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MINIREVIEWS

Management of gastric subepithelial tumors: The role of endoscopy

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Abstract

With the wide use of esophagogastroduodenoscopy, the incidence of gastric subepithelial tumor (SET) diagnosis has increased. While the management of large or symptomatic gastric SETs is obvious, treatment of small (≤ 3 cm) asymptomatic gastric SETs remains inconclusive. Moreover, the presence of gastrointestinal stromal tumors with malignant potential is of concern, and endoscopic treatment of gastric SETs remains a subject of debate. Recently, numerous studies have demonstrated the feasibility of endoscopic treatment of gastric SETs, and have proposed various endoscopic procedures including endoscopic submucosal dissection, endoscopic muscularis dissection, endoscopic enucleation, endoscopic submucosal tunnel dissection, endoscopic full-thickness resection, and a hybrid approach (the combination of endoscopy and laparoscopy). In this review article, we discuss current endoscopic treatments for gastric SETs as well as the advantages and limitations of this type of therapy. Finally, we predict the availability of newly developed endoscopic treatments for gastric SETs.

Key words: Subepithelial tumor; Endoscopy; Stomach; Treatment; Complication

Core tip: Recently, technical advances in endoscopic treatment, including diverse endoscopic procedures, have been performed for the resection of gastric subepithelial tumors (SETs). However, the presence of gastrointestinal stromal tumors with malignant potential is of concern and endoscopic treatment of gastric SETs remains of subject of debate. In this review article, we discuss current endoscopic treatments for gastric SETs as well as the advantages and limitations of this type of therapy. The information presented in this review should be taken into consideration when making decisions concerning endoscopic treatment for gastric SETs.

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INTRODUCTION

The majority of subepithelial tumors (SETs) are considered to be benign in origin; however, some lesions may be malignant, especially if they originate in the muscularis propria (MP) layer[1]. Gastrointestinal stromal tumors (GIST), the most common mesenchymal neoplasms originating in the MP layer of the stomach, are malignant in 10%-30% of cases[2]. According to the National Comprehensive Cancer Network guidelines, all GISTs larger than 2 cm should be resected. For GISTs smaller than 2 cm without high-risk features on endoscopic ultrasonography (EUS), endoscopic follow-up may be recommended[3]. However, endoscopic surveillance has limitations, including delayed diagnosis of malignancy, high cost, hazards associated with repeated endoscopic procedures, patient discomfort related with long-term follow up examinations, and concerns associated with missing the optimum treatment window. Therefore, even for small sized gastric SETs originating in the MP layer, histological confirmation should be obtained if the tumor was not definitely differentiated as benign.

In the past, the standard treatment for gastric SETs was surgical resection, including laparotomy or laparoscopic partial gastrectomy[4], and endoscopy was used for diagnostic purposes, and was rarely used for treatment. However, surgical resection is invasive and associated with possible surgical complications. Recently, numerous reports have proposed that endoscopic resection can be applied to gastric SETs, including GIST[2,5-11]. The purpose of this article was to examine all practical endoscopic methods that should be taken into consideration when deciding whether to perform endoscopic treatment for gastric SETs. Through this process, we provide orientation for endoscopic treatment of gastric SETs.

WHY IS GASTRIC SET DIFFICULT TO TREAT WITH ENDOSCOPY?

Gastric SETs should be treated using endoscopic procedures; however, they remain challenging to treat. Several factors underlie the difficulties associated with endoscopic treatment. First, determining the possibility of malignancy for gastric SETs is difficult before resection. EUS and computed tomography (CT) can aid in but are by no means satisfactory for accurate diagnosis[5,12,13], and are limited in their ability to evaluate tumor size, fibrosis, and MP layer invasion. Thus, establishing a treatment strategy with endoscopy may be difficult. Endoscopic treatments alone do not guarantee complete resection and prevention of cancer recurrence for gastric SETs. Secondly, when endoscopic resection was performed in patients with gastric SETs originating from the MP layer, the complication rate was relatively high, especially for perforation[2,6]. Furthermore, endoscopic resection removes only the tumor without excision of the surrounding normal tissue; therefore, the tumor is likely to be incompletely resected[14-16]. Third, it is difficult to eliminate large or predominantly extraluminal growth of SETs by endoscopy alone[17]. Even the endoscopic full-thickness resection (EFTR) technique that enables treatment of relatively large gastric SETs cannot be used to treat tumors larger than 4 cm with an extraluminal pattern[18,19]. Lastly, the effectiveness of endoscopic treatment is highly affected by the location of the gastric SET. For instance, endoscope retroflexion should be maintained for gastric SETs located on the fundus or cardiac region, which has been shown to be difficult and to have a high perforation risk[20].

CONVENTIONAL AND MODIFIED ENDOSCOPIC SUBMUCOSAL DISSECTION FOR TREATMENT OF GASTRIC SETS

Endoscopic submucosal dissection (ESD) is an effective and safe tissue resection method for the treatment of early gastric cancer (EGC)[7,21]. Although the focus of this technique has been the treatment of EGC, its use has recently been expanded for the treatment of gastric SETs[7,15]. According to a recent study concerning endoscopic resection of SETs using ESD, the overall rate of R0 resection was 81.1% (30/37) and no recurrence was observed in patients with R0 resections during the follow up period[7]. In lesions that were incompletely resected, the tissue acquired was sufficient for all immunohistochemistry studies and, as a result, ESD can aid in confirming SET diagnosis. In a large study published in China, ESD was an effective and feasible treatment option for gastric SETs with diameters no greater than 50 mm originating in the MP layer[6]. The *en bloc* complete resection rate was 92.4% (134/145) and no recurrence was detected during the follow-up period. In our previous study[2], we discovered that tumors $\leqslant$ 2 cm in size or with a positive rolling sign, which indicates that the SET originated from the submucosal layer or has a narrow connection to the MP layer, had high complete resection rates. Moreover, we found that fixed tumor mobility and neurogenic tumors were significantly associated with perforation[2]. We anticipated that lower tumor mobility was associated with broad muscular connections or intramural-type or subserosal-type tumors, for which it is difficult to dissect the SET from adjacent muscle tissue. To treat gastric SETs, conventional ESD is feasible. However, complete resection rates were inconsistent for the MP layer (68.2%-92.4%), and perforation risk was high[2,6,7]. Specifically, endoscopic resection without perforation is challenging in the gastric fundus compared with other locations in the stomach. In a prospective study, conventional ESD using the "Resolution clip" was a feasible and easy method to prevent perforation of gastric fundus SETs[20]. However, this study

Table 1 Publications reporting conventional and modified endoscopic submucosal dissection for upper gastrointestinal subepithelial tumors originating in the muscularis propria

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Lee *et al*[15] (2006)	11	Cardia/body	20.7	60.9	ESD	75.0	0	10.9/N
Jeong *et al*[14] (2011)	64	Cardia/fundus/body/antrum	13.8	34.7	Endoscopic enucleation	92.3	12.3	10.0[1]/N
Liu *et al*[22] (2012)	31	Esophagus/cardia/stomach	22.1	76.8	EMD	96.8	12.9	17.7/N
He *et al*[6] (2013)	144	Cardia/fundus/body/antrum	15.1	63.4	ESD	92.4	14.5[2]/4.8[3]	19.1/N
Chu *et al*[8] (2012)	16	Cardia/fundus/body/antrum	26.1	52.0	Modified ESD with enucleation	93.8	0	14.8/N
Li *et al*[20] (2013)	11	Fundus	18.8	81.0	ESD	90.9	27.2	6.4/N
Chun *et al*[2] (2013)	35	Cardia/fundus/body/antrum	18.0	32.3	ESD	74.3	5.7	6.1/N

[1]Median follow-up period; [2]Perforation; [3]Bleeding. ESD: Endoscopic submucosal dissection; N: None; EMD: Endoscopic muscularis dissection.

in a relatively small number of patients showed a high perforation rate of 30%[20]. Therefore, conventional ESD is limited for removing SETs originating from the MP layer; modified ESD was introduced to solve these problems.

Various modified ESD techniques exist, consisting of a combination of ESD and endoscopic muscularis dissection (EMD). Depending on the degree of connection between the tumor and the muscularis layer, the application ratio of ESD and EMD can be determined. According to Liu *et al*[22], EMD was effective for treatment of gastric SETs originating in the MP layer. In their study, a longitudinal incision was made to cut the overlying mucosa, and electrical or blunt dissection was then used to dissect the SET from the submucosa and MP layers. Finally, the wound was closed with endoscopic clips[22]. Using this method, the complete resection rate was as high as 96.8%, but perforation was also high, at 12.9%. Many trials of SET endoscopic resection using conventional and modified ESD exist (Table 1). In a study published in South Korea, in which the mucosa covering the SETs was eliminated using a coagulation snare to reveal the hidden tumors, the successful complete resection rate by endoscopic enucleation was 92.3% (60/65)[14]; however, the perforation rate was comparatively high (12.3%). The most common location of perforation was the fundus, as it has a thin wall and is difficult to approach endoscopically. Moreover, all perforations occurred in schwannomas and GISTs; these tumors do not have intact tumor capsules and have tight adhesions[14]. Another study demonstrated the feasibility of modified ESD with enucleation for treatment of gastric SETs[8]. Two incisions were performed (longitudinal and transverse), which resulted in more obvious exposure of the tumor and its underlying MP layer, and an easier resection[8]. All tumors were larger than 2 cm, and the complete resection rate was 93.8% (15/16) with no perforation or overt bleeding[8]. This method demonstrates the beneficial results of endoscopic resection compared with surgical resection. Open or laparoscopic surgery can lead to late stenosis and gastroesophageal reflux after surgery, resulting in decreased patient satisfaction. Despite the advantages of endoscopic enucleation, several limitations, including the difficulty of complete removal of tissue with a large enough margin around the tumor[14], are associated with this method. Therefore, if the histologic diagnosis of a SET is highly malignant, clinicians should consider additional treatment. Moreover, in many studies, the follow-up period was short and research was performed at a single center.

ENDOSCOPIC SUBMUCOSAL TUNNEL DISSECTION FOR GASTRIC SETS

Inoue *et al*[23] (2010) investigated peroral endoscopic myotomy (POEM) for endoscopic treatment of achalasia. This method involves creating a submucosal tunnel to create space for endoscopic treatment under the mucosal layer, and can also be used to remove muscle layer lesions. The POEM procedure was applied to SETs originating in the MP layer, and was named endoscopic submucosal tunnel dissection (ESTD), which was introduced in 2012[10,24]. A mucosal incision was made proximal to the lesion, and a submucosal tunnel was created to resect the tumor completely using an electrosurgical knife. After removing the tumor, the mucosal layer was sutured using endoscopic clips. Compared with ESD, this method has several benefits, including fast wound healing and maintaining an intact mucosal layer, thus preventing leakage of bowel contents[10,25]. A Japanese study with a small sample size demonstrated that ESTD resulted in safe resection of SETs without complications[10]. Since then, other studies have shown the efficacy of ESTD for removal of SETs in the esophagus and the cardia, with compete resection rates of 100% (Table 2)[26,27]. According to Liu *et al*[26], esophageal and cardiac SETs originating

Table 2 Publications reporting endoscopic submucosal tunnel dissection for upper gastrointestinal subepithelial tumors originating in the muscularis propria

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Inoue *et al*[10] (2012)	7	Esophagus/cardia	19.0	152	Submucosal endoscopic tumor resection	100	0	5.5/N
Gong *et al*[24] (2012)	12	Esophagus/cardia	19.5	48.3	ESTD	83.3	16.7	NA
Liu *et al*[26] (2013)	12	Esophagus/cardia	18.5	78.3	tEMD	100	66.7	7.1/N
Ye *et al*[25] (2014)	85	Esophagus/cardia/stomach	19.2	57.2	STER	100	9.4	8[1]/N
Zhou *et al*[27] (2015)	21	Esophagogastric junction	23.0	62.9	STER	100	42.9	6[1]/N

[1]Median follow-up period. ESTD: Endoscopic submucosal tunnel dissection; N: None; NA: Not available; tEMD: Tunneling endoscopic muscularis dissection; STER: Submucosal tunneling and endoscopic resection.

in the MP layer were more easily dissected using ESTD than with EMD. Treatment of SET at the esophagogastric junction is difficult due to the interference of esophageal peristalsis and respiration with a detailed endoscopic view and control. ESTD allows for the endoscope to enter into the submucosal tunnel, improving visibility and enabling direct cutting. Moreover, SETs originating from the MP layer can be removed without damage to the mucosa around the lesion, diminishing procedure-related strictures and scars[27]. In another prospective study, ESTD was successful for the treatment of SETs located in the upper gastrointestinal tract, and revealed GIST and lesions in deeper MP layers as risk factors for complications[25]. The ESTD method is relatively safe and results in a high rate of complete resection; however, it is not without limitations. In the majority of studies, ESTD was performed for SETs of the esophagogastric junction, while few studies have been performed to determine the effect of ESTD on SETs of the stomach. Because the stomach mucosa is thick and has greater curvature, submucosal tunneling can be challenging in regions including the gastric fundus and the proximal corpus. Therefore, it is difficult to perform consistent tunneling of the stomach. In addition, large SETs (> 3 cm) are difficult to remove with ESTD because confines of tunneling space may give rise to poor endoscopic visualization and insufficient *en bloc* resection[10,25].

EFTR FOR GASTRIC SETS

Many gastric SETs originate in the deep MP layer. EFTR allows for *en bloc* resection of such SETs, including those tightly connected to the MP layer (Table 3)[18,19,28], which was first reported in 2001 in Japan[29]. In the past, EFTR was only applied to small lesions. The usefulness of EFTR with laparoscopy was reported in animals in a 2006 study; however, it also demonstrated the risk for perforation-induced intraperitoneal infections[30]. In 2011, Zhou *et al*[28] showed the feasibility of EFTR without laparoscopy for gastric SETs originating in the MP layer. This strategy was effective in treating deep gastric SETs with a complete resection rate of 100% (26/26) and no severe complications. These results were mirrored in another study published in China, in which EFTR resulted in successful complete resection (98.0%) without severe complications[18]. However, this study used clip closures and endoloop ligatures as additional closure devices[18], which may have strengthened the suturing technique to avoid gastric perforation. Moreover, endoloop ligatures are simple and do not require specific equipment. Recently, a new technique was introduced using endoscopic suturing devices in EFTR[11]; full-thickness sutures were deployed underneath the subepithelial mass and the SET was removed using an endoscopic electrocautery snare. This technique, explained by Schmidt *et al*[11] as "suture first, cut later", has several advantages including the fact that it is applicable to large tumors (up to 4 cm), it can be applied to tumors at all stomach sites, and it does not require laparoscopic assistance.

While EFTR is effective in treating gastric SETs originating in the MP layer, EFTR without laparoscopy has several limitations, as it is not suitable for the removal of very large tumors, it requires advanced endoscopic skills, and it has a high risk for perforation or peritonitis. Two reports published in Japan investigated the efficacy and feasibility of laparoscopic and endoscopic cooperative surgery (LECS) (Table 3)[31,32]. In this procedure, three-quarters of the tumor submucosal layer was dissected circumferentially using the ESD technique. Then, laparoscopic seromuscular dissection was performed at the three-quarter cut line around the tumor. Finally, the tumor was raised using laparoscopic forceps, and the resection was performed using laparoscopic stapling devices. This method is applicable to gastric SETs irrespective of tumor dimension and site. Additionally, this procedure only requires a minimal area of the stomach to be resected[31,32]. To avoid excessive normal gastric tissue removal, Abe *et al*[33] studied laparoscopy-assisted

Table 3 Publications reporting endoscopic full-thickness resection with or without laparoscopy for gastric subepithelial tumors

Ref.	No. of patients	Location	Mean tumor diameter (mm)	Mean procedure time (min)	Resection method	Complete resection rate (%)	Total complication rate (%)	Mean follow-up period (mo)/recurrence in complete resection patients
Hiki *et al*[31] (2008)	7	Esophagogastric junction/stomach	46	169	LECS	100	0	NA
Abe *et al*[33] (2009)	4	Body	30	201	LAEFR	100	0	8/N
Tsujimoto *et al*[32] (2012)	20	Esophagogastric junction/body/antrum	37.9	157.5	LECS	100	0	20.7/N
Ye *et al*[18] (2014)	51	Fundus/body/antrum	24	52	EFTR	98	0	22.4[1]/N
Mitsui *et al*[36] (2014)	6	Body	22.7	273.5	NEWS	100	0	8/N
Schmidt *et al*[11] (2015)	31	Carida/fundus/body/antrum	20.5	60	EFTR	90.3	9.6[2]/38.7[3]	7 (roughly)/N

[1]Median follow up period; [2]Perforation; [3]Bleeding. LECS: Laparoscopic and endoscopic cooperative surgery; NA: Not available; LAEFR: Laparoscopy-assisted endoscopic full-thickness resection; N: None; EFTR: Endoscopic full-thickness resection; NEWS: Non-exposed endoscopic wall-inversion surgery.

endoscopic full-thickness resection (LAEFR) (Table 3); this technique is a hybrid of natural orifice transluminal surgery. Using the ESD technique, the tissue surrounding the gastric SET was circumferentially incised and the submucosal layer was dissected, and EFTR including the serosal layer was then performed surrounding approximately two-thirds to three-fourths of the tissue surrounding the SET. A laparoscopic full-thickness incision was made to resect and remove the remaining tumor in the peritoneal cavity. Finally, the stomach wall was sutured using laparoscopic hand-sewn closures without linear staples[33]. Advantages of LAEFR include ease and accuracy, a small resection margin, and it is inexpensive compared to other laparoscopic procedures[33]. In addition, an important advantage of LECS and LAEFR is that these methods are appropriate for the treatment of intraluminal gastric SETs in the MP layer. Another recent study showed that indications for endoscopic assistance during laparoscopic resection included growing type (intraluminal) tumors and a tumor size $\leqslant$ 18 mm[34]. It is difficult to determine the correct location and proper resection margin of these tumors by laparoscopy, which could result in excessive tissue elimination. Indeed, complications such as stenosis or deformity can occur. LECS or LAEFR could prevent these side effects, as the resection margin is determined through endoscopy[17].

Some researchers have developed new combinations of endoscopic and laparoscopic treatments for full-thickness resection. A combination of laparoscopic and endoscopic approaches to neoplasia using the non-exposure technique (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS) were developed to avoid malignant tumor dissemination during full-thickness resection[35,36]. The CLEAN-NET procedure involves mucosal marks made during endoscopy and four full-layer stay sutures to fix the mucosal layer to the seromuscular layer. Following submucosal injection of solution, the seromuscular layer is dissected using a laparoscopic electrocautery knife. Then, the full-layer specimen is lifted and dissected using a laparoscopic linear stapler. The CLEAN-NET procedure results in no transluminal communication; therefore, it reduces the risk of potential malignant seeding. However, CLEAN-NET has limitations, such as risk of a mucosal tear, and it is difficult to determine the incision line[35,37-39]. The NEWS procedure is performed as follows. A laparoscopic seromuscular dissection is performed after endoscopic submucosal injection. Then, the seromuscular layer is closed with a laparoscopic suture and the dissected portion is inverted to the luminal side. A circumferential mucosal incision and mucosal layer dissection are made using the ESD technique. The NEWS procedure has various benefits. Similar to CLEAN-NET, the NEWS procedure avoids potential cancer seeding into the peritoneal cavity. Also, it ensures an accurate resection line. The disadvantages of the NEWS procedure are that it is time-consuming and tumor size is limited[5,36,38-40]. The CLEAN-NET and NEWS procedure are effective novel hybrid techniques. However, these methods are rarely applied to treat gastric SETs. Therefore, further studies of these methods are needed for application to gastric SET treatment.

CONCLUSION

To expand the role of endoscopy for the treatment of gastric SETs, several problems must be resolved. First, it is important to determine ways in which to reduce complications associated with endoscopic treatment, focusing specifically on perforation. Carbon dioxide insufflation during endoscopic procedures could be considered as it may reduce the risk of emphysema and pneumoperitoneum[9,27]. Several closing devices for the prevention of procedure-induced perforation have been also described[19,20]. Indeed, methods including OTSC and the "Resolution clip" are efficient in reducing perforation. However, these only apply to a few patients with small perforations and specific lesions sites, and

are not suitable for larger SETs. Thus, the development of new methods to address this limitation is warranted. Secondly, the mean follow-up period of the majority of the studies presented in this review was under 2 years. Although complete resection was preceded by endoscopic treatment, gastric SETs with malignant potential have a risk of recurrence. Therefore, further studies with longer-term follow-up periods and appropriate follow-up duration guidelines after endoscopic SET treatment are required. Next, until now, most studies were performed at a single institute, were retrospective in nature, and only included a small number of participants. Due to the characteristic of SETs, recruitment of a large sample size can be difficult and, thus, may introduce statistical errors including selection bias. Therefore, larger prospective multicenter studies or meta-analyses studying the effects of endoscopic treatment in gastric SETs are warranted. Moreover, the limitations involving large gastric SETs or tumors of the esophagogastric junction or posterior wall must be resolved. As ESTD showed promising results for the treatment of gastric SETs located on the esophagogastric junction, appropriate procedures for other difficult locations should be developed. Finally, a hybrid approach combining endoscopy and laparoscopy should be considered. This method has the advantage of preserving the volume and function of the stomach, and may increase a patient's satisfaction with the procedure. In addition, novel hybrid techniques (CLEAN-NET and NEWS) avoid exposing malignant SETs to the peritoneal cavity. In conclusion, technical modifications and improvements are required to define the role of endoscopy for treating gastric SETs.

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