Submucosal tunneling endoscopic resection for large symptomatic submucosal tumors of the esophagus: A clinical analysis of 24 cases

Guo-Xiang Wang[1], Guang Yu[1], Yan-Li Xiang[1], Yang-De Miu[1], Hong-Gang Wang[1], Mei-Dong Xu[2]

[1]Department of Gastroenterology, Taizhou Municipal Hospital, Taizhou, Zhejiang, China
[2]Endoscopy Center, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

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ABSTRACT

Background/Aims: Studies evaluating submucosal tunneling endoscopic resection (STER) for the treatment of upper gastrointestinal submucosal tumors (SMTs) have recently increased. However, the efficacy and safety of STER for the treatment of large symptomatic SMTs in the esophagus have not been well investigated. The aim of the present study was to evaluate the efficacy and safety of STER for the treatment of large symptomatic SMTs in the esophagus.

Methods: A total of 24 patients with large symptomatic SMTs in the esophagus who underwent STER in our hospitals between January 2015 and May 2018 were included in the study. The tumors were confirmed to be of muscularis propria layer origin. Treatment outcomes, complications, and follow-up results were retrospectively analyzed.

Results: All 24 lesions were resected en bloc with STER. The mean maximum transverse diameter of the lesions was 4.7 (3.5–6.5) cm. The mean maximum longitudinal diameter of the lesions was 2.1 (1.5–3.0) cm. The mean duration from mucosal incision to complete mucosal closure was 65 (50–115) min. Postoperative pathological diagnosis confirmed 18 cases with leiomyomas, 4 cases with stromal tumors, and 2 cases with schwannomas. There were no major complications. There were no residual lesions or disease recurrence during follow-up.

Conclusion: STER is safe and effective for the treatment of large symptomatic SMTs of muscularis propria layer origin in the esophagus.

Keywords: Submucosal tumors, esophagus, symptomatic, submucosal tunneling endoscopic resection

INTRODUCTION

In recent years, the wide adaption of gastroscopy and the advancements in endoscopic ultrasonography (EUS) have greatly improved the endoscopic diagnosis and treatment of esophageal lesions. Furthermore, the detection rate of submucosal tumors (SMTs) in the esophagus has been increasing annually. SMTs with transverse diameters <2.0 cm are generally considered to be low risk (1), and periodical follow-up is generally recommended. However, the management of SMTs with transverse diameters >2.0–5.0 cm remains controversial because of the complex nature and metastatic potential of these tumors. EUS is one of the primary diagnostic tools for SMTs that can provide information on SMT size, shape, location, layer of origin, echo pattern, and malignant potential. However, EUS cannot accurately predict histological diagnoses for all cases, and the diagnoses often depend on operator experience (2,3). Therefore, minimally invasive endoscopic resection and accurate histopathological diagnosis are beneficial in controversial cases.

Submucosal tunneling endoscopic resection (STER) is a newly developed endoscopic technique that was first reported in 2011 by the Shanghai Zhongshan Hospital, showing that it was safe and effective for the treatment of upper gastrointestinal SMTs of muscularis propria layer origin (4). Compared with other conventional endoscopic techniques, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), STER allows the resection of SMTs under direct vision while maintaining mucosal integrity, which should reduce the risk of esophageal perforation and gastrointestinal fistula. The number of studies evaluating STER for the treatment of upper gastrointestinal SMTs has increased in recent years (5-9). However, the efficacy and safety of STER for the treatment of large symptomatic SMTs in the esophagus have not been well investigated. Thus, the aim of the present study was to evaluate the efficacy and safety of STER in 24 cases with large symptomatic SMTs in the esophagus.

Corresponding Author: **Mei-Dong Xu; xu.meidong@zs-hospital.sh.cn**
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METHODS

Patients

A total of 24 patients with large SMTs in the esophagus who underwent STER in our hospitals between January 2015 and May 2018 were included in our retrospective study. Preoperative EUS and contrast-enhanced chest computed tomography (CT) were used to confirm muscularis propria layer origination of esophageal SMTs, and the maximum transverse diameter of the tumors was >3.5 cm. All patients had symptoms, such as dysphagia and retrosternal chest pain prior to treatment. The patients were informed of the potential benefits and risks of the treatment prior to the operation. Written informed consent was obtained from all patients.

Study outcomes

The primary end-points of the present study were complete resection, local recurrence, or distant metastasis during follow-up. The secondary outcome measures included treatment-related adverse events and operation-related parameters, including operation time, length of hospitalization, and medical costs.

STER procedure

The following instruments and equipment were used for STER: standard single-channel gastroscope (GIF-Q260J; Olympus Optical Co. Ltd., Tokyo, Japan), transparent cap (D-201-11802; Olympus), hook knife (KD-620LR; Olympus), IT knife (KD-620LR; Olympus), injection needle (NM-4L-1; Olympus), snare (SD-230U-20; Olympus), Coagrasper hemostatic forceps (FD-410LR; Olympus), hemostatic clips (HX-600-135; Olympus; Resolution, Boston, MA, USA), CO_2 insufflator (Olympus), and ERBE electrosurgical coagulation unit with high-frequency generator (VIO 200D; ERBE Elektromedizin GmbH, Tübingen, Germany).

All patients received general anesthesia via endotracheal intubation and were placed in the left lateral decubitus position. A transparent cap was attached to the distal end of the endoscope. An incision was made at the mucosa located approximately 5 cm proximal to the tumor. A mixed solution of epinephrine and indigo carmine diluted in 0.9% NaCl solution was used for submucosal injection to create a local fluid cushion in the mucosal layer. Then, a 1.5-centimeter mucosal incision was made longitudinally along the esophagus using a hook knife, and the endoscope was inserted through the incision site into the submucosa. The submucosa and muscularis propria layers were gradually separated using a hook knife. A longitudinal tunnel was created between the two layers until the tumor was clearly exposed in the tunnel. The tumor was completely dissected from the surrounding tissues with an intact capsule using a hook knife (or IT knife in some patients). Tumor extraction was then performed using a snare. Intraoperative bleeding was treated with hot biopsy forceps. Hemostatic clips were used to close the tunnel completely from the distal to the proximal end after tumor resection. Video 1 and Figure 1-6 show an example of the STER procedure.

The following tricks and tips are recommended during the STER procedure for the dissection of large SMTs: (1) compared with STER for small tumors, the length of the tunnel should be longer to prevent tearing of the tunnel entrance due to large tumor size and narrow space during operation, (2) the tunnel should be made according to the size of the transverse diameter of the tumor to ensure that it is wide enough and to provide sufficient operating space, and (3) when separating the mucosal side of the tumor, repeated submucosal injections should be made to avoid tunnel mucosa damage.

Postoperative management

Chest CT imaging was selectively performed on day 1 post-STER to screen for operation-related adverse events, such as subcutaneous emphysema, pneumothorax, or pleural effusion. A central venous catheter was inserted through the third or fourth intercostal space instead of the stan-

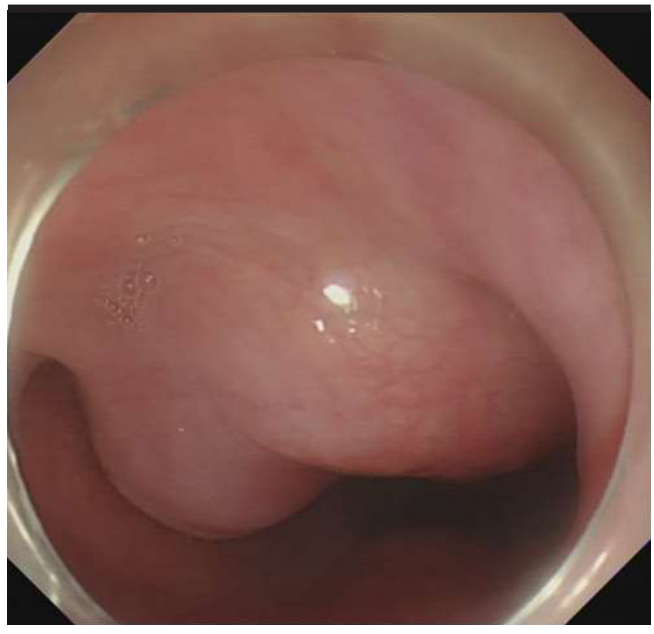

Figure 1. A large submucosal tumor in the esophagus originating from the muscularis propria layer.

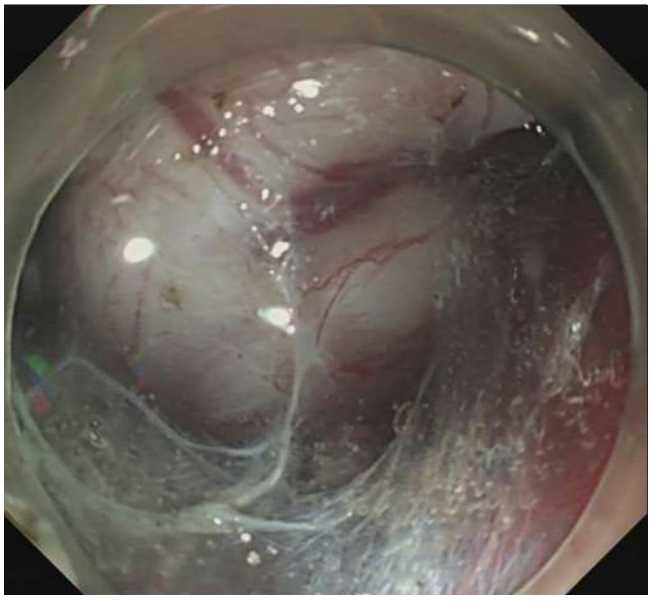

Figure 2. Creation of the submucosal tunnel.

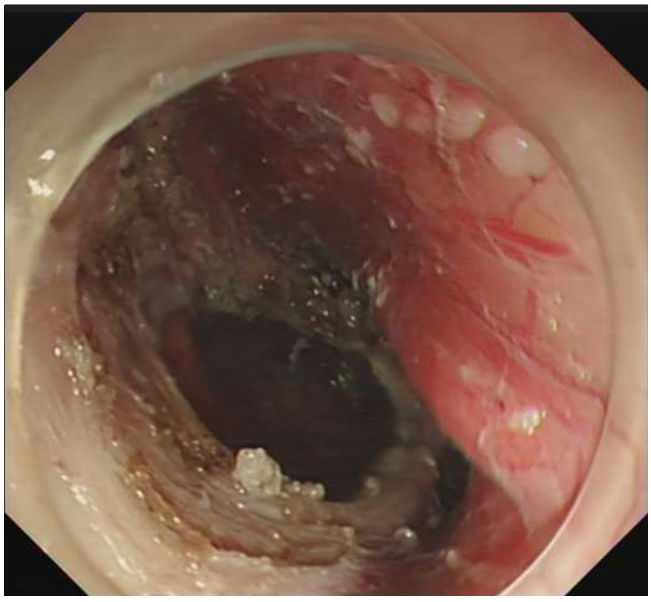

Figure 4. Surgical wound after tumor resection.

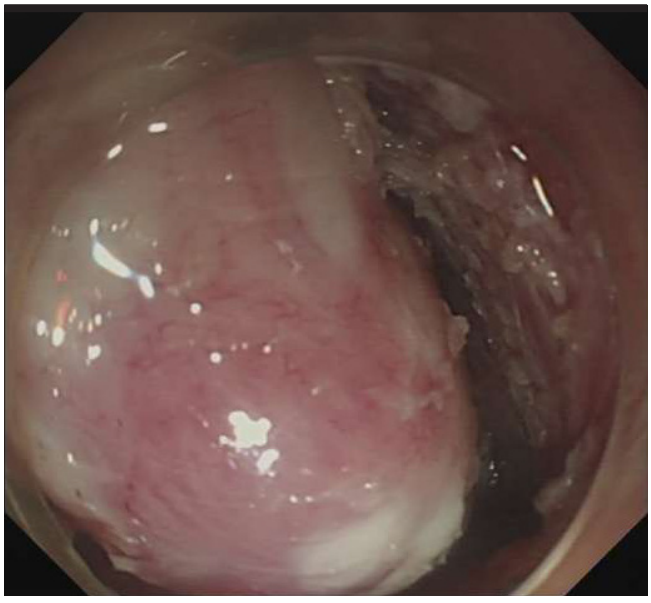

Figure 3. Resection of the tumor.

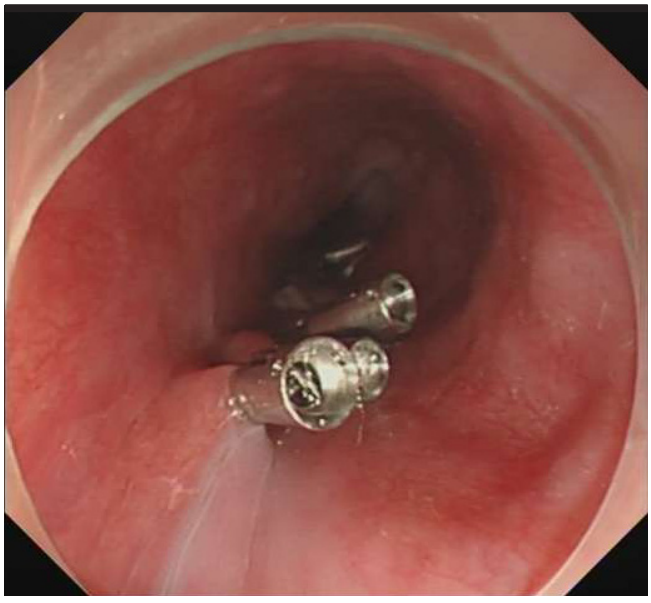

Figure 5. Closure of the tunnel entrance with metal hemostatic clips.

dard chest tube used for drainage in cases of pneumothorax. A 20-gage needle was used to relieve severe pneumoperitoneum that developed during or after surgery.

Postoperative chest pain, dyspnea, abdominal pain or bloating, and signs of purpura or peritonitis were monitored. Postoperative medication included proton pump inhibitors (PPIs) and antibiotics, and dietary restriction was mandatory (24-hour fasting followed by 24-hour liquid diet). After discharge, the patients were instructed to continue taking PPI and maintain a soft-food diet for 2 weeks, as appropriate.

Pathological evaluation

Formalin-fixed specimens were sent for pathological examination, and immunohistochemical staining for S100

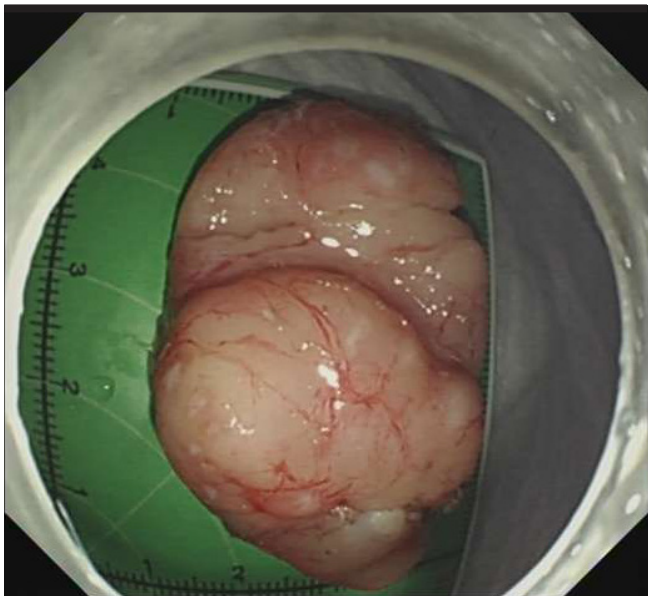

Figure 6. Resected specimen.

protein, SMA, CD117, and CD34 was performed. Complete resection was assessed histopathologically and defined as resection of a tumor with an intact capsule.

Follow-up

All patients underwent postoperative follow-up examinations at 3, 6, and 12 months by endoscopy to assess wound healing, and EUS was used to examine residual lesions or local recurrence. Thereafter, the patients were followed up once a year. Patients with tumors with malignant potential received additional follow-up examinations annually for abdominal ultrasound, chest X-ray, and contrast-enhanced CT to detect distant metastasis.

RESULTS

The datas were summarized as Table 1.

Clinical characteristics

A total of 24 patients were included in the study. The study was composed of 13 male and 11 female patients. The mean age of the patients was 47.8 (32-65) years. Of the 24 patients, 2 had tumors located in the upper esophagus, 7 in the middle esophagus, and 15 in the lower esophagus.

Operation-related parameters

All SMTs were successfully resected via STER with an en bloc resection rate of 100%. The mean maximum transverse diameter of the resected lesions was 4.7 (3.5-6.5) cm. The mean maximum longitudinal diameter of the resected lesions was 2.1 (1.5-3.0) cm. The mean duration from mucosal incision to complete mucosal closure was 65 (50-115) min. The mean complete wound closure required approximately 5 (4-6) hemostatic clips.

Complications

All 24 patients had a small amount of bleeding during the STER procedure, with an average blood loss of 20-30 mL. Successful hemostasis was achieved using electrocoagulation. There were no patients who required blood transfusion. Seven patients had mucosal injuries, but were successfully repaired by hemostatic clips. One patient developed intraoperative pneumoperitoneum, and the gas was relieved by inserting a needle into the lower right abdomen. Two patients had postoperative pneumothorax with subcutaneous emphysema, one with pneumothorax of the left lung and one with bilateral pneumothorax. One of the two patients had spontaneously resolved pneumothorax postoperatively. The other patient received thoracic drainage, and the pneumothorax completely resolved after 3 days upon chest X-ray examination, and the chest drainage tube was then removed. Three patients had a small amount of bilateral pleural effusion, which spontaneously resolved without treatment, on postoperative CT scan. There was no postoperative hematemesis or melena. There were no other complications, such as secondary infections or fistulas, following surgery.

Histopathological results

Routine pathological examination and immunohistochemical staining of the surgical specimens revealed 18 cases with leiomyomas, 4 cases with stromal tumors, and 2 cases with schwannomas. Among the resected tumors, 14 cases had intact capsules, and 10 cases could not be evaluated due to the electrical burn of capsules surrounding the lesions. The complete resection rate of the lesions was 58.3% (14/24) as assessed pathologically.

Length of hospitalization and medical costs

The mean length of hospitalization of the 24 patients was 3 (2-5) days, and the mean medical cost was approximately 7500 (6500-10,000) yuan.

Follow-up

The mean follow-up time of the patients was 27 (6-42) months. During the follow-up period, the symptoms of 16 patients improved or disappeared. There were no local residual tumors, local recurrence, or distant metastases, and there were no tumor-related deaths in any of the patients.

Table 1. Efficacy and safety of STER in patients with large symptomatic submucosal tumors in the esophagus.

Clinical characteristics	
Gender (female/male), n	11/13
Age (years)	47.8 ± 13.9 (32-65)
Operation-related parameters	
Mean maximum transverse diameter (cm)	4.7±1.3 (3.5-6.5)
Mean maximum longitudinal diameter (cm)	2.1±1.1 (1.5-3.0)
Mean operation time (min)	65.0 ± 20 .5 (50-115)
En bloc resection rate	100% (24/24)
Complications	
Delayed bleeding	0% (0/24)
Gastrointestinal fistula	0% (0/24)
Subcutaneous emphysema	8.3% (2/24)
Pneumothorax	8.3% (2/24)
Pneumoperitoneum	4.2% (1/24)
Pleural effusion	12.5% (3/24)
Histopathological evaluation	
Leiomyoma	75.0% (18/24)
Stromal tumor	16.7% (4/24)
Schwannoma	8.3% (2/24)
Complete resection rate	58.3% (14/24)
Length of hospitalization (days)	3±1 (2-5)
Medical costs (yuan)	7500±1000
(6500-10,000)	
Rate of recurrence and metastasis	0% (0/24)

DISCUSSION

According to the most recent World Health Organization classification in 2000, SMTs in the gastrointestinal tract are nonepithelial tumors derived from mesenchymal tissue below the mucosa. Most SMTs, including leiomyomas, lipomas, and hemangiomas, are considered benign lesions. In contrast, leiomyosarcomas and stromal tumors tend to be malignant (10). SMTs may originate from the muscularis mucosa, submucosa, and muscularis propria layer. The wide implementation of gastroscopy and the advancements in EUS technology have greatly improved the detection rate of SMTs in the esophagus. Although EUS can identify the layer of origin and size of SMTs, this technique cannot accurately determine whether the tumors are benign or malignant. SMTs derived from the muscularis propria layer in the esophagus are potentially malignant. As the tumor grows, it may compress or infiltrate the surrounding tissues or progress to distant metastasis; therefore, early diagnosis and treatment are necessary (11). In the present study, all 24 patients had symptoms, such as dysphagia and retrosternal chest pain, and 4 of them were postoperatively diagnosed with esophageal stromal tumors.

Currently, the main treatment modalities for esophageal SMTs include conventional surgical resection and minimally invasive thoracoscopic or endoscopic resection. Many endoscopic treatment options for esophageal SMTs are available. Conventional endoscopic electrotomy or ligation/resection often causes bleeding and perforation and may leave residual tumor. ESD is suitable for tumors originating from the muscularis mucosa and submucosa because it does not destroy the integrity of the muscularis propria layer and is relatively safe to perform. However, SMTs originating from the muscularis propria layer may require full-thickness resection. Although endoscopic full-thickness resection can completely remove SMTs originating from the muscularis propria layer, it destroys the integrity of the esophagus, leading to gastrointestinal fistula and secondary chest infection.

The use of STER for the treatment of upper gastrointestinal SMTs originating from the muscularis propria layer was first reported by the Shanghai Zhongshan Hospital in 2011 (4), and this technology is continually being implemented. STER differs from conventional laparoscopic surgery and natural orifice transluminal endoscopic surgery because it dexterously utilizes the space between the gastrointestinal mucosa and muscularis propria layer for manipulation (12-14). The treatment of esophageal SMTs originating from the muscularis propria layer via STER can achieve complete tumor resection and maintain the integrity of the esophagus, greatly reducing the risk of postoperative complications. However, owing to the space limitation in the tunnel, previous studies have suggested that the transverse diameter of tumors resected using STER should be <3.5 cm. The present study investigated the safety and efficacy of STER for the resection of symptomatic tumors with diameters >3.5 cm. The results show that STER is safe and effective for the treatment of large symptomatic tumors, thus expanding the indications of STER. In the present study, 24 patients with esophageal symptomatic SMT originating from the muscularis propria layer were successfully treated by

STER. The lesions were completely resected, and accurate pathological data were obtained. There were no postoperative complications. The efficacy of STER was the same as conventional resection, but the patients recovered quicker, the mean length of hospitalization was shorter, and mean medical costs were lower. These results fully demonstrated the superiority of minimally invasive STER treatment for large esophageal tumors.

Similar to invasive treatments, complications may potentially occur during and after STER. Major STER-related adverse events include bleeding, perforation, thoracic and mediastinal infections, subcutaneous and mediastinal emphysema, and pneumothorax (15). The greater the transverse diameter of the tumor, the greater the difficulty of STER operation and the risk of complications. The transverse diameter (>3.5 cm), shape, and location of the tumor greatly influence the operation time and occurrence of complications. Tumors with large transverse diameters and irregular shapes promote longer operation times and increase the possibility of serious tunnel mucosal damage, as well as the incidence of complications (16,17). When the tumors are located on the upper esophagus, the difficulty of the surgical procedure increases, the operation time is prolonged, and the risk of complications also increases. The difficulty of the surgical procedure was increased due to the effect of the tunnel opening for patients with tumors located in the upper portion of the esophagus. In our study, the tumors were 3.5-6.5 cm in diameter, with an average of 4.7 cm, and included two tumors located in the upper esophagus. Although excision was successfully completed, the difficulty of the surgical procedure was significantly increased, and the operation time was longer for patients with larger transverse diameters. Overall, eight patients had surgery-related complications, including one case of intraoperative pneumoperitoneum that was relieved by right lower abdominal puncture and drainage; two cases of pneumothorax complicated with postoperative subcutaneous emphysema, of which one patient had postoperative self-absorption, and the other patient had thoracic drainage that was found to be completely absorbed after 3 days via thoracic X-ray examination; and three cases of postoperative bilateral small pleural effusion that was detected by CT scan and spontaneously assimilated without additional treatment.

STER is a high-risk endoscopic technique with its efficacy and safety closely related to the technical proficiency and experience of the operator. Therefore, the operator must first master endoscopic resection techniques, such as EMR and ESD. They must then practice STER repeatedly on isolated animal organs and living animals. After becoming proficient in the technique, they can gradually begin performing STER in human patients under the guidance of experienced surgeons until they can finally perform STER independently. When STER is used to treat SMTs, the tumor capsule should remain intact to prevent tumor rupture and bleeding. The difficulty of performing STER for the resection of esophageal SMTs with transverse diameters >3.5 cm is increased, and the operation should be conducted by experienced surgeons. There are some tricks and tips that are recommended during the STER procedure for the dissection of large SMTs: (1) compared with STER for small tumors, the length of the tunnel should be longer to prevent tearing of the tunnel entrance due to large tumor size and narrow space during operation, (2) the tunnel should be made wide enough according to the size of the transverse diameter of the tumor to provide a better operating space, and (3) when separating the mucosal side of the tumors, repeated injections should be made to avoid damaging the tunnel mucosa.

The present study has some limitations. First, this is a retrospective study with a small sample size. Second, the follow-up time is insufficient to assess long-term outcomes. Large sample studies are required to support the conclusions.

In summary, STER is safe and effective for the treatment of large symptomatic SMTs in the esophagus and can be used to achieve the complete resection of lesions with a low rate of complications and to provide accurate pathological evaluations.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Medical College of Taizhou University & Taizhou Municipal Hospital.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.X.W.; Design - G.X.W.; Supervision - G.X.W.; Resources - G.Y., Y.L., Y.D.M., H.G.W.; Data Collection and/or Processing - G.Y.; Analysis and/or Interpretation - G.X.W., M.D.X.; Literature Search - G.Y.; Writing Manuscript - G.X.W.; Critical Review - M.D.X.

Conflict of Interest: The authors have no conflict of interest to declare.

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Video 1: An example of the STER procedure for a large submucosal tumor in the esophagus.

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