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# Submucosal tunneling endoscopic resection of upper gastrointestinal tract tumors arising from muscularis propria

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**Abstract**

The management of incidentally discovered small upper gastrointestinal (GI) tract submucosal tumors (SMT) remains debatable. In this review, we summarize the evolving experience with submucosal tunneling endoscopic resection (STER) of upper GI SMTs originating from the muscularis propria. From 16 original studies, we reviewed a total of 703 patients with 736 lesions. Of these, 436 were located in the esophagus, 146 in the esophagogastric junction (EGJ) and 154 in the stomach. The composite complete resection rate (CRR) for STER of upper GI tumors arising from the muscularis propria layer was 99.8% (445/446). The composite CRR for STER of esophageal, EGJ and gastric SMTs arising from the muscularis propria layer was 100% (208/208),100% (78/78) and 100% (115/115), respectively. The composite *en bloc* resection rate (EBRR) for STER of upper GI tumors arising from the muscularis propria layer was 94.6% (679/718). The composite EBRR for STER of esophageal, EGJ and gastric SMTs arising from the muscularis propria layer was 98.6% (205/208), 96.2% (75/78) and 97.9% (95/97), respectively. Tumor recurrence rate was 0%. The reported complication rate for STER was high but the majority responded to conservative management. STER is a minimally invasive and efficacious alternative to surgery, especially for patients with small tumors (<3 cm). Careful selection of candidates remains crucial for excluding potentially malignant tumors.

**Keywords** Submucosal tunneling endoscopic resection, gastrointestinal tumor, muscularis propria

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## Introduction

With the widespread use of endoscopy in routine clinical practice and technological advances in endoscopic procedures and techniques, the incidence of gastric submucosal tumors has increased [1]. Upper gastrointestinal (GI) submucosal tumors, especially those <3 cm, are mostly benign in nature [2]. However, some tumors, such as mesenchymal neoplasms (including GI stromal tumors originating from the muscularis propria layer), can turn malignant [3]. In order to obtain an accurate diagnosis, needle biopsy is the first step. However, given the possibility of sampling errors when biopsy specimens are obtained, the malignant potential of the tumor cannot be ruled out completely [3]. Thus, in this case periodic endoscopic observations and/or endoscopic ultrasound (EUS) or resection are the only treatment options available for an asymptomatic GI submucosal tumor [4]. Patients generally opt for tumor resection because of issues with the cost, compliance, stress and the risk associated with repeated endoscopic procedures [5].

Various modalities exist for tumor resection, including surgical procedures (open, laparoscopic or thoracoscopic surgery) [6] and newer endoscopic techniques. Endoscopic submucosal dissection (ESD) has emerged as a potential endoscopic technique in patients with small GI submucosal tumors. However, this technique still has some risk of complications, such as perforation, massive bleeding and incomplete resection, especially for tumors that arise from the muscularis propria layer [5,7].

Submucosal tunneling endoscopic resection (STER) was inspired by ESD as a new technique for resection of upper GI submucosal tumors. In this technique, a submucosal tunnel is created to serve as a working space for endoscope insertion and resection of the tumor. This technique has a lower risk of perforation, since the integrity of GI mucosa is maintained; it offers better wound healing and a lower risk of infection when compared to ESD. Furthermore, this method is better suited

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for tumors arising from the muscularis propria layer, for which ESD resection is difficult because of the deeper tumor origin.

In this review, we summarize the safety and efficacy data on the usage of the STER technique for the resection of upper GI tumors arising from the muscularis propria layer. The indications, techniques, procedure time, length of hospital stay and complications are also discussed.

## Materials and methods

An extensive search of the English-language literature up to February 2016 was performed using PubMed and Google Scholar to identify peer-reviewed original and review articles. The keywords used were "submucosal tunneling endoscopic resection", "gastrointestinal tumor", and "muscularis propria". Only human studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered. The methodology for the selection of studies for our review is shown in Fig. 1.

## Results

Seventeen original articles were considered appropriate for inclusion in this review [8-24]. Two articles [14,24] were from same institute and the time frames of these studies overlapped. Hence, only the study [14] with the longer time interval was included in our review and the other study [24] was excluded to avoid duplication of data. Of the remaining 16 studies, three were case reports [13,16,22], nine were retrospective studies [8,11,12,14,15,17-19,21] and four were prospective studies [9,10,20,23]. All studies except two [16,23] were conducted in China [8-15,17-22], which could have led to bias in our results. The studies included only patients with tumors arising from the esophagus [21,22], EGJ [19,20], stomach [16-18], or a mix of those locations [8-15,23]. The studies are summarized in Table 1.

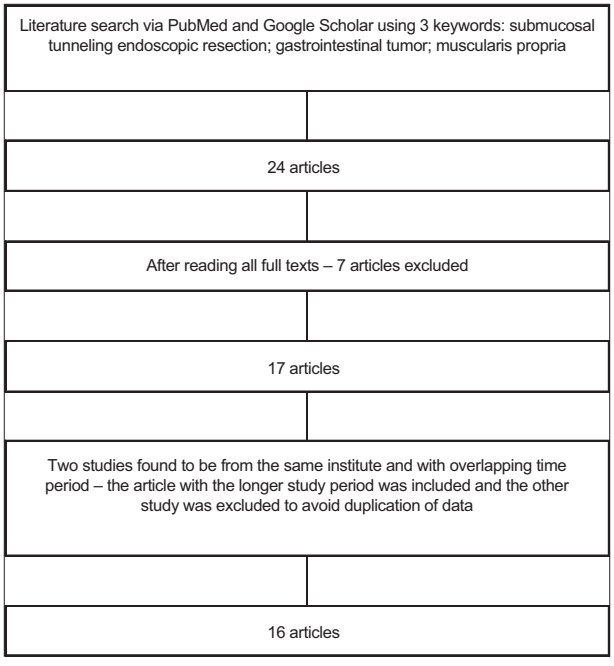


**Figure 1** Methodology for selection of articles for review

### Inclusion criteria

#### *Esophageal/EGJ origin*

Of the four studies, only two clearly described the inclusion criteria for the procedure [19-22]. All subjects had a tumor originating from the muscularis propria layer with a size cutoff ranging from 3.5 cm [20] to 5.5 cm [21], as confirmed by EUS and CT scan. In the study by Tan *et al*, all the patients had Zubrod-Eastern Cooperative Oncology Group (ECOG) performance status (this scale runs from 0 to 4, with 0 being fully functional and asymptomatic, and 4 being bedridden) of 0 or 1 and a histologically confirmed diagnosis of leiomyoma [21].

#### *Gastric origin*

Most of the studies included patients with a tumor originating from the muscularis propria layer with a size of <3 cm and absence of any high-risk features on EUS [16-18].

#### *Mixed*

Tumors originated from the muscularis propria layer, with a size ranging from 1-7.5 cm [9,23]; there was no evidence of any extra luminal growth [8,14,20], tumor or high risk features on EUS [9,12]. Innou *et al* had to offer surgical resection to 2 subjects (out of the initial 9) as there was limited endoscopic visualization due to a large tumor size (6.0 cm and 7.5 cm) [23].

### Exclusion criteria

In only 6 of the 15 reviewed studies were the exclusion criteria clearly defined. Common exclusion criteria included intolerance of anesthesia, refusal of consent, or blood coagulation disorders [9,12,14,20]. One study excluded patients with cardiovascular disease and those who had tumors in the gastric fundus or lesser curvature of the gastric antrum [12]. A few studies also included a tumor size greater than 3 cm among their exclusion criteria [14,15,20].

### Tumor characteristics

Among 703 patients with 736 lesions, there were 436 esophageal, 146 EGJ and 154 gastric SMTs arising from the muscularis propria layer of the GI tract. The size of

tumors originating in the esophagus or EGJ ranged from 0.6 cm to 5.5 cm [13,19-23], while for tumors originating in the gastric region the size ranged between 0.8 cm and 5.0 cm [13,16-18,23]. The other seven studies reported a single mean tumor size irrespective of the location, i.e. esophageal or gastric; hence, the results are not reported together with the above findings [8-12,14,15]. Overall [8-23], the authors reported STER for upper GI tract SMTs arising from the muscularis propria layer with sizes varying from as small as 0.6 cm [20] to as large as 7.0 cm [14].

The majority of resected tumors were leiomyomas [8-23] or GI stromal tumors (GIST) [8-10,12,14,15,17-20,23], with the minority including calcifying fibrous tumors [9,14,18], schwannomas [14,15,20], nerve sheath tumors [18], glomus tumors [10,14,18], intramuscular lipomas [20], aberrant pancreas [23], or granular cell tumors [20]. The heterogeneity among the tumor characteristics of patients across the individual studies is summarized in Table 1.

## Technique

A standard single accessory channel gastroscope (GIF-Q260J), a dual-channel gastroscope (GIF-2T240, Olympus), or a transparent cap (D-201-11802, Olympus) were the devices used by most physicians to perform the procedure [13-23]. One study described the use of a dual-channel endoscope (GIF-Q260J; Olympus) with a plastic fitted cap (MH-583; Olympus) [16].

All procedures were performed under general anesthesia and required a skilled and experienced endoscopic surgeon. Only one study described the experience of the performing endoscopic surgeon in terms of the number of ESD procedures conducted in the past [8].

In a porcine model, the ESD technique was used to create a submucosal tunnel and was shown to be a technically feasible and an effective access method for natural orifice transluminal endoscopic surgery (NOTES) [25]. This technique has been the basis for peroral endoscopic myotomy (POEM) for esophageal achalasia [26]. STER is a relatively new technique inspired from ESD and POEM for the treatment of upper GI tumors. A mucosal incision is made approximately 5 cm proximal to the SMT, followed by injection of dilute indigo carmine or methylene blue dye to create a mucosal bleb. A 2-cm incision is made at the top of the mucosal bleb [10]. This is followed by a submucosal tunnel, which is created by dissecting the muscle fibers [10]. Once the tumor is located, tumor enucleation is carried out under direct endoscopic visualization using an insulated tip knife, hook knife or hybrid knife depending on the surgeon's preference [10]. After tumor resection, the sub-mucosal tunnel is lavaged with normal saline and hemostasis is obtained [10]. Finally, the mucosal incision site is closed with 4-6 hemostatic clips.

## Procedure time

For tumors of esophageal or EGJ origin, the mean procedure time was 120.1 min (range: 15-365 min) [19-23]. For gastric tumors, the mean procedure time was shorter at 86.7 min (range: 25-320 min) [16-18,23]. Overall, the procedure time for STER of SMTs arising from the muscularis propria layer of the upper GI tract ranged from as short as 15 min [14, 20] to as long as 365 min [23].

A few subjects had more than one lesion, which would result in a longer total procedure time and could thus potentially create bias in the interpretation of above results. Details of the procedure times for each individual study are summarized in Table 1.

## Complication rate

There was a wide variation in the rate of reported complications across the studies, varying from as low as 0% [13,16,22,23] to as high as 42.9% [19]. The most common complications found in the studies were pneumothorax, subcutaneous emphysema, pneumomediastinum, pneumoperitoneum and pleural effusion [8-12,14,15,17-21]. Mucosal tunnel perforation and chest pain were reported in a few cases [12]. Esophageal fistula and diverticulum were rare [14]. The majority of the complications were managed conservatively with good outcomes [8-12,14,15,17-21]. In the study by Chen *et al*, the composite complication rate was 23.4% but only 10% of the procedures required an intervention for the management of complications [14]. Likewise, Wang *et al* reported a complication rate of 8.8%, but none of the patients required a repeat surgical intervention [12].

A few common adverse events, such as pneumothorax, pneumomediastinum, pneumoperitoneum and subcutaneous emphysema, are really consequences of the technique and not complications, as reported by authors from different studies. To give a better understanding of the true complication rate, we have compiled the individual incidence rate for adverse events across each study in Table 1.

## Post-procedure discharge instructions

Postoperative discharge instructions were provided for the patients in order to promote faster healing and reduce complications. In general, patients were advised to remain on nil per os for at least 24 h before resuming their normal diet [9,12-14,16,18-21]. Some studies instructed the patients to remain on only a liquid diet for 3 days before gradually returning to their normal diet over 2 weeks [12,13,21]. In one study, subjects underwent endoscopy the day after the procedure and a contrast study to rule out leakage before oral nutrition was permitted [23]. Apart from dietary instructions, patients were also prescribed intravenous/oral proton pump Inhibitors during and after the operation for a period of 3 days to around 4 weeks, depending on the surgeon's preference [8,9,12-21]. Antibiotics were also prescribed, usually for 3 days, to prevent any postoperative infections [12-15,18,20,21]. No specific choice of antibiotic therapy was mentioned in any of the studies. A few studies also prescribed homeostatic agents to prevent postoperative bleeding and ensure early recovery [8,17,18,20].

**Table 1** Summary of individual studies

| Author/Year/ Location | Study type | Inclusion criteria | Number of subjects | Number of lesions | Distribution of lesions | Mean size of lesion (range) | Pathologic diagnosis |
|---|---|---|---|---|---|---|---|
| Lu *et al* 2014, China [8] | Single-center, retrospective study | 1. Upper GI submucosal tumor (SMT) originating from muscularis propria (MP) layer between 2010-2014, confirmed by endoscopic ultrasound (EUS)<br>2. Size: <3 cm without extraluminal involvement confirmed by CT or S? | 42 | 45 | 1. Esophageal: 29<br>2. Gastric: 16 | 1.2 (0.8-1.6) | 1. Leiomyoma<br>2. Gastrointestinal stromal tumors (GIST) |
| Ye *et al* 2013, China [9] | Single-center, prospective study | 1. SMT originating from MP layer confirmed by EUS and CT<br>2. Size: <1-3 cm with no high risk features on EUS | 85 | 85 | 1. Esophageal: 60<br>2. Gastric: 25 | 1.9 (1.0-3.0) | 1. Leiomyoma<br>2. GIST<br>3. Calcifying fibrous tumor |
| Xu *et al* 2011, China [10] | Single-center, prospective study | Upper GI SMTs originating from MP layer between June 2010 and March 2011 | 15 | 15 | 1. Esophageal: 9<br>2. Gastric: 6 | 1.9 (1.2-3.0) | 1. Leiomyoma<br>2. GIST<br>3. Glomus tumor |
| Zhang *et al* 2014, China [11] | Single-center, retrospective study | Upper GI SMT arising from MP layer confirmed on EUS | 23 | 49 | 1. Esophageal: 42<br>2. Gastric: 7 | 1.5 (0.8-3.5) | Leiomyoma |

| Mean procedure time (min) (range) | Complications | Follow-up interval and modality | Complete resection rate (absolute number) | Tumor recurrence rate | *En bloc* resection rate (absolute number) |
|---|---|---|---|---|---|
| 84.4 (55.3-113.5) | Composite complication rate: data not available (DNA)<br>a. Perforation: 6/45 (13.3%)<br>b. Air leakage: 1/45 (2.2%) | 1. Surveillance endoscopy at 2 month (m) and 6 m post procedure and annually thereafter<br>2. Mean follow up: 8.7 m | Composite: 97.7% (44/45) | 0% | Composite: 97.7% (44/45) |
| 57.2 (30-115) | Composite complication rate: 9.4%<br>a. Pneumothorax: 6/85 (7.1%)<br>b. Subcutaneous emphysema: 8/84 (9.5%)<br>c. Pneumoperitoneum: 4/85 (4.7%) | 1. Surveillance endoscopy at 1,3,6 m and EUS for residual tumor at 3 m<br>2. Follow-up range: 2-19 m<br>3. For GIST: In addition to EUS and endoscopy for local recurrence, annual US abdomen, CT scan and CXR annually for distant metastasis (indefinitely) | 1.Esophageal: 100% (60/60)<br>2. Gastric: 100% (25/25) | 0% | 1. Esophageal: 100% (60/60)<br>2. Gastric: 100% (25/25) |
| 78.7 (25-130) | Composite complication rate: 13.3%<br>a. Pneumothorax and subcutaneous emphysema: 1/15 (6.7%)<br>c. Pneumoperitoneum: 1/15 (6.7%) | 1. Surveillance endoscopy and EUS at 1,2,4 and 6 m to assess healing and check for residual tumors<br>2. Follow-up range: 1-6 m | 1.Esophageal: 100% (9/9)<br>2. Gastric: 100% (6/6) | 0% | 1. Esophageal: 100% (9/9)<br>2. Gastric: 100% (6/6) |
| 40 (20-75) | Composite complication rate: DNA<br>a. Pneumothorax: 2/23 (8.7%)<br>b. Subcutaneous emphysema: 3/23 (13.0%)<br>c. Pneumomediastinum and pneumoperitoneum: 1/23 (4.3%)<br>d. Thoracic effusion: 2/23 (8.7%)<br>All complications were managed conservatively. | Follow-up range: 3-36 m (Median: 18 m) | 1.Esophageal: 100% (42/42)<br>2. Gastric: 100% (7/7) | 0% | 1. Esophageal: 100% (42/42)<br>2. Gastric: 100% (7/7) |

(*Contd...*)

**Table 1** *Continued...*

| Author/Year/ Location | Study type | Inclusion criteria | Number of subjects | Number of lesions | Distribution of lesions | Mean size of lesion (range) | Pathologic diagnosis |
|---|---|---|---|---|---|---|---|
| Wang *et al* 2015, China [12] | Single-center, retrospective study | 1. SMT originating from the MP layer confirmed by CT and EUS<br>2. EUS shows no high risk features of malignancy<br>3. No signs of metastasis or invasion outside digestive tract during CT<br>4. Age between 18-70 years and Zubrod-ECOG Performance status 0 or 1 | 80 | 83 | 1. Esophageal: 67<br>2. Gastric: 16 | 2.3 (1.0-5.5) | 1. Leiomyoma<br>2. GIST |
| Chen *et al* 2015, China [13] | Case report | Upper GI SMT arising from MP layer confirmed on EUS | 1 | 2 | 1. Esophageal: 1<br>2. Gastric: 1 | 1.Esophagus: 2.5 x 1.2 cm<br>2. Gastric: 3 x 1.5 cm | Leiomyoma |
| Chen *et al* 2016, China [14] | Retrospective study | SMT originated from the MP layer without restriction of extraluminal growth | 290 | 290 | 1. Esophagus: 199<br>2. EGJ: 68<br>3. Gastric: 23 | 2.1 (1.0-7.0) | 1. Leiomyoma<br>2. GIST<br>3. Calcifying fibrous tumor<br>4. Schwannomas<br>5. Glomus tumor |
| Liu *et al* 2013, China [15] | Retrospective study | Upper GI SMT arising from MP layer confirmed on EUS | 12 | 12 | 1. Esophageal: 7<br>2. Gastric: 5 | 1.9 (1.0-3.0) | 1. Leiomyoma<br>2. GIST<br>3. Schwannoma |
| Jeong *et al* 2015, Korea [16] | Case report | 1. SMT originating predominantly from the MP layer, confirmed on EUS<br>2. Size: 2 cm | 1 | 1 | Gastric: 1 | 2.5 | Leiomyoma |
| Lu *et al* 2014, China [17] | Retrospective study | 1. SMT originating from MP layer, confirmed on EUS<br>2. Size: 0.8-5.0 cm | 18 | 18 | Gastric: 18 | 2.1 (0.8-5.0) | 1. Leiomyoma<br>2. GIST |

| Mean procedure time (min) (range) | Complications | Follow-up interval and modality | Complete resection rate (absolute number) | Tumor recurrence rate | *En bloc* resection rate (absolute number) |
|---|---|---|---|---|---|
| 61.2 (25-160) | Composite complication rate: 8.8% (none required surgical intervention)<br>a. Pneumothorax: 1/80 (1.3%)<br>b. Subcutaneous emphysema: 2/80 (2.5%)<br>b. Mucosal perforation of tunnel: 1/80 (1.3%)<br>c. Chest pain: 3/80 (3.8%) | 1. Surveillance endoscopy at 1,3, 6 and 12 m and annually thereafter. EUS performed at 1 and 12 m<br>2. Follow-up range: 1-33 m (Mean: 10.2 m) | 1. Esophageal: 100% (67/67)<br>2. Gastric: 100% (16/16) | 0% | 1. Esophageal: 98.5% (66/67)<br>2. Gastric: 93.8% (15/16) |
| DNA | Composite complication rate: 0% | Endoscopy at day 6 and 1 m | 1. Esophageal: 100% (1/1)<br>2. Gastric: 100% (1/1) | 0% | 1. Esophageal: 100% (1/1)<br>2. Gastric: 100% (1/1) |
| 43 (15-200) | Composite complication rate: 23.4% (10% of procedures required intervention for the complication)<br>a. Subcutaneous emphysema: 61/290 (21.0%)<br>b. Pneumothorax: 22/290 (7.6%)<br>c. Pneumoperitoneum: 15/290 (5.2%)<br>d. Mucosal injury: 3/290 (1.0%)<br>e. Bleeding: 5/290 (1.7%)<br>f. Thoracic effusion: 49/290 (16.9%)<br>g. Esophageal pleural fistula: 1/290 (0.3%)<br>h. Esophageal diverticulum: 2/290 (0.7%) | 1. Standard endoscopy at 3,6 and 12 m and annually thereafter<br>2. CT scan was performed the day after the procedure to check for complications | DNA | 0% | Composite: 89.3% (259/290) |
| 78.3±25.5 (range 50-130) min | Composite complication rate: DNA<br>a. Subcutaneous and mediastinal emphysema: 8/12 (66.7%)<br>b. Pneumothorax: 4/12 (33.3%)<br>c. Pneumoperitoneum: 3/12 (25%)<br>d. Small pleural effusion: 2/12 (16.7%) | 1. Standard endoscopy and EUS at 2 and 6 m, annually thereafter<br>2. Follow-up range: 2-15 m (Mean: 7.1 m) | 1. Esophageal: 100% (7/7)<br>2. Gastric: 100% (5/5) | 0% | 1. Esophageal: 100% (7/7)<br>2. Gastric: 100% (5/5) |
| 90 | Composite complication rate: 0% | Surveillance endoscopy at 2 m | Gastric: 100% (1/1) | DNA | Gastric- 0% (0/1) |
| 75.1 (40-100) min | Composite complication rate: 11.1%<br>a. Perforation- 1/18 (5.6%)<br>b.Pneumoperitoneum - 1/18 (5.6%) | Standard endoscopy at 2 and 6 m, annually thereafter | Gastric: 100% (18/18) | DNA | DNA |

(*Contd...*)

**Table 1** *Continued...*

| Author/Year/ Location | Study type | Inclusion criteria | Number of subjects | Number of lesions | Distribution of lesions | Mean size of lesion (range) | Pathologic diagnosis |
|---|---|---|---|---|---|---|---|
| Li *et al* 2014, China [18] | Retrospective study | 1. SMT originating from MP layer, confirmed on EUS<br>2. Size: 1.0-5.0 cm | 32 | 32 | Gastric: 32 | 2.3 (1.0-5.0) | 1. Leiomyoma<br>2. GIST<br>3. Glomus tumor<br>4. Nerve sheath tumor<br>5. Calcifying fibrous tumor |
| Zhou *et al* 2015, China [19] | Retrospective study | SMT originating predominantly from the MP layer, confirmed by CT and EUS | 21 | 21 | EGJ: 21 | 2.3 (1.0-4.0) | 1. Leiomyoma<br>2. GIST |
| Wang *et al* 2014, China [20] | Prospective study | 1. SMT originating predominantly from the MP layer without restriction of extraluminal growth, confirmed by CT and EUS<br>2. Size of tumor: < 3.5 cm | 57 | 57 | EGJ: 57 | 2.2 (0.6-3.5) | 1. Leiomyoma<br>2. GIST<br>3. Intramuscular lipoma<br>4. Granular cell tumor<br>5. Schwannoma |
| Tan *et al* 2015, China [21] | Retrospective study | 1. SMT originating from the MP layer confirmed by CT and EUS with confirmed histologic diagnosis of leiomyoma<br>2. Size of lesion: 3.5–5.5 cm<br>3.Zubrod-ECOG performance status 0 or 1 | 18 | 18 | Esophageal: 18 | 4.1 (3.5-5.3) | Leiomyoma |
| Liu *et al* 2015, China [22] | Case report | SMT originating predominantly from the MP layer, confirmed by CT and EUS<br>2. Size: 5.0 x 3.0 cm | 1 | 1 | Esophageal: 1 | 5.5×3.5×3.0 | Leiomyoma |
| Inoue *et al* 2011, Japan [23] | Prospective study | Suspected or confirmed GIST or leiomyoma, confirmed on EUS<br>2. Size: > 2.0 cm<br>3. Observed growth on follow up | 7 | 7 | Esophageal: 3<br>2. Gastric: 4 | 1.Esophagus: 1.5 x 1.0 x 0.9 cm<br>2. Gastric: 2.1 x 1.4 x 1.1 cm | Leiomyoma<br>2. GIST<br>3. Aberrant pancreas |

| Mean procedure time (min) (range) | Complications | Follow-up interval and modality | Complete resection rate (absolute number) | Tumor recurrence rate | *En bloc* resection rate (absolute number) |
|---|---|---|---|---|---|
| 51.8 (25-125) min | Composite complication rate: DNA<br>a. Pneumothorax with subcutaneous emphysema- 3/32 (9.4%)<br>b. Pneumoperitoneum - 6/32 (18.8%)<br>c. Bleeding- 1/32 (3.1%)<br>d. Pleural effusion- 3/32 (9.4%)<br>e. Subphrenic infection- 1/32 (3.1%) | 1. Follow-up range: 6-32 m | Gastric: 100% (32/32) | 0% | Gastric: 100% (32/32) |
| 62.9 (45-90) min | Composite complication rate:42.9%<br>a. Perforation- 9/21 (42.9%) | 1. Surveillance endoscopy at 1, 3, 6 m and EUS at 3 m.<br>2. Follow-up range: 2-14 m | EGJ: 100% (21/21) | 0% | EGJ: 85.7% (18/21) |
| 47 (15-120) min | Composite complication rate: DNA<br>a. Subcutaneous emphysema- 12/57 (21.0%)<br>b. Pneumothorax- 5/57 (8.8%)<br>c. Pleural effusion- 2/57 (3.5%)<br>d. Pneumoperitoneum- 3/57 (5.2%) | Follow up range: 6-24 m | EGJ: 100% (57/57) | 0% | EGJ: 100% (57/57) |
| 75.00±27.17 min | Composite complication rate: 16.7%<br>a. Subcutaneous emphysema: 1/18 (5.6%) (conservative management)<br>b. Chest pain: 1/18 (5.6%) (conservative management)<br>c. Mucosal laceration: 1/18 (5.6%) (required metal stent placement) | 1. Surveillance endoscopy or barium swallow 1, 6 and 12 m and annually thereafter<br>2. Mean follow up: 10.9 m | Esophageal: 100% (18/18) | 0% | Esophageal: 88.9% (16/18) |
| 45 min | Composite complication rate: 0% | 1. Surveillance endoscopy 3, 6, and 12 m<br>2. Follow up period: 12 m | Esophageal: 100% (1/1) | 0% | Esophageal: 100% (1/1) |
| 1. Esophagus: 182.7 (90-365) min<br>2. Gastric- 129.8 (40-320) min | Composite complication rate: 0% | 1. Surveillance endoscopy on the day following procedure and then annually | 1. Esophageal: 100% (3/3)<br>2. Gastric: 100% (4/4) | DNA | 1. Esophageal: 100% (3/3)<br>2. Gastric: 100% (4/4) |

*SMT, submucosal tumor; MP, muscularis propria; EUS, endoscopic ultrasound; DNA, data not available; Min, minutes; M, month*

### Hospital stay duration

#### *Esophageal or EGJ origin*

The mean hospital stay duration varied from 2.7 to 6.0 days. Wang *et al* described a mean hospital stay duration of 2.7 days with a range of 2-6 days [20]. Zhou *et al* [19] and Tan *et al* [21] described mean hospital stay durations of 4.3 and 6.0 days, respectively, with ranges from 3-7 and 4.81-7.19 days.

#### *Gastric origin*

Only one [18] of the three studies [16-18] provided the details of hospital stay length for the planned intervention. Li *et al* reported a mean hospital stay duration of 3.9 days with a range of 2- 9 days [18].

#### *Mixed*

The mean hospital duration for studies including all tumors, irrespective of their location, varied from 3.2-5.4 days [9,11,12,14].

### Follow up

The follow-up period and modalities varied between different studies as per their protocols. Most of the authors reported using standard endoscopy to confirm the healing at the original site of the resected lesion and also to rule out any residual tumor or local recurrence [8-22]. These surveillance endoscopies were performed every 3-6 months over the first year post procedure and then annually thereafter. Few authors reported using EUS in addition to standard endoscopy as part of the post-procedure surveillance [9,10,12,15,19]. In the study by Ye *et al*, the authors reported using noninvasive tests such as CT scan, abdominal US and chest radiograph on an annual basis to rule out distant metastasis among subjects with GIST, in addition to the use of endoscopy and EUS to rule out local recurrence [9]. The follow-up interval varied widely across different studies and even within a given study, from as short as 1 month [10,12] to as long as 36 months [11]. The details from individual studies are summarized in Table 1.

## Outcome

The authors used two terms to define the outcomes in their respective studies. Complete resection rate (CRR) is used to define the percentage of subjects in whom total resection of the tumor was achieved. *En bloc* resection rate (EBRR) is used to define the percentage of subjects in whom the tumor was resected with an intact capsule. In our article, we reviewed 703 patients with 736 lesions from 16 individual studies, of which 436 were located in the esophagus, 146 in the EGJ and 154 in the stomach [8-23].

CRR was reported by all studies [8-13,15-23] except one [14]. One study did not reported location-specific CRR for STER of upper GI tract tumors [8]. Thus we could not include the data from this study while calculating location-specific CRR [8]. The composite CRR for STER of upper GI tract tumors arising from muscularis propria layer was 99.8% (445/446) [8-13,15-23]. The composite CRR for STER of esophageal, EGJ and gastric SMTs arising from MP layer was 100% (208/208) [9-13,15,21-23], 100% (78/78) [19,20] and 100% (115/115) [9-13,15-18,23] respectively.

EBRR was reported by all studies [8-16,18-23] except one [17]. Two studies did not reported location specific EBRR for STER of upper GI tract tumors [8,14]. Thus we could not combine the data from these studies while calculating location specific EBRR [8,14]. The composite EBRR for STER of upper GI tract tumors arising from the muscularis propria layer was 94.6% (679/718) [8-16,18-23]. The composite EBRR for STER of esophageal, EGJ and gastric SMTs arising from the muscularis propria layer was 98.6% (205/208) [9-13,15,21-23], 96.2% (75/78) [19,20] and 97.9% (95/97) [9-13,15,16,18,23], respectively. None of the studies reported any tumor recurrence after the initial STER procedure for upper GI tract tumors during the specified follow-up period [8-15,18-22].

## Concluding remarks

STER is a safe, minimally invasive and efficacious alternative approach to surgery for tumors arising from the muscularis propria layer, especially for patients with small tumors (<3 cm). The composite CRR for STER of upper GI tract tumors arising from the muscularis propria layer was 99.8% (445/446). The composite CRR for STER of esophageal, EGJ and gastric SMTs arising from the muscularis propria layer was 100% (208/208), 100% (78/78) and 100% (115/115), respectively. The composite EBRR for STER of upper GI tract tumors arising from the muscularis propria layer was 94.6% (679/718). The composite EBRR for STER of esophageal, EGJ and gastric SMTs arising from the muscularis propria layer was 98.6% (205/208), 96.2% (75/78) and 97.9% (95/97), respectively. The tumor recurrence rate was 0%. The overall reported complication rate for STER was high, but a very small percentage of these required secondary interventions and the majority responded to conservative management. The heterogeneity among the tumor characteristics of patients across the included studies should be taken into consideration when interpreting the above results. Furthermore, as the majority of the studies were from China, the conclusions from our review have potential for bias. Careful selection of candidates by preoperative endoscopy, EUS and cross-sectional imaging is important in order to identify benign and exclude potentially malignant tumors. The STER technique is currently restricted to specialized centers and is performed by highly qualified endoscopists. There is a need for head-to-head randomized controlled trials comparing STER to surgery and other available techniques, such as endoscopic full thickness resection, with a long follow up to guide future decisions in

our approach to upper GI submucosal tumors arising from the muscularis propria.

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