addition, tumor capsule rupture might cause tumor recurrence or metastasis. Therefore, only tumors less than 3.5 cm in diameter should be removed *via* endoscopic procedures. This is a relatively strict rule for endoscopic management. Note that tumors with high-risk EUS features, such as irregular borders, cystic spaces, ulcerations, echogenic foci, or heterogeneity, are not suitable for those endoscopic treatments.

There is no standard for the selection of endoscopic operation methods for small gastric SETs that originate from the MP layer. Endoscopist experience and tumor characteristics, such as the size, depth, location, and extraluminal or endoluminal growth of the tumor, are the main factors in deciding which surgical method to employ. Generally, for gastric SETs with endoluminal growth, ESE is a favorable choice, whereas for extraluminal growth, EFTR is another favorable choice. In areas suitable for establishing a submucosal tunnel, such as in the greater curvature of the gastric antrum, the lesser curvature of gastric body, or the cardia adjoining to the gastric fundus, STER is also a favorable choice, but should be performed only by an experienced endoscopist.

CONCLUSION

Although there are some complications or adverse events associated with endoscopic operation, such as perforation, massive bleeding, and subcutaneous emphysema, endoscopic operation provides a new option for the management of gastric SETs that originate from the MP layer, which is superior to surgical operation in terms of keeping the normal structure and function of the stomach and improving the long-term quality of life. However, to successfully achieve complete resection and reduce the potential risk of complications, endoscopists need to skillfully master technical details of every endoscopic procedure and choose wisely according to the tumor characteristics, such as the size, depth, location, and extraluminal or endoluminal growth of the tumor. In addition, careful postoperative management and close follow-up, especially for some patients with complications or adverse events, are also vital to

optimize treatment outcomes.

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