Current status of submucosal tunneling endoscopic resection for gastrointestinal submucosal tumors originating from the muscularis propria layer (Review)

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Received June 22, 2016; Accepted July 7, 2017

DOI: 10.3892/ol.2017.6869

Abstract. Gastrointestinal submucosal tumors (SMTs) have been increasingly identified via the use of endoscopic ultrasonography, and removal is often recommended for SMTs that are >2 cm in diameter or symptomatic. Submucosal tunneling endoscopic resection (STER), also known as submucosal endoscopic tumor resection, endoscopic submucosal tunnel dissection or tunneling endoscopic muscularis dissection, is a novel endoscopic technique for treating gastrointestinal SMTs originating from the muscularis propria layer, and has been demonstrated to be effective in the removal of SMTs with a decreased rate of recurrence by clinical studies. STER may be performed for patients with esophageal or cardia SMTs, and its application has expanded beyond these types of SMTs due to modifications to the technique. The present study reviewed the applications, procedure, efficacy and complications associated with STER.

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Abbreviations: SMT, submucosal tumor; EUS, endoscopic ultrasonography; ESD, endoscopic submucosal dissection; ESE, endoscopic submucosal excavation; STER, submucosal tunneling endoscopic resection; MP, muscularis propria

Key words: submucosal tumor, gastrointestinal neoplasm, gastrointestinal surgical procedures, submucosal tunneling endoscopic resection

1. Introduction

Following the identification of a gastrointestinal submucosal tumor (SMT), periodic surveillance using endoscopy and endoscopic ultrasonography (EUS) remains a major strategy, but the use of this strategy is associated with multiple concerns, including patient compliance and stress, cost-effectiveness, and the risks associated with repeated endoscopic procedures and delayed diagnosis of malignancy (1,2). Furthermore, certain tumors exhibit malignant potential, particularly those that originate from the muscularis propria (MP) layer or are large in diameter (1). Therefore, removing these SMTs is crucial. Current methods to remove SMTs include surgery and endoscopic resection, compared with the latter, surgical approaches are more invasive and associated with increased costs and a longer hospital stay. Endoscopic resection is a first-line treatment for SMTs ≤50 mm in diameter (1,2). Alternative methods include endoscopic submucosal dissection (ESD), endoscopic submucosal excavation (ESE) and endoscopic full-thickness resection, but these may be associated with unsatisfactory outcomes due to incomplete resection and/or the risk of perforation during the procedure (3-5). Submucosal tunneling endoscopic resection (STER) has emerged as a novel technique for treating upper gastrointestinal SMTs and has yielded promising results (6-17). STER possesses multiple advantages over other endoscopic methods, including the maintenance of mucosal integrity, the facilitation of an increased rate of healing and a decreased risk of pleural/abdominal infection. In addition, the submucosal tunnel helps to maintain a clear visual field, which facilitates an improved response to intraoperative bleeding. The present study summarized the current status of STER, including its applications, procedure, efficacy and complications.

2. Preoperative assessment

Prior to performing STER, the presence, originating layer, size, and the presence or absence of malignancy-associated risk features of the SMT should be confirmed. The SMT should also be distinguished from extrinsic compression or hemangioma. Esophagogastroduodenoscopy and colonoscopy may be used to locate the lesion, and EUS and computerized tomography (CT) may be used to determine the originating layer, size and risk features of the SMT (1).

3. Applications of STER

STER for esophageal and cardia SMTs ≤35 mm. STER is a complicated procedure with a decreased space for operation in the submucosal tunnel, and therefore was initially performed for esophageal and cardia SMTs, with most researchers recommending a maximum resectable lesion size of 35 mm (6-10). With STER being increasingly applied for patients with multiple types of SMT, STER has been modified multiple times and its application has expanded further. The patient selection diagram for candidates of STER at the Second Xiangya Hospital of Central South University (Changsha, China) was provided (Fig. 1).

STER for gastric SMTs. The stomach possesses specific anatomical and physiological features, including a large lumen, increased flexibility, an unfixed position and thick mucosa, that render generating a submucosal tunnel more challenging compared with doing so in the esophagus, and not all gastric SMTs are suitable for STER. In addition to those in the cardia, STER may be used as a treatment for SMTs located in the gastric corpus or fundus proximate to the cardia, the lesser curvature of the gastric corpus and the greater curvature of the gastric antrum. Lu *et al* (18) treated 18 patients with gastric fundus SMTs using STER; 19 tumors were removed, en bloc resection was achieved for all the patients and the mean tumor size was 21 mm (range, 8-50 mm). Lu *et al* (19) treated 45 patients with gastric SMTs using STER, 43 cases were successfully treated and 47 tumors were removed. The SMTs were all located in the cardia, the gastric fundus proximate to the cardia or the gastric antrum. En bloc resection was achieved for all the patients and the mean tumor size was 14 mm (range, 5-50 mm). Li *et al* (20) reported on 32 patients with gastric SMTs who were treated using STER without severe complications. Of these SMTs, 12 were located in the gastric corpus proximate to the cardia, 3 in the gastric fundus proximate to the cardia, 6 in the lesser curvature of the gastric corpus and 11 in the greater curvature of the gastric antrum. En bloc resection was achieved for all the patients and the mean tumor size was 23 mm (range, 10-50 mm).

STER for multiple SMTs. Although the majority of the SMTs in the MP layer are solitary, multiple studies have reported the presence of multiple SMTs (11,13,18,19,21,22). Chen *et al* (21) reported a patient simultaneously exhibiting esophageal and cardia SMT, and the two SMTs were successfully removed using STER with a single tunnel. Zhang *et al* (22) treated 23 patients with multiple SMTs in the upper gastrointestinal tract using STER. A total of 49 SMTs were removed and 3 of the patients exhibited three coexisting tumors.

STER for esophageal and cardia SMTs >35 mm. Although the majority of researchers recommended a maximum resectable lesion size of 35 mm during STER due to the decreased space for operation in the submucosal tunnel, STER has been applied multiple times for SMTs >35 mm, with the largest SMT reported to undergo STER, to the best of our knowledge, being 70 mm (23-29). Wang *et al* (15) retrospectively analyzed the clinical data of 80 patients with a total of 83 SMTs, 70 of which were ≤35 mm and 13 of which were >35 mm, and demonstrated that STER resulted in a similar efficacy and rate of complications for SMTs ≤35 mm and those >35 mm, although an increased operative duration was demonstrated for the latter compared with the former.

STER for rectal SMTs. The rectum possesses a thin mucosa and a tortuous lumen, thereby rendering the generation of a submucosal tunnel more challenging compared with doing so in the esophagus. To the best of our knowledge, only one center has reported the use of STER in patients with rectal SMTs. Hu *et al* (30) treated 12 patients with rectal SMTs using STER; en bloc resection was achieved for all the patients and the median size of the resected tumors was 14 mm (range, 10-30 mm). No severe complications were detected and no recurrence was revealed during the 4-33 month follow up.

4. STER procedure

The STER procedure in The Second Xiangya Hospital of Central South University (Fig. 2) is typically performed with the patient in the supine or lateral position under general anesthetic and with the airway intubated. CO_2 insufflation is recommended (29).

Identification of the tumor. The tumor is identified and accurately located. For SMTs that are challenging to locate, including SMTs proximate to the fundus of the stomach, the submucosal injection of indigo carmine or methylene blue may be performed to help locate the tumor and guide the direction of subsequent tunneling (20).

Submucosal injection. A fluid cushion is subsequently generated through a submucosal injection consisting of saline solution with indigo carmine 3-5 cm from the SMT. Typically, epinephrine is added to the solution to decrease the risk of intraoperative bleeding. For rectal or gastric SMTs, the submucosal injection is performed 2-3 cm from the SMT (19,20,30).

Generating tunnel entry. A 2 cm, longitudinal mucosa incision is used to generate tunnel entry. A further submucosal dissection of ≥0.5 cm along the sides of the longitudinal incision is made to facilitate tumor extraction and gas diffusion (15,31). For SMTs >35 mm, the mucosal incision may be increased to the size of the short dimension of the tumor (32).

Generating the tunnel. A submucosal tunnel extending 2 cm from the tumor is generated between the submucosal and MP layers using the ESD method. The selection of ESD knives depends on surgical experience; available knives include dual, hybrid, triangular-tip and hook knives. The dissection plane should be maintained proximate to the MP to decrease the risk of injury to the mucosal flap. The tunnel should be sufficiently wide and its width should increase according to the diameter

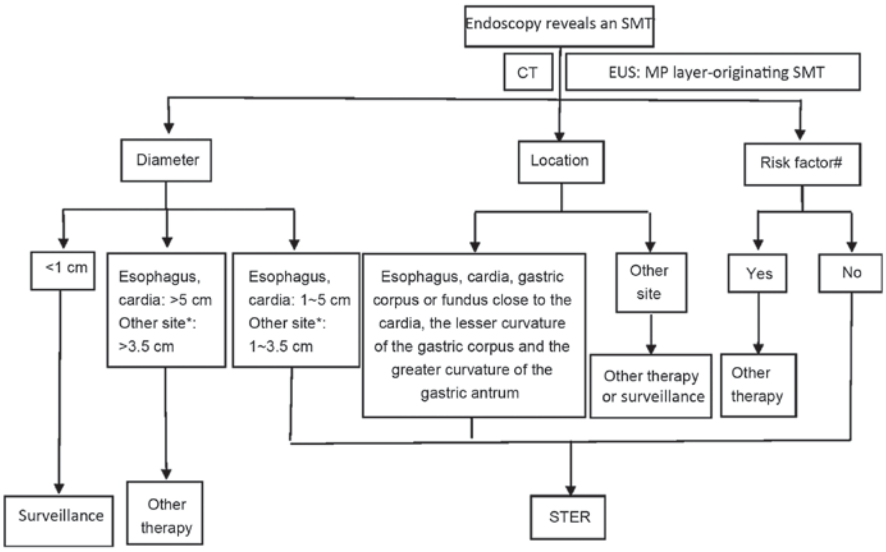

Figure 1. Patient selection diagram for candidates for STER at the Second Xiangya Hospital of Central South University (Changsha, China). *Gastric corpus or fundus proximate to the cardia, the lesser curvature of the gastric corpus and the greater curvature of the gastric antrum. #Ulceration or erosion at the tumor site; EUS reveals an irregular border, or internal heterogeneity, including an anechoic area (i.e. necrosis), echogenic loci (i.e. bleeding), heterogeneous enhancement or regional lymph node swelling; CT reveals metastasis or invasion out of the gastrointestinal tract; a Zubrod-Eastern Cooperative Oncology Group Performance Status ≥2; patient exhibits severe cardiopulmonary disease or blood coagulation disorders. SMT, submucosal tumor; CT, computerized tomography; EUS, endoscopic ultrasonography; MP, muscularis propria; STER, submucosal tunneling endoscopic resection.

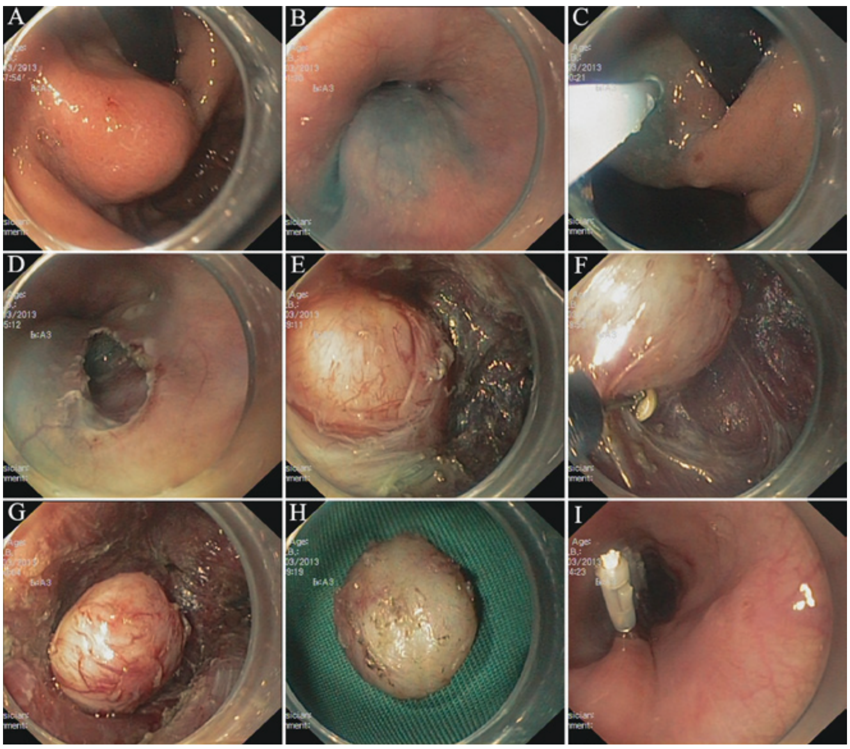

Figure 2. Submucosal tunneling endoscopic resection procedure in the Second Xiangya Hospital of Central South University (Changsha, China). (A) Submucosal tumor in the gastric fundus proximate to the cardia. (B) Submucosal injection. (C) The marked location of the tumor. (D) Tunnel entry. (E) The submucosal tumor. (F) Tumor dissection. (G) The dissected tumor in the tunnel. (H) The resected tumor. (I) Mucosal entry closure.

of the SMT to ensure a satisfactory endoscopic view of the SMT and sufficient space for resection and facilitate submucosal dissection and gas diffusion (32).

Dissection of the tumor. The tumor is dissected at the MP layer. Complete resection without damaging the tumor capsule is recommended. For SMTs originating from the deep MP layer or exhibiting a tight connection with the underlying MP or serosal layers, a full-thickness resection, including the lesion, its underlying MP and serosa is generally performed (10,15,32). For patients with gastric SMTs undergoing full-thickness resection, the SMT should be prevented from lodging in the abdominal cavity, potentially by using laparoscopic assisted endoscopic surgery.

Removing the tumor. Although small SMTs may be easily removed from the tunnel and extracted from the body, doing so for SMTs >35 mm in the upper gastrointestinal tract may prove challenging. While removing SMTs from the upper gastrointestinal tract, the tumor is grasped such that its long dimensions are respectively parallel and transverse to the long axis of the esophagus, and the tumor may be easily extracted through the tunnel orifice and the upper esophageal sphincter (32). If preoperative imagery, endoscopy and clinical examination suggest a benign tumor, a snare may be used following the completion of resection to cut the tumor while still in the tunnel into ≥2 pieces to facilitate its extraction from the tunnel (32). An alternative approach is to generate a second 'window', either in the area of the tumor or through a distal mucosal incision to facilitate en bloc extraction for large leiomyomas (24,26).

Closing the tunnel entry. Following the removal of the SMT, the wound surface should be repeatedly washed to decrease the risk of residual tumor cells. Subsequently, several clips are applied to close the tunnel entry.

Managing the resected tumor. The specimens are then fixed, embedded with paraffin, and sectioned. Hematoxylin and eosin and immunohistochemical staining are performed to detect cluster of differentiation (CD) 34, CD117, S100 calcium binding proteins, desmin, survival of motor neuron 1, marker of proliferation Ki-67 and gastrointestinal stromal tumor 1.

Postoperative management. The postoperative symptoms of patients are monitored, including fever, chest or abdominal pain, dyspnea, cyanosis, distention and peritonitis. Thoracoabdominal radiography, second look endoscopy or CT is performed for selected patients with postoperative symptoms 2 days following the operation. Generally, patients are kept *nil per os* for 24 h, subsequently placed on a liquid diet for multiple days to a week, and gradually returned to a normal diet following this. Intravenous antibiotics and potentially hemostatics are administered to patients for 3 days. For patients with upper gastrointestinal SMTs, intravenous proton pump inhibitors are administered for 3-7 days and orally administered for multiple weeks following this. For rectal SMTs, it is necessary to ensure stools remain soft and defecation easy (30).

5. Efficacy of STER

Currently, >20 studies have been published with outcome data based on >700 patients (6-20,22,29,30,32-35). In these studies, therapeutic success was recorded for >77% of patients and en bloc resection was achieved in >85% of patients, while irregularly shaped or larger tumors were risk factors in piecemeal resection (33). Of the SMTs reported in these studies, >95% were leimyomas or gastrointestinal stromal tumors, while the other reported tumors included lipomas, schwannomas, calcifying fibrous, glomus, granular cell and nerve sheath tumors, proliferating collagen fibers, degenerated nodes and aberrant pancreatic tissue. No recurrence was detected for the patients of these studies. To the best of our knowledge, there are no randomized, controlled trials comparing STER with other treatments of SMTs, but three retrospective studies have been published.

Comparing STER and ESD. Wang *et al* (34) retrospectively assessed the clinical data of 39 patients with esophageal leiomyoma, 18 of which received STER and 21 of which received ESD, and demonstrated that the efficacy and complications of the two techniques were comparable, though STER was associated with decreased operating time and duration of hospital stay, and an increased rate of incision healing compared with ESD.

Comparing STER and ESE. Lu *et al* (35) retrospectively analyzed the clinical data of 77 patients with upper gastrointestinal SMTs, 42 of which received STER and 35 of which received ESE, and demonstrated that the efficacy and complications of the two techniques were comparable, though STER decreased air leakage for SMTs by >10 mm compared with ESE.

Comparing STER and video-assisted thoracoscopic surgery (VATS). Tan *et al* (32) retrospectively evaluated the clinical data of 31 patients with esophageal leiomyoma (diameter, 35-55 mm), 18 of which received STER and 13 of which received VATS, and revealed that the efficacy of the two techniques were comparable, though STER was associated with decreased operation time, a reduced decrease in hemoglobin level, and decreased cost and duration of hospital stay compared with VATS.

6. Complications of STER

In the aforementioned >20 studies, STER has been performed with a decreased rate of serious complications, and no STER-associated mortality has been reported. Nonetheless, efforts should be taken to decrease the risk of adverse events, recognize them when they occur, and manage them appropriately following identification. According to a previously published, large-scale study consisting of 290 patients with SMTs who underwent STER, the overall incidence of complications was 23.4% (68/290), and only 10.0% of procedures (29/290) required intervention for complications (29). Furthermore, the study demonstrated that irregular shape, the location of the tumor in the deep MP layer, increased procedure time, and air insufflation were risk factors for major STER-associated complications.

Intraoperative complications

Aspiration. An important consideration in the use of STER is the risk of aspiration during induction and intubation, and communicating with the anesthesiologist is crucial to decrease this. Standard airway protection methods should be used, including a rapid induction sequence, to decrease the risk of aggressive aspiration of mouth contents during intubation.

Bleeding. Bleeding may occur at any time during STER, but usually results in <100 ml blood loss and may be immediately controlled via coagulation with the tip of a knife. However, the availability of electrosurgical hemostatic forceps for the coagulation of larger vessels is essential. Chen *et al* (29) reported a rate of 1.7% (5/290) for major bleeding (>200 ml). All of those cases were managed endoscopically and blood transfusion was not required.

Mucosal laceration. Mucosal lacerations may occasionally occur and the majority are small (<1 cm) and may be closed using ≥1 clip. In the aforementioned >20 studies, mucosal laceration occurred in a total of 15 patients and in each case the laceration was closed using clips without leakage (10,15,16,18,19,29). Two case reports have reported on large esophageal mucosal lacerations, which were managed using stent insertions (26,28).

Gas-associated complications. Gas-associated complications include subcutaneous emphysema, pneumothorax, pneumoperitoneum, and mediastinal emphysema. Gas-associated complications are the most common complications of STER and may occur in ≤66.7% of patients undergoing STER (10). Those patients who undergo full-thickness resection exhibit an increased rate of gas-associated complications, though the majority of these are clinically insignificant and may resolve spontaneously (7,10,12,13,29). Thoracic drainage is recommended for pneumothorax in patients with lung collapse >30% and symptoms that include dyspnea, and lung puncture is recommended for patients with pneumoperitoneum or emphysema and more apparent symptoms (29). CO_2 is recommended as the insufflation gas instead of air. For CO_2 insufflator set-ups that allow adjustments to CO_2 flow, the lower flow setting should be set once the submucosal tunnel, and particularly the MP, is breeched. Regardless of whether an adjustable CO_2 insufflator is used, the endoscopist should use insufflation sparingly while in the submucosal tunnel. In all the aforementioned studies, STER was not discontinued for any patients exhibiting intraoperative complications.

Postoperative complications

Fistula. The most challenging potential complication of STER is leakage from the associated fistula. In >700 patients undergoing STER that have been described, leaks were uncommon, and no leak-associated mortalities have been reported. Only one leak (esophageal-pleural fistula; <0.2%) was reported and it was managed using clips and thoracic drainage (29).

Infection. Infection includes mediastinitis, peritonitis, subphrenic and intra-tunnel infections, and symptoms include chest/abdominal pain and a fever >38˚C. In all the aforementioned >20 studies, significant infection was uncommon, and mediastinitis, subphrenic and intra-tunnel infections have been reported in 1, 1 and 2 patients, respectively (14,16,29). All the reported cases of infection were controlled through conservative management, and no infection-associated mortalities have been reported.

Pleural or mediastinal effusion. The majority of effusions are reactive, but may be considered a normal postoperative change and, as with peroral endoscopic myotomy for treating patients with achalasia (36), clinically significant effusions are uncommon. In the >700 patients undergoing STER that have been described, 16 (2%) and 1 exhibited clinically significant pleural and mediastinal effusion, respectively, and these cases of effusion were treated using antibiotics and/or drainage (10,13,14,29).

Bleeding. Although postoperative bleeding is a potential concern, no cases of postoperative bleeding have been reported in the aforementioned >20 studies. Other, rare complications that have been anecdotally presented and may be study-dependent and of decreased general significance include wound pain and diverticulum formation (15,16,29).

7. Conclusions

It is estimated that >1,000 STERs have been performed globally over the last 5 years (37). The previous studies that reported the outcomes of >700 STERs (mean follow up, 3.5-22.7 months), demonstrating an en bloc resection rate of 85.7-100%, negligible severe morbidity, and no mortality or recurrence. In addition, ≤10% of the patients enrolled in these studies exhibited intervention-requiring complications. These favorable outcomes suggested that STER may represent a promising treatment for patients with SMTs. However, STER remains a complicated endoscopic surgery that requires a multidisciplinary team with expertise in surgery and advanced endoscopy, and the patients for which STER is performed should be selected carefully.

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