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Endoscopic Treatment of Subepithelial Tumors

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Gastrointestinal subepithelial tumors (SETs) are generally found during endoscopy and their incidence has gradually increased. Although the indications for the endoscopic treatment of patients with SETs remain to be established, the feasibility and safety of endoscopic dissection, including the advantages of this method compared with surgical treatment, have been validated in many studies. The development of endoscopic techniques, such as endoscopic submucosal dissection, endoscopic enucleation, endoscopic excavation, endoscopic submucosal tunnel dissection, submucosal tunnel endoscopic resection, and endoscopic full-thickness resection has enabled the removal of SETs while reducing the occurrence of complications. Here, we discuss the endoscopic treatment of patients with SETs, outcomes for endoscopic treatment, and procedure-related complications. We also consider the advantages and disadvantages of the various endoscopic techniques. **Clin Endosc 2018;51:19-27**

Key Words: Endoscopic resection; Gastrointestinal tract; Subepithelial tumor

INTRODUCTION

Subepithelial tumors (SETs) in the gastrointestinal tract were previously treated exclusively using surgical resection.¹ However, SETs with the ingrowth type are difficult to surgically remove, because it does not allow for the visualization of the gastrointestinal tract lumen. In addition, surgical resection may result in gastrointestinal deformation, impaired function due to excessive tissue removal, and other complications. Following technical advances in endoscopic treatment, the endoscopic dissection of gastrointestinal SETs was proposed.²⁻⁶ Novel endoscopy devices have allowed better dissection control, opening up a new horizon for the endoscopic treatment of patients with gastrointestinal SETs.^{6,7} Conventional and modified endoscopic submucosal dissections (ESDs) are effec-

tive and safe methods that allow tissue resection for the treatment of lesions in the subepithelial layers of the gastrointestinal tissue. Excellent results have also been reported in patients with gastrointestinal SETs, including those originating from the muscularis propria (MP) layer using endoscopic tunneling techniques and endoscopic full-thickness resection (EFTR).⁶⁻⁸ In this brief review, we discuss the current techniques used in the endoscopic treatment of patients with gastrointestinal SETs.

ENDOSCOPIC MUCOSAL RESECTION

The small sized SETs (1 to 2 cm) can be resected with endoscopic mucosal resection (EMR) using snare. This method, like standard snare polypectomy, places the snare under the SET and resects it with electrocautery. Before resection, it is necessary to confirm whether the tumor can move without being fixed. This method is mainly used for resecting tumors originating in the muscularis mucosa or submucosa.⁹⁻¹¹ Endoscopic submucosal resection with a ligating device (ESMR-L) is a method in which tumor is aspirated into the ligation device and band to deploy the lesion. Then, snare resection is performed under the band. Lee et al. showed that ESMR-L was successfully performed in all patients with esophageal SETs

Received: January 2, 2018 **Revised:** January 12, 2018

Accepted: January 15, 2018

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without perforation.¹² However, complete resection of SETs larger than 1 cm in diameter is very difficult, since the diameter of the ligation device is limited to 1 cm. The transparent cap is also a tool that can be used for EMR. ESMR with a transparent cap is performed as follows. The cap is attached to the tip of endoscopy and a snare is positioned within the cap. After endoscopic suction of the lesion into the cap, the lesion is removed using prepositioned snare.¹³ These EMR and modified EMR are relatively easy and safe, however it is difficult to remove larger sized SETs (>2 cm) or those originating from the MP layer.

ENDOSCOPIC SUBMUCOSAL DISSECTION

ESD is well established as an effective treatment for gastric adenoma and early gastric cancer.¹⁴ Recently, the application of ESD for the treatment of SETs has been extended beyond mucosal lesions of the gastrointestinal tract (Table 1, Fig. 1).^{4,6} Lee et al. reported the feasibility of the removal of SETs from the MP layer and a complete success rate of 75% in patients treated with ESD.¹⁵ None of the patients in that study had severe complications including perforation or massive hemorrhage. In another study, researchers demonstrated that ESD was an effective and safe method for removing gastric SETs; the overall rate of R0 resection was 81.1% and none of the patients had disease recurrence.⁴ Notably, the success rate for R0 resection was influenced by the site of tumor origin. In particular, the R0 resection rate was 100% for tumors in the submucosa layer and 68.2% for those in the MP layer. In these cases, endoscopic ultrasonography may contribute to the achievement of complete SET resection.⁴ Chun et al. identified the appropriate indications for ESD for the treatment of patients with gastric SETs originating from the MP layer.² The complete resection rate in their series of patients was 74.3%, and tumor size <20 mm and a positive rolling sign were significantly linked to complete resection. In addition, fixed tumor mobility was significantly associated with perforation, because a tumor with less mobility has a more extensive muscular connection, and is thus difficult to remove from adjoining muscle tissue.² Despite its efficacy and safety, ESD may not be appropriate for SETs originating in the MP layer, as evidenced by the inconsistent complete resection rates and the relatively high (up to 15%) risk for perforation.²⁻⁴ Therefore, other types of endoscopic dissection are needed to treat these tumors.

Modified ESD techniques have recently been introduced, such as endoscopic excavation (Table 1). In this method, the mucosa overlying the lesion is cut, rather than making a circumferential incision. The SET is then dissected from the submucosal

or MP layer before the incision site is closed with endoscopic clips (Fig. 2).^{16,17} With this technique, gastric and esophageal SETs were almost completely (96.8%) removed, but the perforation rate was also high (12.9%).¹⁶ Endoscopic excavation has been widely used in patients with esophageal SETs. It was successfully performed in small esophageal SETs originating from the MP layer (95.6%).¹⁷ Although procedure-related perforation occurred in 8.9% of the patients in that study, recovery was achieved in all of the cases with conservative management. Another study demonstrated the feasibility of endoscopic enucleation in the MP layer of patients with gastric SETs.¹⁸ An insulated-tip knife and snare were used in the elimination of these tumors and the rate of successful resection was high (92.3%), but so was the perforation rate (12.3%). The investigators also analyzed factors that may cause perforation in endoscopic dissection. All of the perforations arose in gastrointestinal stromal tumors (GISTs) and schwannomas, because they are tightly attached to the surrounding tissue and have an incomplete tumor capsule. Another important factor was tumor location. The most common site of perforation was the fundus, and the perforation rate was significantly higher than that of other sites ($p<0.001$). This can be attributed to the thin gastric wall of the fundus and the relatively difficult endoscopic approach, compared with that needed for SETs in other locations. Chu et al. showed that the modified ESD with enucleation was effective in patients with gastric SETs >2 cm in diameter.¹⁹ Moreover, endoscopic dissection was possible even for large SETs, which were otherwise treated surgically. Nonetheless, despite the advantages of ESD and modified ESD methods, the limitations include the relatively high rate of procedure-related complications (particularly, perforation) and the inability to achieve complete resection in some cases. Furthermore, given the short follow-up duration of the above-mentioned studies, SETs suspected of being malignant should continue to be treated surgically rather than via endoscopic dissection.

ENDOSCOPIC SUBMUCOSAL TUNNELING

Peroral endoscopic myotomy (POEM), which was developed by Inoue et al., is currently the standard of care in patients with achalasia.²⁰ The POEM technique creates a submucosal tunnel enabling endoscopic procedures under the mucosal layer as well as the treatment of the MP layer lesions with only a low risk for contamination and leakage after closure. Submucosal tunneling has been applied to the endoscopic dissection of gastrointestinal SETs, a procedure referred to as endoscopic submucosal tunnel dissection (ESTD) or sub-

Table 1. Clinical Outcomes of Endoscopic Submucosal Dissection for Gastrointestinal Subepithelial Tumors

Study	Nation	No. cases (tumors)	Location of lesion	Size of tumor, mm, mean	Procedure time, min, mean	Resection method	Complete resection rate (%)	Adverse events (%)	Pathologic diagnosis	Mean follow up period and recurrence, mo
Lee et al. (2006) ¹⁵	Taiwan	11 (12)	Stomach (cardia/body)	20.7	60.9	ESD	75.0	0	GIST (8) Leiomyoma (4)	10.9 No recurrence
Hoteya et al. (2009) ²¹	Japan	9 (9)	Stomach	38.0	116.1	ESD	100.0	0	Leiomyoma (2) Carcinoid (2) GIST (1) Others (4)	17.3 No recurrence
Jeong et al. (2011) ¹⁸	South Korea	64 (65)	Stomach (cardia/fundus/body/antrum)	13.8	34.7	Endoscopic enucleation	92.3	12.3	Leiomyoma (32) GIST (26) Others (5)	10.0 No recurrence
Liu et al. (2012) ¹⁶	China	31 (31)	Esophagus Stomach	22.1	76.8	Endoscopic excavation	96.8	12.9	GIST (16) Leiomyoma (15)	17.7 No recurrence
Bialek et al. (2012) ⁴	Poland	37 (37)	Stomach	25.0 (median)	N/A	ESD	81.1	5.4	GIST (17) Leiomyoma (10) Ectopic pancreas (3) Others (7)	21 (median) No recurrence
Chu et al. (2012) ¹⁹	Taiwan	16 (16)	Stomach (cardia/fundus/body/antrum)	26.1	52.0	Modified ESD with enucleation	93.8	0	GIST (14) Leiomyoma (2)	14.8 No recurrence
Chun et al. (2013) ²	South Korea	35 (35)	Stomach (cardia/fundus/body/antrum)	18.0	32.3	ESD	74.3	5.7	Leiomyoma (21) GIST (10) Others (4)	6.1 No recurrence
He et al. (2013) ³	China	144 (145)	Stomach (cardia/fundus/body/antrum)	15.1	63.4	ESD	92.4	4.8 ^{c)/} 14.5 ^{b)}	GIST (89) Leiomyoma (52) Others (4)	19.1 No recurrence
Li et al. (2013) ²²	China	11 (11)	Stomach (fundus)	18.8	81.0	ESD	90.9	27.2	GIST (8) Leiomyoma (3)	6.4 No recurrence
Zhang et al. (2013) ²³	China	212 (212)	Stomach (fundus/body/antrum)	16.5	46.1	Endoscopic excavation	96.2	4.2 ^{c)/} 15.1 ^{b)}	Leiomyoma (115) GIST (97)	26.0 No recurrence
Catalano et al. (2013) ²⁴	Italy	20 (20)	Stomach	29.0 (median)	119.1 (median)	ESD	90.0	15.0	GIST (10) Leiomyoma (3) Others (7)	21 (median) N/A ^{d)}
Ye et al. (2015) ¹⁷	China	45 (45)	Esophagus	11.0	N/A	Endoscopic excavation	95.6	8.9	Leiomyoma (38) GIST (5)	N/A

ESD, endoscopic submucosal dissection; GIST, gastrointestinal stromal tumor; N/A, not available.

^{a)}Bleeding; ^{b)}Perforation; ^{c)}Massive bleeding; ^{d)}Five-year disease-specific survival rate was 100% (among the ten GIST patients).

mucosal tunnel endoscopic resection (STER) (Table 2).²⁵⁻²⁷ Benefits include the retention of an intact mucosal layer, fast wound healing, and avoidance of the leakage of bowel material. Inoue et al. performed a submucosal endoscopic tumor resection that included the creation of a submucosal tunnel.²⁵ The key steps of the procedure are: making a mucosal incision proximal to the SET, creating the submucosal tunnel, dissecting the tumor from the overlying mucosal/submucosal and muscular layers under direct endoscopic viewing, and endoscopic hemostasis followed by closure of the mucosal incision using endoscopic clips. In that study, all of the SETs in the esophagus and cardia were resected completely and no complications occurred.²⁵ Gong et al. also showed the feasibility of ESTD in patients with upper gastrointestinal SETs.²⁶ All of the tumors were located in the esophagus and cardia, and 83.3% were removed by *en bloc* resection. In a prospective large study of STER in patients with SETs, the procedure was successful in all cases (100%) and no residual or recurrent tumors were detected.²⁷ The complication rate was 9.4%, and all of the complications were successfully treated using conserva-

tive management. GISTs and tumors originating deeper in the MP layer were risk factors for postoperative complications. Endoscopic dissection is more difficult for SETs located in the esophagogastric junction than in other locations, because the narrow space and esophageal peristalsis interfere with detailed endoscopic control. Nonetheless, a complete resection rate of 100% in patients with SETs at the esophagogastric junction was reported.²⁸ None patients had disease recurrence or procedure-related esophageal stricture during follow-up. Compared with studies on submucosal tunneling techniques in patients with esophageal SETs, the utility of this approach in gastric SETs has been less well examined. In their study, Li et al. examined the clinical effects of STER in patients with gastric SETs,²⁹ and reported a complete resection rate of 100% and all of the adverse events could be managed conservatively. In addition, a recent report evaluated the long-term outcome of STER in patients with upper gastrointestinal SETs.³⁰ The 180 patients who underwent STER were free from disease recurrence during a median follow-up of 36 months. Despite these successes, the limitations of ESTD and STER must be

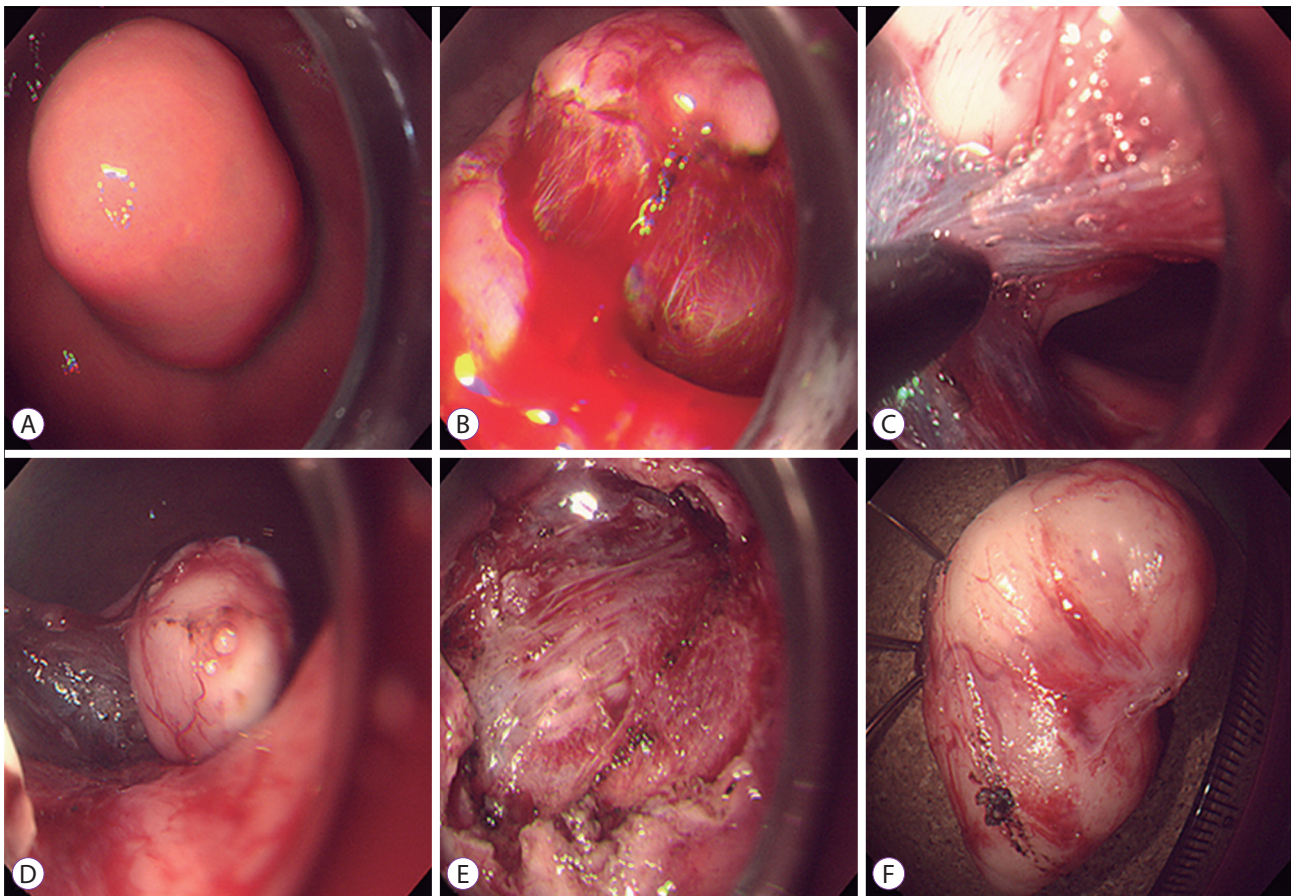


Fig. 1. Endoscopic submucosal dissection of a gastrointestinal stromal tumor. (A) A large subepithelial tumor is observed at the high body of the stomach. (B, C) Circumferential incision and submucosal dissection of the tumor is performed. (D) Most of the subepithelial tumor is exposed to the lumen. (E) A post-endoscopic submucosal dissection ulcer is observed. (F) The resected specimen (tumor size is 2.4 cm).

kept in mind, particularly their difficult use in tumors located in the fundus and proximal corpus, because of the difficulty tunnel creation, the considerably thick gastric mucosa, and the complicated removal of SETs >4 cm in diameter.

ENDOSCOPIC FULL-THICKNESS RESECTION WITHOUT LAPAROSCOPY

EFTR is the preferred treatment option for patients with gastrointestinal SETs originating from the deep MP layer and exhibiting predominantly extraluminal growth (Table 3). Zhou et al. showed that EFTR without laparoscopy was effective for the removal of gastric SETs originating from the MP layer.³¹ The EFTR procedure is as follows: after precutting, a circumferential incision is made in the MP layer around the tumor; an incision is then made in the serosal layer around the tumor; full-thickness resection of the tumor, including the serosal layer, is performed; and the perforated gastric wall is sutured using endoscopy clips. The mean tumor size was 28 mm and

the complete resection rate was 100%. There were no major complications and no recurrences during the mean follow-up. Another study also demonstrated the feasibility of EFTR for gastric SETs arising from the MP layer.³² A complete resection rate of 98% was achieved and none of the patients had severe adverse events. The use of clip closure and Endoloop ligature (additional closure devices) may have contributed to the prevention of gastric perforation. New suturing devices have also been used to correct the perforations that may occur during EFTR. Schmidt et al. recommended the use of these devices to place one to three full-thickness sutures underneath the tumor, after which resection is performed.⁵ Although perforations occurred in 9.6% of the patients treated in this manner, all were managed endoscopically. An advantage of this “suture first, cut later” method is that it can be used to treat relatively large (approximately 4 cm) SETs regardless of their location in the stomach and without the need for laparoscopy.⁵ While EFTR is feasible for lesions of any shape and located on any side of the lumen, it should be noted that EFTR without laparoscopy assistance requires a high-quality endoscopic technique and

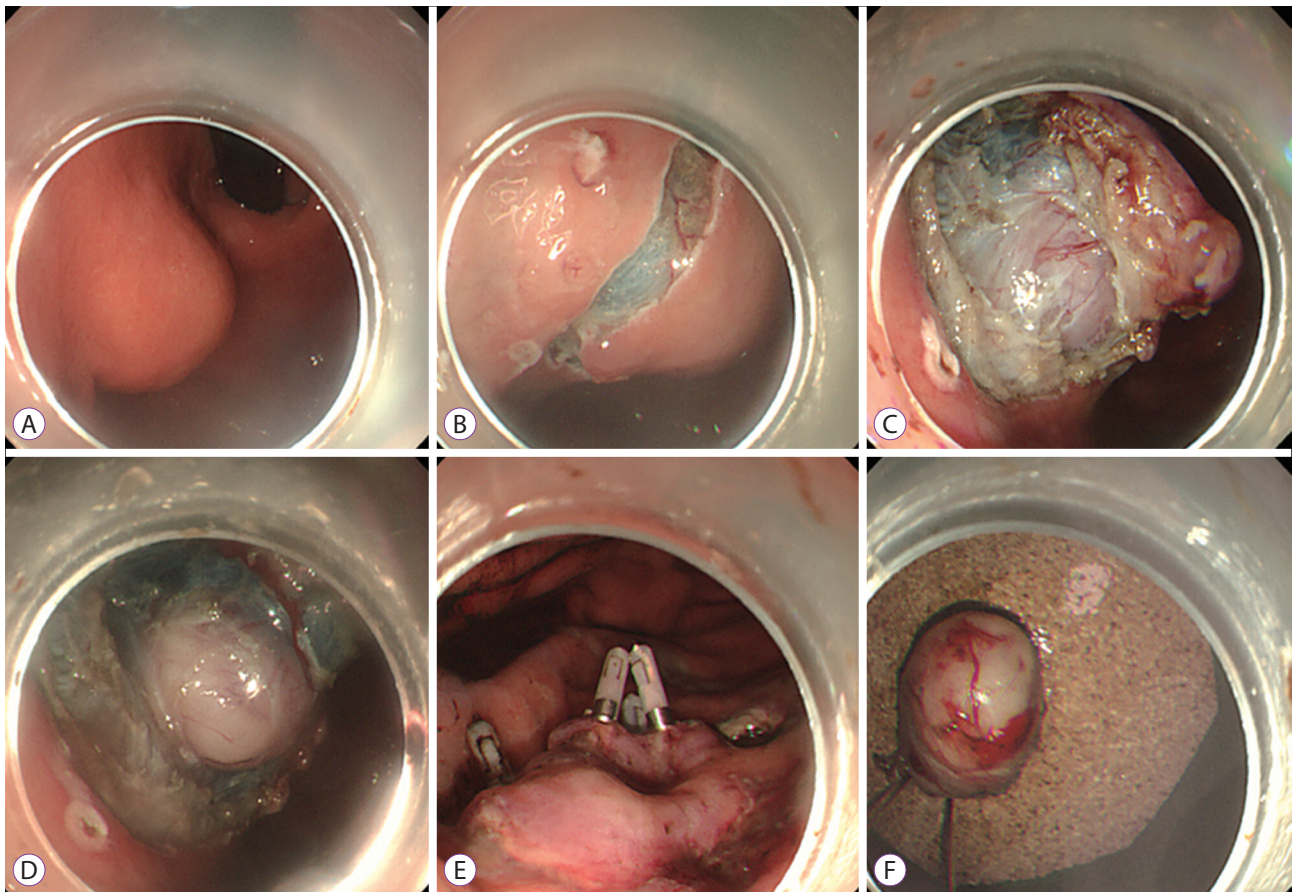


Fig. 2. Endoscopic excavation with clipping of a gastrointestinal stromal tumor. (A) A large and round subepithelial tumor is found at the high body of the stomach. (B-D) After the mucosa overlying the lesion is cut, the subepithelial tumor is excavated from the muscularis propria layer. (E) The wound is closed endoscopic clips. (F) The resected specimen (tumor size is 2.0 cm).

Table 2. Clinical Outcomes of Endoscopic Submucosal Tunneling Technique for Gastrointestinal Subepithelial Tumors

Study	Nation	No. cases (tumors)	Location of lesion	Size of tumor, mm, mean	Procedure time, min, mean	Resection method	Complete resection rate (%)	Adverse events (%)	Pathologic diagnosis	Mean follow up period and recurrence, mo
Inoue et al. (2012) ²⁵	Japan	7 (7)	Esophagus Stomach (cardia)	19.0	152.4	Submucosal endoscopic tumor resection	100.0	0	Leiomyoma (5) GIST (1) Aberrant pancreas (1)	5.5 No recurrence
Gong et al. (2012) ²⁶	China	12 (12)	Esophagus Stomach (cardia)	19.5	48.3	ESTD	83.3	16.7	GIST (7) Leiomyoma (5)	N/A
Xu et al. (2012) ³³	China	15 (15)	Esophagus Stomach (cardia)	19.0	78.7	STER	100.0	13.3	Leiomyoma (9) GIST (5) Glomus tumor (1)	3.9 No recurrence
Liu et al. (2013) ³⁴	China	12 (12)	Esophagus Stomach (cardia)	18.5	78.3	tEMD	100.0	66.7	Leiomyoma (9) GIST (2) Schwannoma (1)	7.1 No recurrence
Ye et al. (2014) ²⁷	China	85 (85)	Esophagus Stomach	19.2	57.2	STER	100.0	9.4	Leiomyoma (65) GIST (19) Calcifying fibrous tumor (1)	8.0 (median) No recurrence
Wang et al. (2014) ³⁵	China	57 (57)	Esophagogastric junction	21.5	47.0	STER	100.0	21.0 ^a /8.8 ^b / 5.2 ^c /3.5 ^b	Leiomyoma (46) GIST (7) Others (4)	12.0 No recurrence
Lu et al. (2014) ³⁶	China	18 (19)	Stomach (fundus)	20.1	75.1	TCTT	100.0	11.1	GIST (13) Leiomyoma (6)	5 (median) No recurrence
Zhou et al. (2015) ²⁸	China	21 (21)	Esophagogastric junction	23.0	62.9	STER	100.0	42.9	Leiomyoma (15) GIST (6)	6 (median) No recurrence
Li et al. (2015) ³⁹	China	32 (32)	Stomach (cardia/ fundus/body/ antrum)	23.0	51.8	STER	100.0	43.8	Leiomyoma (18) GIST (11) Fibrous tumor (11) Others (2)	28.0 No recurrence
Wang et al. (2015) ³⁷	China	80 (83)	Esophagus Stomach (cardia)	23.2	61.2	STER	97.6	8.8	Leiomyoma (68) GIST (15)	10.2 No recurrence
Chen et al. (2017) ³⁰	China	180 (180)	Esophagus Stomach	26.0 (median)	45.0 (median)	STER	90.6	8.3	Leiomyoma (146) GIST (28) Others (6)	36 (median) No recurrence

GIST, gastrointestinal stromal tumor; ESTD, endoscopic submucosal tunnel dissection; N/A, not available; STER, submucosal tunnel endoscopic resection; tEMD, tunneling endoscopic muscularis dissection; TCTT, transcardiac endoscopic tunneling technique.

^aEmpysema, ^bPneumothorax, ^cPneumoperitoneum, ^dPleural effusion.

Table 3. Clinical Outcomes of Endoscopic Full-Thickness Resection without Laparoscopy for Gastrointestinal Subepithelial Tumors

Study	Nation	No. cases (tumors)	Location of lesion	Size of tumor, mm, mean	Procedure time, min, mean	Resection method	Complete resection rate (%)	Adverse events (%)	Pathologic diagnosis	Mean follow up period and recurrence, mo
Zhou et al. (2011) ³¹	China	26 (26)	Stomach (fundus/body)	28.0	105.0	EFTR	100.0	0	GIST (16) Leiomyoma (6) Others (4)	8.0 No recurrence
Ye et al. (2014) ³²	China	51 (51)	Stomach (fundus/body/antrum)	24.0	52.0	EFTR	98.0	0	GIST (30) Leiomyoma (21)	22.4 No recurrence
Schmidt et al. (2015) ⁵	Germany	31 (31)	Stomach (cardia/fundus/body/antrum)	20.5	60.0	EFTR	90.3	9.6 ^{a)/} 38.7 ^{b)}	GIST (18) Ectopic pancreas (3) Leiomyoma (2) Others (8)	7.0 No recurrence
Guo et al. (2015) ³⁸	China	23 (23)	Stomach (fundus/body/antrum)	12.1	40.5	EFTR	100.0	9.0	GIST (19) Leiomyoma (4)	3.0 No recurrence

EFTR, endoscopic full-thickness resection; GIST, gastrointestinal stromal tumor.

^{a)}Perforation; ^{b)}Bleeding.

large SETs cannot be easily removed. In addition, there is a risk for intraperitoneal infection after the procedure if mucosal suturing is inadequate.

ISSUES TO OVERCOME IN THE ENDOSCOPIC DISSECTION OF GASTROINTESTINAL SETS

Several unsolved issues remain regarding the use of different endoscopic dissection techniques to treat gastrointestinal SETs. First, the clear endoscopic treatment indication for gastrointestinal SETs has yet to be determined. A very large tumor with primarily extraluminal growth or widespread involvement of the MP layer may be better treated surgically because the incidence of procedure-related complications following endoscopic dissection is relatively high and the rate of *en bloc* resection is low. Second, there is no optimal tumor-surveillance protocol for patients treated with endoscopic resection. Both considerations carry added weight for SETs with malignant potential. Third, the rate of complications arising from endoscopic procedures is still troublesome, particularly for SETs originating from the MP layer. Finally, the feasibility of endoscopic treatment may differ according to the location of the SET, whereas this is not a concern with surgical treatment. In particular, endoscopic approaches to SETs involving the fundus or cardia are challenging and the risks for procedural adverse events and incomplete resection are therefore relatively high.

CONCLUSIONS

Endoscopic treatment of gastrointestinal SETs is feasible, but before the role of endoscopy can be expanded, several limitations have to be addressed, particularly the currently high rate of complications, specifically perforations. Moreover, if perforation occurs, secondary complications such as emphysema and intraperitoneal infection must be prevented. Carbon dioxide insufflation and recently developed closing devices may contribute to lowering the perforation rate. While numerous studies have evaluated the efficacy of endoscopic dissection for SETs, prospective comparative studies seeking to determine the indication for endoscopic dissection versus surgery are needed, as are long-term follow-up studies to evaluate recurrence after endoscopic dissection of SETs. A hybrid approach combining endoscopy and laparoscopy may turn out to be the best method for SETs that are difficult to treat using endoscopy alone and will increase patients' satisfaction. Finally, the experience and skill of the endoscopist are obvi-

ously important factors in achieving complete resection and minimal complications. In conclusion, endoscopic treatment is a technically feasible procedure for the treatment of patients with gastrointestinal SETs, but technical advances and additional studies are needed to improve the clinical outcome of patients with endoscopically treated SETs.

Conflicts of Interest

The authors have no financial conflicts of interest.

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