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Endoscopic Submucosal Tunnel Dissection for Upper Gastrointestinal Submucosal Tumors Originating from the Muscularis Propria Layer: A Single-Center Study

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Background/Aims: In recent years, endoscopic submucosal tunnel dissection (ESTD) has gained popularity worldwide. The aim of this study was to evaluate the safety and efficacy of ESTD in treating upper gastrointestinal submucosal tumors (SMTs) in a large-volume endoscopic center. **Methods:** Patients with SMTs were enrolled in this study between January 2012 and January 2015. Demographic data, clinical data, and treatment outcome were collected and analyzed. **Results:** Seventy SMTs originating from the muscularis propria (MP) layer were identified in 69 patients. All patients successfully underwent the ESTD procedure. The mean procedure time was 49.0±29.5 minutes, and the mean tumor size was 18.7±7.2 mm. Among all lesions, the majority (70.0%) were located in the esophagus, 12.9% in the cardia, and 17.1% in the stomach. Complete resection was achieved in 67 lesions (95.7%). Perforation occurred in three patients (4.3%), who were treated by endoclips. Pneumothorax occurred in two patients (2.9%) and was successfully managed by thoracic drainage. During a median follow-up of 18.1 months, patients were free of local recurrence or distant metastasis. **Conclusions:** Our results demonstrated the feasibility and safety of ESTD in treating upper gastrointestinal SMTs originating from the MP layer. Large-scale comparative studies with other treatment methods should be conducted in the future. **(Gut Liver 2017;11:620-627)**

Key Words: Endoscopic submucosal tunnel dissection; Submucosal tumor; Upper gastrointestinal; Treatment outcome

INTRODUCTION

Gastrointestinal (GI) submucosal tumors (SMTs) are not rare, and with increasing use of esophagogastroduodenoscopy and improvement of diagnostic modalities, they are estimated to increase. Gastrointestinal stromal tumor (GISTs) are the most common among SMTs of the stomach, which usually considered to the candidate for resection.[1] Nowadays, laparoscopic or open surgery,[2] endoscopic submucosal dissection (ESD),[3,4] and endoscopic full-thickness resection (EFR) with or without laparoscopic assistance,[5,6] were reported to resect SMTs worldwide. However, these above treatments have some limitations. Surgical approaches are more invasive and often require longer hospital stay. ESD and EFR have the complication of perforation, which may be difficult to close and even require surgery.

In 2010, Inoue *et al*.[7] reported peroral endoscopic myotomy (POEM) for treating achalasia, in which a submucosal tunnel is created to provide working space for cutting the circular muscle layer to treat achalasia. Driven by the innovation, we successfully utilized a similar technique, endoscopic submucosal tunnel dissection (ESTD) for the management of esophageal and gastric SMTs.[8] Since then, we continued to use this technique in our clinical practice, and also tried to employ this novel endoscopic method to manage other lesions in the stomach. Therefore, we aimed to examine the safety and efficacy of ESTD in upper GI SMTs in this study.

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MATERIALS AND METHODS

1. Patients

Between January 2012 and January 2015, 69 patients, with upper GI SMTs originating from the muscularis propria (MP) identified by upper endoscopy and endoscopic ultrasonography (EUS) were treated by ESTD at Department of Gastroenterology, Nanfang Hospital, Southern Medical University, China. Indication for ESTD procedure were as follows: (1) the tumor was 1 to 4 cm in diameter; (2) EUS examination showed that the tumor originated from the MP layer; (3) the patient could tolerate anesthesia with tracheal intubation; and (4) the patient consented to ESTD in our center. The data were prospectively collected and retrospectively reviewed. All patients were informed of a detailed explanation of the treatment and complications of the procedure, and the possibility of additional surgery because of complications or pathological diagnosis of resected specimens. Informed patient consent was obtained before the ESTD procedures. This study was approved by the ethics committee of the Nanfang Hospital, Southern Medical University (Guangzhou, China).

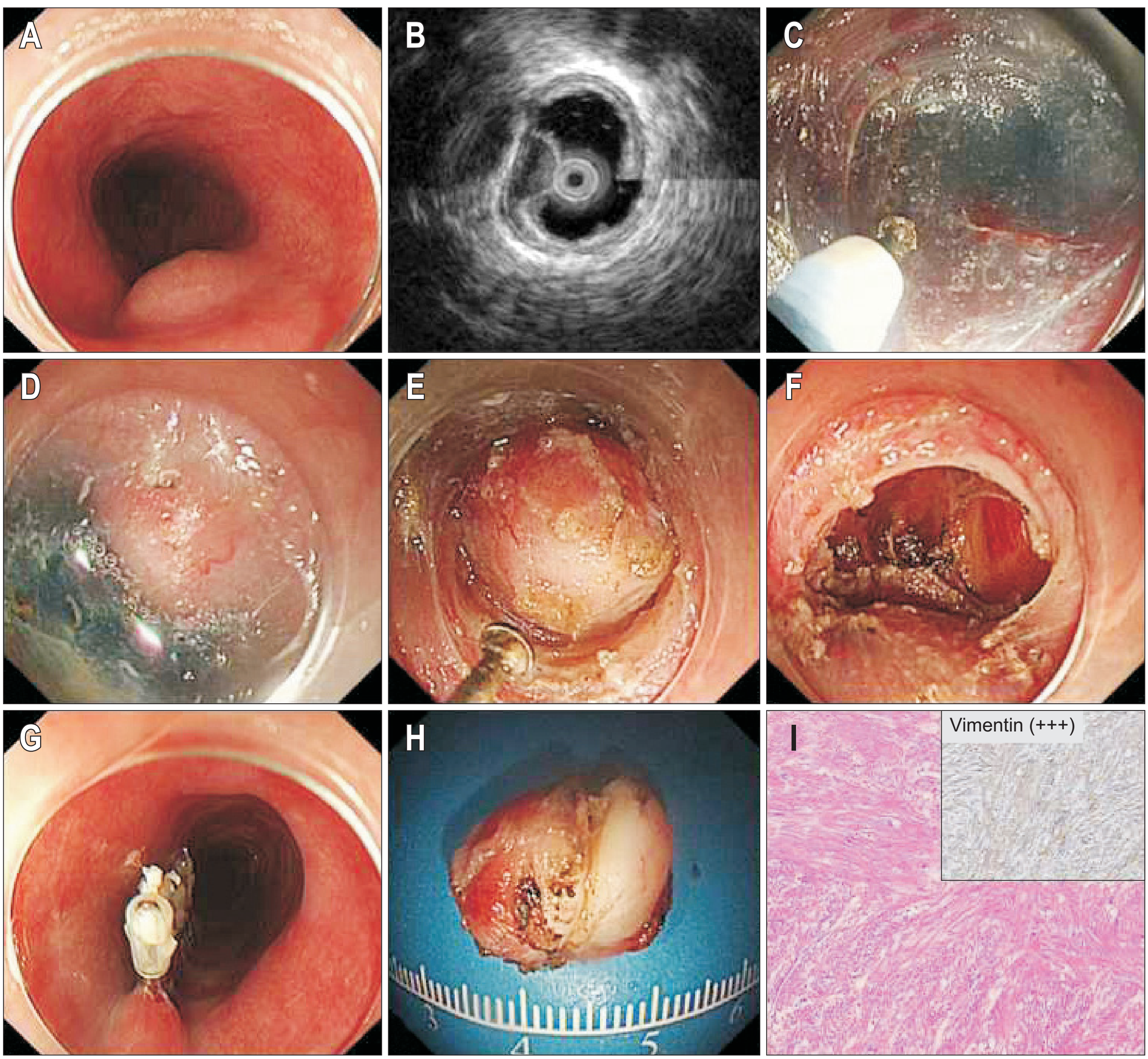

Fig. 1. Case illustration of endoscopic submucosal tunnel dissection for esophageal submucosal tumors (SMTs). (A) SMT located at the posterior wall of the mid-esophagus. (B) Endoscopic ultrasonography revealed an 18.7×11.2 mm hypoechoic submucosal lesion. (C, D) A 2-cm longitudinal mucosal incision was made approximately 4 cm proximal to SMT; submucosal dissection was performed, creating a submucosal tunnel until the tumor was visible. (E) Dissection was performed along the margin of the tumor. (F) Endoscopic view of the submucosal tunnel after removal of the tumor. (G) Endoclips were used to close the entry of the submucosal tunnel. (H, I) Pathological examination revealed that the resected specimen was a 15-mm leiomyoma, and positive staining (H&E stain, ×20) with vimentin was observed on the upper right side.

2. Endoscopic equipment and procedures

A forward-viewing endoscope (GIFQ240Z; Olympus, Tokyo, Japan) was attached with a transparent distal cap (MH-588; Olympus). A hook knife (KD-620L; Olympus) or a hybrid knife (Erbe, Tübingen, Germany) was used to dissect both the submucosal layer and the tumors. A coagulating forceps (Coagrasper, FD-410L; Olympus) was used for hemostasis. A carbon dioxide (CO_2) insufflator (UCR; Olympus) was used during all the procedure. VIO 200 D electrogenerator (Erbe) was used for electrosurgery. Hemostatic clips (EZ-CLIP, HX-110QR, Olympus; or Resolution, M00522610, Boston Scientific, Boston, MA, USA) were applied for closing the tunnel entry. All the ESTD procedures were performed by a single operator (W.G.).

The procedures were performed with the patients under general anesthesia with endotracheal intubation. CO_2 insufflation was used during the procedure. The standard steps of the procedure were described previously (also see Figs 1-3).[8]

1) Creation of the submucosal tunnel

The mixed solution of 10 mL saline with 0.3% indigo carmine and 1:100,000 epinephrine was injected 4 to 5 cm proximal to

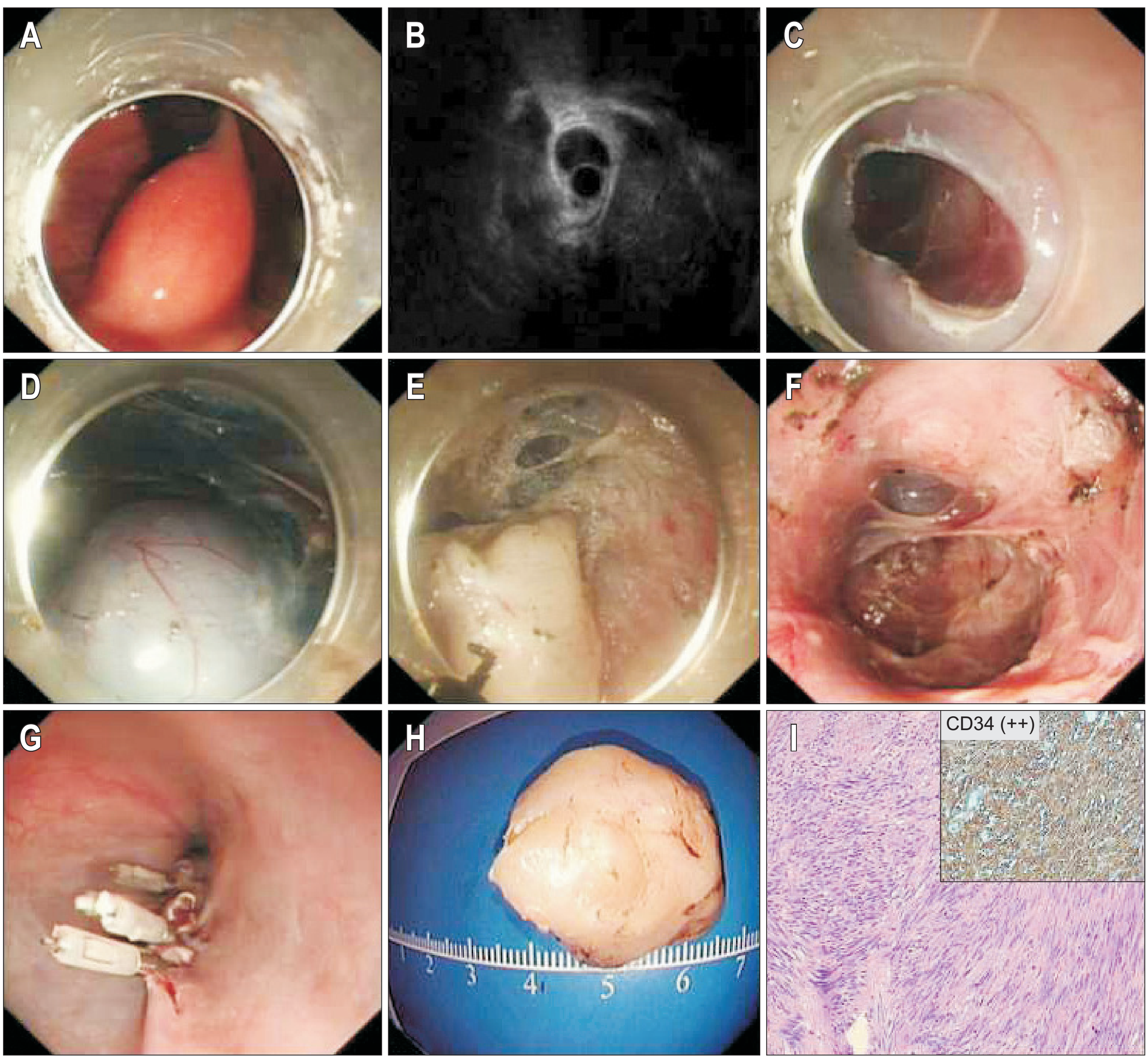

Fig. 2. Case illustration of endoscopic submucosal tunnel dissection for the cardiac submucosal tumor (SMT). (A) SMT located at the cardia. (B) Endoscopic ultrasonography revealed a 21.9×15.9 mm hypoechoic submucosal lesion. (C, D) A 2-cm longitudinal mucosal incision was made in the esophagus approximately 4 cm proximal to the SMT; submucosal dissection was performed, creating a submucosal tunnel until the tumor was visible. (E) Dissection was performed along the margin of the tumor. (F) Endoscopic view of the submucosal tunnel after removal of the tumor. (G) Endoclips were used to close the entry to the submucosal tunnel. (H, I) Pathological examination showed that the resected specimen was a 25-mm gastrointestinal stromal tumor, and positive staining (H&E stain, ×20) with CD34 was observed on the upper right side.

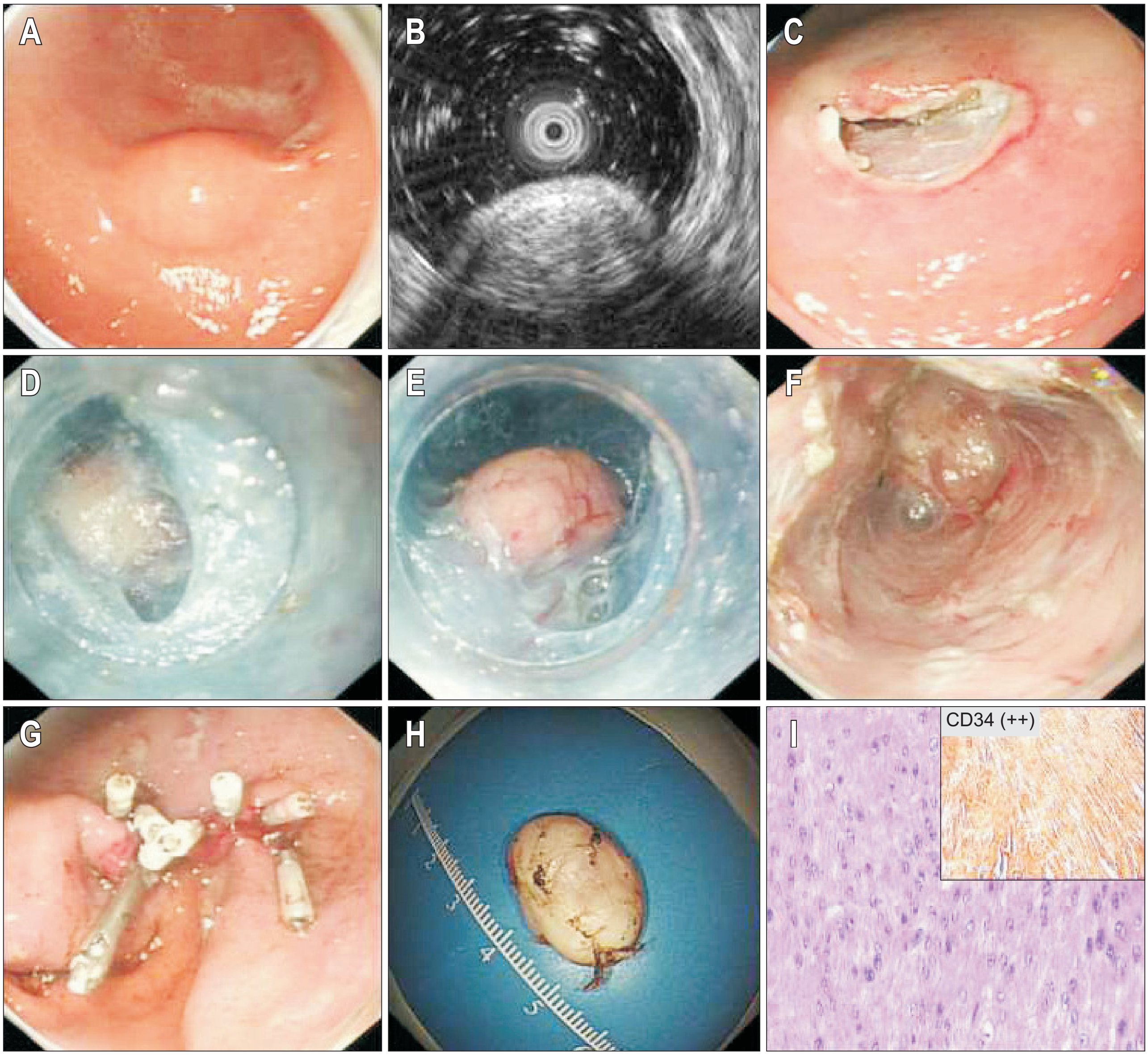

Fig. 3. Case illustration of endoscopic submucosal tunnel dissection for submucosal tumors (SMTs) at the greater curvature side of gastric antrum. (A) SMT located at the greater curvature side of the gastric antrum. (B) Endoscopic ultrasonography revealed a 24.7×9.8 mm hypoechoic submucosal lesion. (C) A 2-cm longitudinal mucosal incision was made approximately 4 cm proximal to SMT. (D) Submucosal dissection was performed, creating a submucosal tunnel until the tumor was visible. (E) Dissection was performed along the margin of the tumor. (F) Endoscopic view of the submucosal tunnel after removal of the tumor. (G) Endoclips were used to close the entry of the submucosal tunnel. (H, I) The resected specimen was a 24-mm gastrointestinal stromal tumor, and positive staining (H&E stain, ×20) with CD34 was observed on the upper right side.

the SMTs, until the mucosa was fully lifted. A 2-cm longitudinal mucosal incision was made on the mucosal layer, creating an entry to the submucosal layer. Then a submucosal tunnel was created downwards with ESD until the tumor was exposed.

2) Dissection of the SMTs

Dissection was performed along the margin of the tumor with a hook knife or a hybrid knife. The tumor was then removed and the visible vessels and bleeding area in the tunnel were carefully coagulated.

3) Closure of mucosal entry

The mucosal entry site, usually 2-cm long, was closed with hemostatic clips. During the procedure, endoscopic hemostasis was performed with the knife itself or with a hemostatic forceps when active bleeding was noticed. After completion of procedure, preventive coagulation was routinely performed for all visible vessels on the submucosal tunnel using hemostatic forceps or argon plasma coagulation.

3. Postprocedure management

Patients were fasted from food and water for 48 hours, being given parenteral nutrition instead. Proton pump inhibitors and antibiotics were routinely used for 3 days. The common complications of ESTD include pneumothorax, perforation and bleeding. Pneumothorax was suspected when decreasing of oxygen saturation occurred, and confirmed by chest X-ray or computed tomogram (CT). Perforation was defined as tunnel mucosa perforation, and recognized endoscopically or by presence of free air on abdominal plain radiograph or CT. Bleeding was defined as an oozing or spurting bleeding observed and requiring the use of coagulating forceps or endoclips.

4. Histopathological evaluation

Resected specimens were retrieved and immediately fixed in a 10% buffered formalin solution. Hematoxylin and eosin staining was followed by immunohistochemical staining (CD34, CD117, actin, S-100, desmin, vimentin, and Ki-67) for differential diagnosis. "*En bloc* resection" was defined as a tumor removed in a single piece. "Complete resection" was defined as a tumor removed as a single piece and the capsule of the tumor was intact.[9]

5. Follow-up

All patients were scheduled to take a follow-up visit at 3, 6 months and 1 year after ESTD for upper endoscopy and EUS. If there is no residual tumor, follow-up is performed annually.

6. Statistical analysis

Data were collected and analyzed by means of descriptive statistics (mean, standard deviation, or median, and range). Frequencies and percentages were calculated for categorical variables. All data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Baseline Characteristics of Patients

Variable	Value
No. of patients	69
Age, yr	48.0±11.2 (19–69)
Sex, female/male	24/45
Presenting symptoms	
Asymptomatic	52 (75.4)
Epigastric discomfort	7 (10.1)
Chest discomfort	5 (7.2)
Dysphagia	3 (4.3)
Regurgitation	2 (2.9)
Tumor location	
Esophagus	49 (70.0)
Cardia	9 (12.9)
Stomach	12 (17.1)

Data are presented as mean±SD (range) or number (%).
The sum total of lesions is 70 since a patient has two lesions.

RESULTS

1. Baseline characteristics of patients

The baseline characteristics of patients were shown in Table 1. Seventy SMTs lesions in 69 patients were removed by ESTD. Mean age of the patients was 48.0±11.2 years (range, 19 to 69 years), and female-to-male ratio was 24:45. Fifty-two patients (75.4%) were asymptomatic and their tumors were discovered incidentally during routine physical examination. The most common presenting symptom that patients reported was epigastric discomfort (n=7, 10.1%). Of all the lesions, 49 (70.0%) were located in the esophagus, nine (12.9%) in the cardia and 12 (17.1%) in the stomach.

Table 2. Clinicopathologic Outcome of Endoscopic Submucosal Tunnel Dissection for Patients with Submucosal Tumors

	Overall
Operation time, min	49.0±29.5 (30–150)
Insufflation	
Air	4 (5.8)
CO_2	65 (94.2)
Tumor size, mm	18.7±7.2 (10–40)
No. of tumors based on size	
≤20 mm	53 (75.7)
>20 mm	17 (24.3)
En bloc resection	67 (95.7)
Complete resection	67 (95.7)
Complication	
Perforation	3 (4.3)
Pneumothorax	2 (2.9)
Subcutaneous emphysema	4 (5.8)
Pneumoperitoneum	1 (1.4)
Delayed bleeding	0
Pathologic diagnosis	
Leiomyoma	59 (84.3)
Esophagus	49/59 (83.1)
Cardia	7/59 (11.9)
Gastric antrum	3/59 (5.0)
Gastrointestinal stromal tumor	11 (15.7)
Cardia	2/11 (18.2)
Gastric fundus	6/11 (54.5)
Gastric antrum	3/11 (27.3)
Hospital stay, day	5.8±1.5 (3–10)
Follow-up time, mo	18.1 (6–35)
Recurrence rate, %	0

Data are presented as mean±SD (range), number (%), or median (range).
The sum total of lesions is 70 since a patient has two lesions.

2. Clinical outcomes of ETSD

ESTD was performed successfully in all cases. No one was converted to laparoscopy or thoracoscopy. All SMTs originated from the MP layer. As shown in Table 2, the average lesion size was 18.7±7.2 mm (range, 10 to 40 mm). The mean required time for the procedure was 49.0±29.5 minutes (range, 30 to 150 minutes). In the early period (before June 2012), the air insufflation was used in four cases during the procedure. Then, CO_2 insufflation was applied in the remaining cases (n=65). All tumors were resected successfully, with an *en bloc* and complete resection rate of 95.7% (67 of 70 lesions), respectively. Three esophageal tumors were resected in several pieces owing to larger size (40 mm). Three perforations were recognized during the procedure and were successfully treated by endoscopic clipping. No delayed perforation occurred in all the patients. Two patients experienced subcutaneous emphysema and a decreasing of oxygen saturation during the procedure, X-ray examination verified the occurrence of pneumothorax in them. Both of patients were treated with thoracic drainage, and they recovered satisfactorily after chest tube placement for 1 week. Sole subcutaneous emphysema occurred in two patients, and disappeared spontaneously after procedure. One patient developed pneumoperitoneum, which were resolved spontaneously without special treatment. No other intraoperative and immediate postoperative complications, including delayed bleeding and infections occurred. The mean length of the hospital stay was 5.8±1.5 days (range, 3 to 10 days).

3. Histopathological examination and follow-up

Histopathological examination identified 59 cases of leiomyoma (84.3%) and 11 cases of GIST (15.7%). According to pathological results, 49 leiomyoma (49/59, 83.1%) located in the esophagus, seven (7/59, 11.9%) in the cardia, and three (3/59, 5.0%) in the gastric antrum; with regard to GIST, two (2/11, 18.2%) in the cardia, six (6/11, 54.5%) in the fundus, and three (3/11, 27.3%) in the antrum. Based on the mitotic index (less than five mitotic figures noted per 50 high-power fields), the 11 GISTs were low-risk. During a median follow-up of 18.1 months (range, 6 to 35 months), there was no recurrence or distant metastasis, and no postprocedure leakages or other major complications occurred.

DISCUSSION

For the treatment of upper GI SMTs, laparoscopic or open surgery is usually regarded as the standard approach; however, with the development of ESD, endoscopic resection also become available and is regarded recently as minimally invasive resection methods for smaller lesions. Although ESD and EFR have come to be regarded recently as minimally invasive resection methods for SMTs, they can be associated with the major complication of perforations;[10] these can be difficult to close sometimes and may require resort to surgery. The emerging endoscopic method, ESTD has been proved to be safe and effective for treating upper GI SMTs in several pilot studies.[8,9,11-14]

Three years ago, we published our preliminary results of ESTD for treating esophageal and cardiac SMTs.[8] After that, we continued to use this novel technique for the management of upper GI SMTs. In this study, we enrolled 69 cases of patients with 70 SMTs, all of whom underwent the treatment of ESTD. We found that ESTD not only was feasible and effective for SMTs in the esophagus and cardia, but also in the stomach. All tumors were resected successfully, the mean procedural time was 49.0 minutes, which was comparable to other studies (range, 40 to 78.3 minutes).[12-15] Due to the large size (40 mm), three esophageal tumors were piecemeal resected. There may be a concern whether piecemeal resection could result into the recurrence of tumor. However, no tumor, including the piecemeal resected ones, occurred recurrence during the follow-up period.

Among our cases, 12 SMTs located in the stomach, including six in the fundus and six in the antrum. Due to the large lumen, relatively high instability and thicker mucosa, it would be more difficult to create submucosal tunnel in the stomach than esophagus. So at early period of the study, we only included patients with SMTs in the esophagus or the cardia. After gaining enough operational experience of ESTD for esophageal SMTs, we then began to perform gastric ESTD. According to our experience, it is relatively easier to perform ESTD in the gastric fundus adjacent to cardia, the lesser curvature of gastric body, and the greater curvature of gastric body and antrum than the others. As for the SMTs located in the gastric fundus near to cardia, we used trans-cardiac submucosal tunneling way to resect the tumor. This method has two advantages: for one thing, it is performed in a direct vision, so it can avoid retroflexion of endoscope; for another, the mucosal incision was made in the esophagus, which can prevent the erosion or pollution of gastric juice. Due to the thickness of the gastric mucosa, infolding of the mucosa at the resection site easily occurs. Some authors recommended using balloon dilatation to reverses the folding of the mucosa and facilitate incision closure.[16] We also met such a problem during procedure in some cases, but it can be solved by repeated insufflation and suction in the stomach. By using this method, the gastric mucosa became unfolded and incision site was closed successfully.

We also encountered two SMTs in one patient. Both of them located in the esophagus, and were resected simultaneously in one procedure. No complication occurred in this patient. Other authors also described the feasibility of ESTD for GI multiple SMTs. Chen *et al*.[17] succeeded to resect two separate esophageal and cardia SMTs under the same submucosal tunnel. Zhang *et al*.[15] expanded this experience, and applied ESTD for treating 23 patients with 49 multiple SMTs from MP layer in upper GI tract. They reported that all the SMTs were resected completely by

ESTD technique, and the complications was managed conservatively. Therefore, based on our experience and the literatures, ESTD can be also used to treat multiple upper GI SMTs, which can avoid repeated procedures.

With regard to procedure-related complication, the incidence of perforation was 4.3% (3/69). These cases were managed endoscopically using endoclips and no additional surgery was required. Two patients had pneumothorax and subcutaneous emphysema, and another two had only subcutaneous emphysema. Majority of these gas-related complications occurred in the air insufflation group, while subcutaneous emphysema occurred only in one patient with CO_2 insufflation. CO_2 insufflation is safe, quick absorption, decrease intraprocedural, postprocedural pain and recovery time,[18] and it can also reduce the risk of mediastinal emphysema and air embolization. Endoscopic CO_2 insufflation has been recommend as a routine tool in another similar endoscopic technique, POEM procedure,[19] and it also should be routinely used in the ESTD procedure. There was no delayed bleeding in any patient as we coagulated all the potential bleeding areas in the submucosal tunnel before closing the tunnel entry.

Overall, ESTD was effective and safe for the management of upper GI SMTs. Complete resection of tumors without local recurrence were observed in our patients. It has several advantages over other treatment modalities. First of all, through the submucosal tunnel, SMTs can be dissected and resected under direct endoscopic vision, and bleeding spot can be detected immediately and managed successfully by hemostasis. Second of all, it has been reported ESD could resulted in a perforation rate from 6.1% to 15% for treating lesions originating from the MP layers of upper GI tract,[4,20,21] which may carry the potential risk of digestive tract leakage and secondary infection. But ESTD procedure allows that the mucosa layer above the SMTs is not resected, thereby maintaining the integrity of the GI tract mucosa. Finally, the entry to the submucosal tunnel can be easily closed with several clips.

We acknowledged that our study has several limitations. Firstly, it is nonrandomized design and do not involved large number of cases due to relative low incidence of SMTs. Secondly, our follow-up length was short; hence, we cannot comment on long-term efficacy. Thirdly, all procedures in this series were performed by a single endoscopist in a single-center, so a selection bias might be present and the results may not be generalizable.

In conclusion, our study demonstrated the feasibility and safety of ESTD in the treatment of upper GI SMTs originating from the MP layer. Further large-scale comparative studies with other methods should be conducted to determine widespread application of this technique.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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