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Submucosal 1-tunnel endoscopic resection for treating upper gastrointestinal multiple submucosal tumor originating from the muscularis propria layer

A report of 12 cases

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Abstract

To explore the feasibility and efficacy of submucosal 1-tunnel endoscopic resection (1-tunnel STER) for the treatment of multiple upper gastrointestinal submucosal tumors (GI-SMTs) originating from the muscularis propria (MP) layer.

A total of 12 patients with multiple upper GI-SMTs (no less than 2 SMTs) who underwent 1-tunnel STER from April 2013 to October 2017 were included. Clinical data on general characteristics, operation-related parameters, adverse events, and follow-up results were recorded and analyzed.

All 12 patients underwent 1-tunnel STER successfully, and the mean operation time was 92.1 ± 40.8 minutes. A total of 30 SMTs were resected, out of which 27 were in the esophagus and 3 were in the stomach. The mean diameter was 15.0 ± 8.2 mm (range, 3–38 mm). All the SMTs were resected en bloc uneventfully. The SMTs comprised 28 leiomyomas and 2 gastric stromal tumors (low risk). No recurrence was noticed during a mean follow-up of 24.9 ± 15.3 months (range, 1–52 months).

One-tunnel STER may serve as a feasible and effective technique for the treatment of multiple upper GI-SMTs originating from the MP layer. A large-scale prospective study is warranted for a confirmative conclusion.

Abbreviations: CT = computerized tomography, EBL = endoscopic band ligation, EFR = endoscopic full-thickness resection, EGD = esophagogastroduodenoscopy, ESD = endoscopic submucosal dissection, ESE = endoscopic submucosal excavation , EUS = endoscopic ultrasonography, GIST = gastrointestinal stromal tumor, MP = muscularis propria, SMT = submucosal tumor, STER = submucosal tunneling endoscopic resection.

Keywords: endoscopic surgery, submucosal tumor, submucosal tunneling endoscopic resection

1. Introduction

Esophagogastroduodenoscopy (EGD) and endoscopic ultrasonography (EUS) have been increasingly performed in the recent years, as a result of which the detection rate of upper gastrointestinal submucosal tumors (GI-SMTs) has increased.[1] Though most of the SMTs are solitary, multiple SMTs can exist in rare cases. Endoscopic resection has been recommended for the treatment of selective upper GI-SMTs because it has been demonstrated to be safe, effective, and minimally invasive. Currently available methods for endoscopic resection include endoscopic submucosal dissection (ESD), endoscopic submucosal excavation (ESE), endoscopic band ligation (EBL), endoscopic full-thickness resection (EFR), and submucosal tunneling endoscopic resection (STER).[1,2] Although theoretically feasible, simultaneous endoscopic resection of multiple GI-SMTs by the aforementioned endoscopic methods, besides STER, may enlarge the wound, and increase the procedure duration which is thought to be associated with an increased risk of complications.

STER is a relatively novel therapeutic technique, first reported in 2012, for treating SMTs located in the esophagus and/or cardia.[2–5] In this approach, a submucosal tunnel is created between the submucosal and muscularis propria (MP) layer, and endoscopic resection is performed within the tunnel. Compared with the other endoscopic methods mentioned above, STER maintains mucosal integrity, thus theoretically decreasing the risk of pleural/abdominal infection.[6–8] Further, within the submucosal tunnel, endoscopic removal of multiple SMTs can be achieved with only 1 mucosectomy. However, some of the SMTs are not located in a straight line or may even be located in the opposite direction, which makes it difficult to remove them in a single straight submucosal tunnel. Moreover, little is known about 1-tunnel STER for treating multiple upper GI-SMTs.[9–11] In the present study, we retrospectively collected the clinical data on STER for multiple upper GI-SMTs to explore its feasibility and efficacy.

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2. Patients and methods

2.1. Patients

The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, and all the participating patients signed informed consent forms. Inclusion criteria for the study were as follows:

1. existence of multiple upper GI-SMTs (≥2) as shown on EGD and/or computerized tomography (CT), with the SMTs originating from the MP layer as confirmed by EUS;
2. the absence of any high-risk malignant features on EUS, such as internal heterogeneity, irregular borders, heterogeneous enhancement, and so on;
3. the absence of metastasis or invasion outside the GI tract as observed on CT;
4. The diameter of the largest SMT was ≥20 mm, or an increase in diameter during endoscopic surveillance, or presence of related symptoms in the patient, or the strong desire expressed by the patients to remove the SMT though it was <20 mm in diameter or asymptomatic; and
5. patients consent to receive a STER procedure.

Patients with severe cardiopulmonary disease (could not tolerate general anesthesia) or those with severe blood coagulation disorders were excluded from the study. Twelve consecutive patients were included between April 2013 and October 2017. Their general characteristics (age, gender), tumor-related parameters (number, size, location, etc), procedure-related parameters (duration, complications, etc), duration of hospital stay, and follow-up results were retrospectively collected and recorded.

2.2. Equipment for STER

All the STER procedures were performed under general anesthesia by an experienced endoscopist. A carbon dioxide insufflator (UCR; Olympus) was used for insufflation during the procedure. While most of the procedures were completed using dual knives (KD-650Q; Olympus), some employed a hybrid knife (ERBE), and an insulation-tip knife (KD611L, IT2; Olympus) to help dissect the SMTs during the STER procedure. Other equipment and accessories used included a high-frequency generator (VIO 200D; ERBE), an argon plasma coagulation unit (APC300; ERBE), an injection needle (NM-4L-1; Olympus), and hemostatic clips (HX-600–90; Olympus).

2.3. STER procedure

The procedure of 1-tunnel STER was as follows:

1. a virtual line was created along the axis with the most number of SMTs located nearby, and the submucosal injection was administered at about 3 cm from the most proximal SMT;
2. the tunnel entry was created: a 1.5 to 2.0 cm longitudinal mucosal incision was made by a dual or hybrid knife;
3. a submucosal tunnel was created between the submucosal and the MP layers, ensuring that all the SMTs were exposed during tunnel creation. The endoscope was extracted from the submucosal tunnel if there was any difficulty in finding the SMT during tunnel creation, and methylene blue was injected at the site of the SMT to locate the tumor and preset the tunnel route;
4. dissection of all the SMTs. The SMTs were dissected if they were too large and they interfered with further tunnel creation;
5. Closure of the mucosal entry after careful hemostasis upon resection of all the SMTs. Figure 1 depicts the procedure of 1-tunnel STER.

2.4. Postoperative management

Patients were nil per os (NPO) for 48 hours, followed by a liquid diet for another 72 hours, and then returned to a normal diet within the following 2 weeks. Intravenous proton pump inhibitors were recommended for 3 days after STER. On postoperative day 2, a thoracoabdominal radiography was performed to check for the occurrence of procedure-related complications such as pneumoperitoneum, emphysema, pneumothorax, and so on.

2.5. Pathological evaluation

The resected specimens were fixed and embedded in paraffin for pathological evaluation. Hematoxylin and eosin (HE) staining was performed to evaluate the general characteristics of the SMTs, and immunohistochemical (IHC) staining (such for SMA, CD117, CD34, Ki67, Dog-1, S-100, etc) was carried out to further determine the pathologic diagnosis. En bloc resection is defined as the presence of the intact fibrous capsule in the resected tumor and the absence of any remnant of tumor observed on endoscopy.

2.6. Follow-up management

Patients were asked to undergo a surveillance endoscopy at 3, 6, and 12 months after STER treatment, and then annually to observe healing of the mucosal incision and check for the presence of residual tumor. Usually an EGD was performed first, and an EUS and/or CT was performed if any abnormality was found during EGD examination.

3. Results

From April 2013 to October 2017, a total of 12 patients meeting the inclusion criteria were included. The male to female ratio was 9:3 (Table 1), with a mean age of 48.8 ± 8.9 years. Seven of them were asymptomatic, and the SMTs were found during a regular health examination. The other 5 patients had nonspecific symptoms such as epigastric pain, discomfort, heartburn, and foreign body sensation.

One-tunnel STER was successfully performed in all 12 patients, and the mean operation duration was 92.1 ± 40.8 minutes, with a mean tunnel length of 8.75 cm (range, 5–14 cm). A total of 30 SMTs were resected, of which 27 were located in the esophagus and 3 in the stomach, with no obvious complications. Of the 12, 4 of the patients had 2 SMTs located adjacent to each other, whereas the SMTs were at a distance of 1 to 6 cm in the other patients. The mean diameter was 15.0 ± 8.2 mm (range, 3–38 mm). Seven patients had a large SMT ≥2 cm in diameter. All the SMTs were resected en bloc and comprised of 28 leiomyomas and 2 gastric stromal tumors (classified as low-risk grade according to the National Comprehensive Cancer Network [NCCN] guideline).[12] The mean duration of hospital stay was 5.5 ± 1.0 days. No recurrence was noticed during a mean follow-up of 24.9 ± 15.3 months (range, 1–52 months).

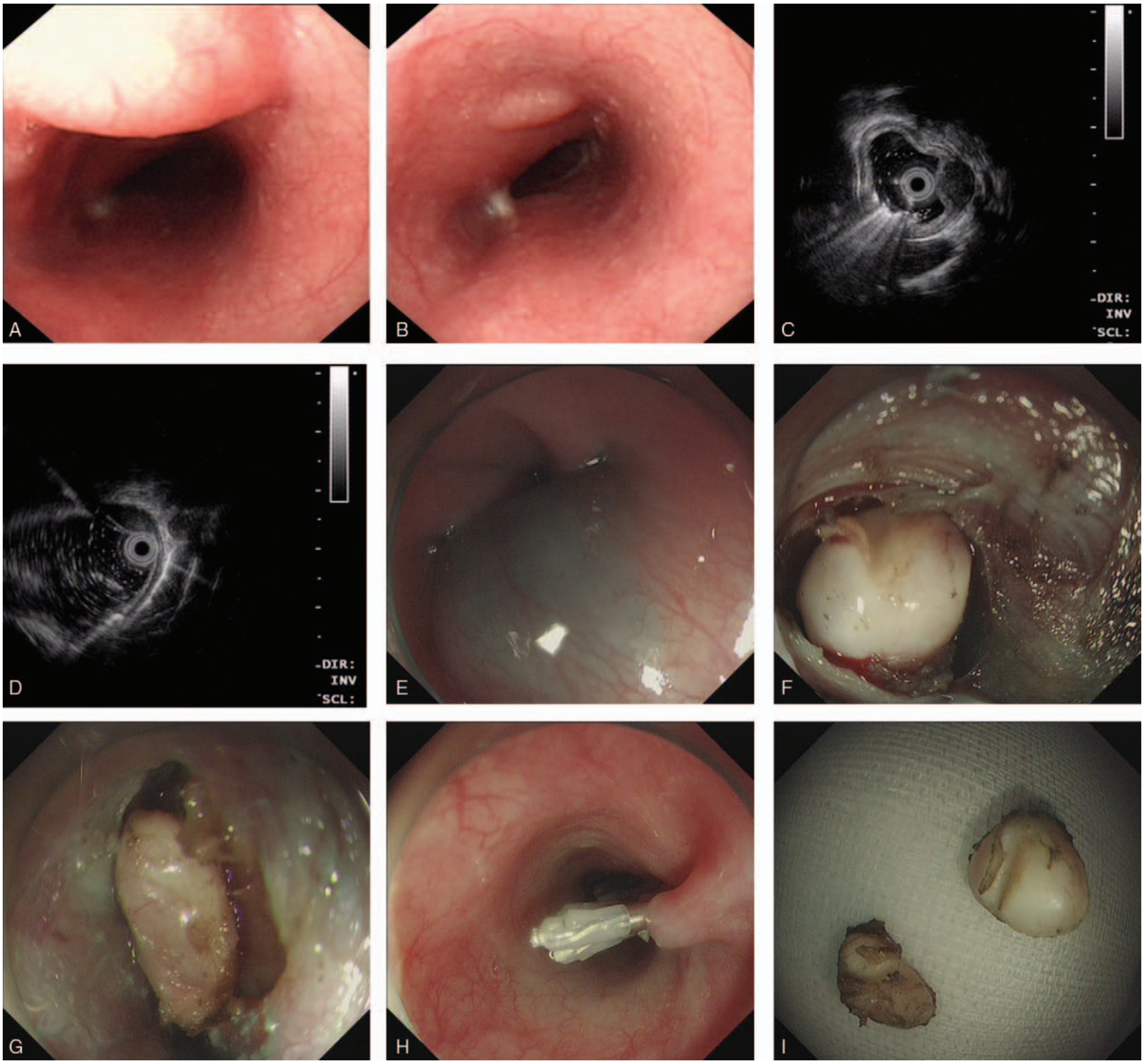

Figure 1. Case illustration of 1-tunnel submucosal tunneling endoscopic resection for multiple esophagus submucosal tumors (SMTs). A–B, Endoscopic images showing 2 SMTs, respectively; C–D, Endoscopic ultrasonography images showing 2 SMTs, respectively; E, Submucosal injection; F, Dissection of the first SMT; G, Dissection of the second SMT; H, The tunnel entry was closed with several clips; I, The resected 2 SMTs.

4. Discussion

In the present study, all the 30 upper GI-SMTs were resected en bloc by 1-tunnel STER method, and no obvious complication or recurrence was noticed, which suggests that 1-tunnel STER is a feasible and effective method for treatment of multiple upper GI-SMTs.

In most of the patients, upper GI-SMT is present as a solitary tumor. The occurrence of multiple upper GI-SMTs is a rare event, and only a few cases have been reported.[13–17] Most of the reported cases were found in the stomach in patients with familial gastrointestinal stromal tumors (GISTs) or neurofibromatosis type 1 and were diagnosed as GISTs.[13,16] In the present study, 10 patients had multiple SMTs in the esophagus, 1 patient had multiple SMTs in the stomach, and 1 had SMTs in both the esophagus and stomach. Further, 28 of the resected 30 SMTs were diagnosed as leiomyomas, and 2 were gastric GISTs.

Due to its rarity, no consensus has been reached regarding the treatment of multiple upper GI-SMTs, and the treatment is largely the same as with solitary SMTs, which include surgery and endoscopic treatment. Although surgery by an open or laparoscopic approach enables a thorough resection of all the SMTs, it is an invasive method associated with higher risk and cost. Endoscopic resection has been proven to be safe and effective for upper GI-SMTs no larger than 50 mm in diameter, and available methods include EBL, ESD, ESE, EFR, and STER.[1,2] Although all the above endoscopic methods are theoretically feasible, simultaneous endoscopic resection of multiple upper GI-SMTs by EBL, ESD, ESE, or EFR would enlarge the wound surface and increase the procedure duration, which potentially increases the risk of complications.

STER is a relatively novel endoscopic technique for the treatment of upper GI-SMTs originating from the MP layer.[2–5] The biggest advantage of STER is that it can maintain mucosal

Table 1

Clinical characteristics of the 12 patients.

Case NO.	Sex	Age, yr	Location	Complain	Tunnel length, cm	Diameter, mm	Tumor on opposite position, Yes/No	Operation time, min	Pathology	Hospital stay, days	Follow-up, months
1	Male	30	Esophagus (36 cm from the incisor), Cardia	Physical examination	11	25, 30	No	120	Leiomyoma	6	52
2	Female	57	Esophagus (25, 28 cm from the incisor)	Foreign body sensation	8	23, 10	No	75	Leiomyoma	7	46
3	Male	43	Esophagus (26 cm from the incisor)	Physical examination	6	20, 8	No	60	Leiomyoma	5	46
4	Male	45	Esophagus (38 cm from the incisor)	Heartburn	6	16, 8	No	60	Leiomyoma	5	35
5	Male	46	Esophagus (30, 35 cm from the incisor)	Physical examination	10	12, 8	No	70	Leiomyoma	5	21
6	Female	63	Esophagus (18, 21, 23 cm from the incisor)	Epigastric pain	10	25, 10, 10	No	80	Leiomyoma	4	20
7	Male	50	Gastric fundus	Physical examination	5	30, 6	No	150	Gastric stromal tumor (low risk)	7	19
8	Male	61	Esophagus (25, 33 cm from the incisor)	Physical examination	13	38, 15	No	110	Leiomyoma	6	16
9	Male	50	Esophagus (27, 30 cm from the incisor)	Epigastric pain	8	20, 15	Yes	80	Leiomyoma	5	16
10	Female	54	Esophagus (26 cm from the incisor)	Physical examination	6	12, 10	No	60	Leiomyoma	4	15
11	Male	47	Esophagus (23–32 cm from the incisor)	Epigastric discomfort	14	18, 16, 15, 10, 8, 7, 3	Yes	190	Leiomyoma	7	12
12	Male	39	Esophagus (26, 29 cm from the incisor)	Physical examination	8	16, 5	Yes	50	Leiomyoma	5	1

integrity. Further, STER has been demonstrated to be superior to surgical or other endoscopic methods in recent studies. We and 2 other groups have found similar efficacy between STER and thoracoscopic surgery for large esophageal leiomyoma. However, STER has been associated with a shorter operation time and hospital stay, as well as a decrease in hemoglobin levels and costs.[18–20] Wang et al[6] found that compared to ESD, STER can promote wound healing and reduce the operating duration and length of hospital stay, while it did not compromise the success rate or increase the rate of complications. Compared with ESE, STER is a preferable choice in terms of preventing air leakage symptoms for SMTs >10 mm in diameter.[7] Further, we found similar treatment efficacy between STER and EFTR for treating gastric GISTs, but patients who received STER had a shorter suture time and needed fewer number of clips to close the gastric-wall defect.[8] Additionally, within the submucosal tunnel, while STER enables complete resection of multiple SMTs with only 1 wound, other endoscopic treatments may leave multiple wounds, except in the case of adjacent SMTs.

However, some of the SMTs were not located in a straight line, or even in the opposite direction, rendering it difficult to include all of them in a straight submucosal tunnel. Only a few cases have been reported concerning STER for multiple GI-SMTs, and the maximal number of SMTs reported in a patient has been 3.[10,11,21,22] In the present study, 30 SMTs were found in 12 patients (the maximal number of SMTs was 7 in a patient),[23] and all of them were successfully removed by the STER technique within 1 tunnel. No obvious complication or recurrence was noticed, suggesting that 1-tunnel STER is feasible and effective for treating multiple upper GI-SMTs.

The STER technique has several complications. According to a large-scale study of 290 cases who underwent STER, the overall rate of complications was 23.4% (68/290), while only 10% required intervention for complications.[24] Among these complications, gas-related complications and pleural effusion were predominant, with most complications being regarded as normal postoperative changes in another similar technique - peroral endoscopic myotomy.[25] Further, the authors found that irregular shape, the location of tumor in the deep MP layer, long procedure time and air insufflation were risk factors for complications requiring intervention.[24] In the present study, no obvious complications occurred. Possible reasons include:

1. all the patients did not receive CT examination after STER, which is more sensitive in detecting complications such as gas-related complications, and pleural effusion compared to radiography. Thus, some minor complications may have been missed in the present study;
2. carbon dioxide insufflator rather than air insufflator was used in the present study;
3. the diameter of the SMTs was relatively small, and their shape was regular;
4. all the procedures were performed by an experienced endoscopist, who had performed more than 50 STER and 300 ESD procedures before conducting the study;
5. the small sample size may also be a reason for lack of complications noted in the present study.

STER is a relatively complex procedure, particularly for those with multiple SMTs, as technical modifications may be necessary compared to the procedure for a single SMT. Based on our experience, there are several points that may be helpful:

1. an awareness of the location of every SMT and creation of a submucosal tunnel along the virtual line on the axis where

most of the tumors are closely located to enable easy SMT location and reduce excessive submucosal dissection;

2. if it is difficult to find the SMT, extract the endoscope from the submucosal tunnel, and inject methylene blue at the site of the next SMT to locate the tumor and preset the tunnel route. If the SMTs are located on the opposite wall, a tortuous submucosal tunnel could be created;
3. it is recommended that all the SMTs be located before dissecting them. If the proximal SMT is too large to hinder the subsequent endoscopic procedure, dissect it before finding the next SMT.

There are several limitations to the present study. First, this was a single center, retrospective study. Second, only 12 cases, which is a relatively small sample size, were enrolled in the study due to the rarity of multiple upper GI-SMTs. In conclusion, our study shows that 1-tunnel STER is feasible and effective for treating multiple upper GI-SMTs originating from the MP layer. Randomized studies with large sample size are warranted to further confirm our conclusion.

Author contributions

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