**Retrospective Study**

Predictors of difficulty of endoscopic resection for submucosal tumors originating from muscularis propria layer at the esophagogastric junction

Endoscopic resection of SMT at EGJ

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Abstract

BACKGROUND
Endoscopic resection approaches, including endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER) and endoscopic full-thickness resection (EFTR) have been widely used for the treatment of submucosal tumors (SMTs) located in the upper gastrointestinal tract. However, compared to the SMTs located in the esophagus or stomach, endoscopic resection of SMTs from the esophagogastric junction (EGJ) is much more difficult because of the sharp angle and narrow lumen of the EGJ. SMTs originating from the muscularis propria (MP) in EGJ, especially those grow extraluminally and adhere closely to the serosa, makes the endoscopic resection even more difficult.

AIM
To investigate the predictors of difficult endoscopic resection for SMTs from the MP layer at the EGJ.

METHODS
A total of 90 patients with SMTs from the MP layer at the EGJ were included in the present study. The difficulty of endoscopic resection is measured by long procedure time, failure of en bloc resection and intraoperative bleeding. Clinicopathological, endoscopic and follow-up data were collected and analyzed. Statistical analysis of independent risks for piecemeal resection, long operative time, and intraoperative bleeding were assessed using univariate and multivariate analyses.

RESULTS
According to the location and growth pattern of the tumor, 44 patients underwent STER, 14 patients underwent EFTR, and the remaining 32 patients received standard ESD procedure. The tumor size was 20.0 mm (range 5.0 - 100.0 mm). 47 out of 90 Lesions (52.2%) were regularly shaped. The overall en bloc resection rate was 84.4%.
The operation time was 43 min (range 16 - 126 min). Intraoperative bleeding rate was 18.9%. No adverse events that required therapeutic intervention occurred during or after the procedures. Surgical approach had no significant correlation with en bloc resection, long operative time and intraoperative bleeding. Large tumor size (≥30 mm) and irregular shape of the tumor were independent predictors for piecemeal resection (OR 7.346, P = 0.032 and OR 18.004, P = 0.029, respectively), long operative time (≥60 min) (OR 47.330, P = 0.000 and OR 6.863, P = 0.034, respectively) and intraoperative bleeding (OR 20.631, P = 0.002 and OR 19.020, P = 0.021, respectively).

CONCLUSION
Endoscopic resection is an effective treatment for SMTs in the MP layer at the EGJ. Tumors with large size and irregular shape were independent predictors for difficult endoscopic resection.

**Key Words:** Submucosal tumor; Esophagogastric junction; Muscularis propria; Submucosal tunneling endoscopic resection; Endoscopic submucosal dissection; Endoscopic full-thickness resection


**Core Tip:** The present study, for the first time, discussed the predictors of the difficulty of endoscopic resection, including various approaches of submucosal tunneling endoscopic resection (STER), endoscopic full-thickness resection (EFTR) and endoscopic submucosal dissection (ESD), for submucosal tumors (SMTs) originating from the muscularis propria (MP) layer at the esophagogastric junction (EGJ). Our data showed that tumors with greater size and irregular shape were the independent predictors of
difficult endoscopic resection, which is mainly measured by piecemeal resection, long operative time and intraoperative bleeding.

**INTRODUCTION**

Submucosal tumors (SMTs) of the esophagogastric junction (EGJ) are defined as tumors located partially or fully within the area 1 cm proximal to and 2 cm distal to the squamo-columnar junction [1]. Previously, a common view was that periodical endoscopic surveillance was recommended for SMTs smaller than 2.0 cm, which were generally considered benign [2–3], while surgical intervention was the preferred treatment for large lesions. However, some gastrointestinal stromal tumors (GISTs) have malignant potential [4]. The enlargement of tumor may deprive patients of the opportunity of minimally invasive surgery and lay a great psychological burden on patients. Furthermore, surgical resection of cardia may lead to lifelong gastroesophageal reflux and severely impair the quality of life in patients.

In the past decades, endoscopic therapeutic technology has developed rapidly. Endoscopic resection approaches, including endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER) and endoscopic full-thickness resection (EFTR) have been widely used for the treatment of SMTs located in the upper gastrointestinal tract [5–7]. However, compared to the SMTs located in the esophagus or stomach, endoscopic resection of SMTs from the EGJ is much more difficult because of the sharp angle and narrow lumen of the EGJ [8]. SMTs originating from the muscularis propria (MP) in EGJ, especially those grow extraluminally and adhere closely to the serosa, makes the endoscopic resection even more difficult accompanied with long operation time, failure of en bloc resection, perforation, intraoperative and delayed bleeding.

To date, there have been very few reports on the endoscopic excision of SMTs originating from the MP layer at the EGJ by ESD, STER or EFTR [9–12]. Only limited studies have demonstrated the predictors associated with the difficulty of endoscopic resection [13,14], which is mainly measured by long procedure time, failure of en bloc...
resection, or intraoperative and postoperative complications, including perforation and bleeding. The aim of the present study is to identify the predictors of technical difficulty during endoscopic resection of SMTs originating from the MP layer at the EGJ.

MATERIALS AND METHODS

Patients
This was a retrospective study including 90 consecutive patients admitted to Endoscopy Center, Shanghai East Hospital, Tongji University School of Medicine between March 2019 and March 2021. Patients who met the following criteria were included: (1) SMTs, which located at the EGJ, originating from the MP layer as confirmed by endoscopic ultrasonography (EUS) without restriction of extraluminal growth; (2) tumor size ≤100 mm; (3) age > 18 years, irrespective of gender; (4) no evidence of lymph node involvement or distant metastasis. The patients with severe cardiopulmonary diseases, coagulation disorders or take drugs to promote bleeding such as ticlopidine, aspirin or warfarin were excluded. All patients signed informed consent. The study protocol was in accordance with the guidelines for clinical research and was approved by the Institutional Review Board and the Ethical Review Committee of the Hospital.

Definitions
The tumor with an oval or globular shape was defined as regularly-shaped tumor, while the horseshoe-shaped, ginger-shaped, lobulated or polygonal tumor was classified as irregularly-shaped tumor. The tumor which was partially located above the anatomic EGJ with the distal edge failed to reach the squamo-columnar junction was considered as esophagocardiac tumor. The tumor of which the center was within the anatomic EGJ and that straddled the squamo-columnar junction was named cardiac tumor. The tumor that was partially located below the anatomic EGJ with the proximal edge failed to reach the squamo-columnar junction was defined as gastrocardiac tumor [15].
En bloc resection is defined as a tumor removed in a single piece, with the capsule intact. Complete resection is defined as a tumor removed with no apparent residual tumor at the resection site (assessed macroscopically by the endoscopist) and with negative margins on pathologic examination. A tumor with an oval or globular shape was defined as a tumor with regular shape [16]. Procedure time was defined as the time from the beginning of the injecting to the withdrawal of the endoscope. Intraoperative bleeding was defined as bleeding which could not be controlled by single session of hemocoagulation and needs multiple hemoclips and hemocoagulation. No visible bleeding or trivial bleeding which stops spontaneously or easily controlled by single session of hemocoagulation is classified into no bleeding group [17].

**Endoscopic equipment and accessories**

The operation was performed by a single-channel endoscope (GIF-Q260J, Olympus, Tokyo, Japan) and/or a dual-channel endoscope (GIF-2TQ260M, Olympus). A carbon dioxide insufflator (UCR, Olympus) was used in all the procedures. Other equipment and accessories included a high-frequency generator (VIO 200 D, ERBE, Germany), an argon plasma coagulation (APC 2, ERBE), an endoscopic flushing pump (Olympus Medical Systems), a transparent cap (D-201-11804, Olympus Medical Systems), an injection needle (VIN-23, COOK Medical Europe Ltd.), a HookKnife (KD-620LR, Olympus Medical Systems), a dual knife (KD-650L, Olympus Medical Systems), an insulated-tip knife (KD-611L, IT2, Olympus Medical Systems), sterile hot snare (MTN-PFS-A-28/23, MTN-PFS-E-36/23, Micro-Tech, Nanjing, China), hemostatic clips (ROCC-D-26-195-C, ROCC-F-26-195-C, Micro-Tech, Nanjing, China), and Coagrasper (HBF-23/2000, Micro-Tech, Nanjing, China). A mixed solution of glycerin fructose containing 10% glycerol, 5% fructose, and indigo carmine was used for submucosal injection.

**Procedures of endoscopic resection**

All patients received general anesthesia with endotracheal intubation. The patient was placed in a left lateral decubitus position. For tumors located in esophagocardiac or
cardiac region, STER was mainly selected. ESD was chosen for gastrocardiac SMTs. EFTR was chosen for the tumors with a predominant extraluminal growth pattern located in gastrocardiac region.

Briefly, ESD was performed in a standardized way starting with injection, mucosal incision, and submucosal dissection at the lesion’s distal margin[4]. Afterward, the tumor was dissected along the capsule. Any macroscopic vessels on the wound surface were electrically coagulated by argon plasma coagulation to prevent delayed bleeding, and metal clips were used to close the deeply dissected areas if needed. If there is muscularis defect after ESD, purse-string suture should be performed. The STER procedure includes creation of the submucosal tunnel, resection of the SMT, tumor retrieval, hemostasis and closure of the tunnel entry site with 4 to 6 metal clips(Figure 1)[18]. EFTR consists of five steps: marking of the tumor location, submucosal injection, exposure of the lesion, full-thickness resection and purse-string suture with Nylon loops and metal clip (Figure 2) [19].

Post-operative management

The post-operative observations mainly included complaints of chest or abdominal pain, fever, and gas-related complications such as subcutaneous emphysema, pneumothorax, pneumoperitoneum, and mediastinal emphysema. All patients fasted for one day and were administrated with proton pump inhibitor and antibiotics. The patients were started on fluid food first and gradually transitioned to a normal diet when there were no abnormal clinical manifestations.

Histopathological assessment

Resected specimens were fixed in 10% formalin for 48h. Immunohistochemical staining for CD117, CD34, smooth muscle actin (SMA), and S-100 markers were used to identify tumor subtype. The histological type was determined using the 2010 WHO classification of digestive tumors [20].

Follow-up

All patients were followed up with standard endoscopy at 3, 6, and 12 mo during the first year to observe the healing of the wound and to check for residual tumor or
recurrence and thereafter annually. For patients with gastrointestinal stromal tumors (GISTs), a contrastenhanced CT scan/MRI every 6 to 12 mo was recommended.

**Statistical analysis**

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 25.0, Chicago, IL, USA). Continuous variables were presented as median (range) and qualitative data were presented as frequencies. Statistical analysis of independent risks for piecemeal resection, long operative time, and intraoperative bleeding were assessed using univariate and multivariate analyses. The relationship between age and tumor size was analyzed by Pearson correlation analysis. *P*<0.05 was considered as the cut-off value for statistical significance.

**RESULTS**

**Clinical characteristics**

Ninety patients with SMTs originating from the MP layer at the EGJ were included in the present study (Table 1). There were 42 males and 48 females, with a mean age of 55.5 years (range 25.0–74.0 years). The tumor size was 20.0 mm (range 5.0–100.0 mm). The tumor size of GISTs was 18.0 mm (range 8.0–34.0 mm). 47 out of 90 lesions (52.2%) were regularly shaped, while the remaining lesions (43/90, 47.8%) were irregularly shaped. Of the 90 SMTs, 25 tumors were located in the esophagocardiac region, 26 tumors were located in the cardiac region, and 39 was defined as gastrocardiac tumor. In terms of the growth pattern, 17 tumors were predominantly extraluminal, and 73 were predominantly intracavitary. There was a significant negative correlation between age and tumor size (Figure 3A).

**Therapeutic outcomes and complications**

In the present study, 44 patients underwent STER, 14 patients underwent EFTR, and the remaining 32 patients received standard ESD procedure. The tumors with size larger than 4.0 cm accounted for 31.8%, 7.1% and 9.4% of all tumors in STER group, EFTR group and ESD group, respectively (Figure 3B). All lesions were successfully
removed and the complete resection rate was 100%. The operation time was 50 min (range 18–126 min) in STER group, 55 min (range 23–108 min) in EFTR group and 36 min (range 16–116 min) in ESD group. 76 out of 90 tumors were en bloc resected, whereas 14 Lesions underwent piecemeal resection. The en bloc resection rate was 77.3%, 92.9% and 90.6% in STER group, EFTR group and ESD group, respectively. Although the en bloc resection rate in STER group decreased compared to that in EFTR group and ESD group, the decrease is not statistically significant. The en bloc resection rate of GIST was 100% (18/18).

Intraoperative bleeding which needs multiple hemoclips and hemocoagulation occurred in 8 (8/44, 18.2%), 3 (3/14, 21.4%) and 6 (6/32, 18.8%) patients in STER group, EFTR group and ESD group, respectively (Table 2). None of the patients had bleeding more than 150 mL. No adverse events that required therapeutic intervention occurred during or after the procedures. All defects could be closed completely using metal clip or Purse-string suture with Nylon loops and metal clip if needed. A 20-gauge needle was used to relieve the pneumoperitoneum during EFTR. Two patients had low grade fever which was relieved quickly without any treatment during the post-operation period. Mild abdominal pain and chest pain which were spontaneously disappeared 2 days after procedure, were reported in 2 and 2 patients, respectively. None of the patients presented delayed bleeding, secondary peritoneal or abdominal infection, GI tract leak, or postoperative stenosis. There were 71 Leiomyoma (78.9%), 1 schwannomas (1.1 %), and 18 GISTs (20%, 11 with very low risk, 5 with low risk, 2 with moderate risk) (Table 1).

**Resection rate, procedure time and intraoperative bleeding**

As shown in Table 3, younger age (<60 years), tumors with larger size and irregular shape, and were significant risk factors for piecemeal resection. The piecemeal resection rate in tumors with large size and irregular shape was significantly higher than that in tumors with small size and regular shape, respectively. The piecemeal resection rate of tumors in patients with younger age (<60 years) was higher than that
with older age (>60 years). Other clinical characteristics including sex, tumor location, growth pattern, tumor surface, histopathology and surgical approach had no significant impact on piecemeal resection.

According to univariate and multivariate analysis, risk factors for long operative time (≥60 min) includes the shape and size of the tumor. As shown in Table 3, the tumor size in the group of long operative time (≥60 min) was significantly larger than that in the group of short operative time group (<60 min). Moreover, the most majority of tumor in the group of long operative time (≥60 min) exhibited an irregular shape, while the tumors in the group of short operative time group (<60 min) were prone to be regular.

Similarly, large tumor size and irregular shape were independent risk factors of intraoperative bleeding (Table 3). The occurrence of intraoperative bleeding had no significant correlation with age, sex, tumor location, surgical approach, growth pattern, tumor surface and histopathology.

**Follow-up**

The overall median follow-up period was 16.4 months (range 6.0-26.0 months), and all patients were free from stenosis of EGJ, residual, local recurrence or distant metastasis during the follow-up period. None of the patients died during the follow-up period.

**DISCUSSION**

The present study, for the first time, discussed the predictors of the difficulty of endoscopic resection, including various approaches of STER, EFTR and ESD, for SMTs originating from the MP layer at the EGJ. Our data showed that tumors with greater size and irregular shape were the independent predictors of piecemeal resection, long operative time and intraoperative bleeding.

To date, endoscopic resection has been considered as an effective, reliable and safe method to remove the SMTs in the deep layer of EGJ. The difficulty of endoscopic
resection is mainly measured by long procedure time, failure of en bloc resection, or intraoperative and postoperative complications. As previously reported, there were no serious complications during the operation, such as major bleeding, perforation or death, indicating that all complications were controllable [11][15][16][21]. In the present study, 90 SMTs which originated from the MP layer at the EG were included. The location of SMTs mainly determines which approach of endoscopic resection is chosen to remove the lesion. STER, which is developed by professor Xu Meidong for the resection of upper gastrointestinal SMTs originating from the MP layer, is the first choice for tumors located in esophagocardiac or cardiac region, since it has advantages in maintaining the integrity of gastroesophageal mucosa [18]. ESD is an alternative approach for resection of gastrocardiac SMTs for which the submucosal tunnel between the submucosal and MP layer is not always easy to create. EFTR was mainly selected for tumors with a predominant extraluminal growth pattern located in gastrocardiac region.

No major intraoperative or delayed bleeding and perforation occurred during the procedure. No sign of postoperative stenosis was found during the follow-up period. This may be related to the absence of circumferential lesions. There was a circular lesion in the middle esophagus in our center. No stenosis occurred after STER resection, but muscularis defect was the reason of diverticular appearance. Stenosis depends on the area of mucosal defect after ESD and EFTR resection.

Our data revealed that although there was no significant difference, the operation time in STER group and EFTR group increased compared to that in ESD group. This result may be attributed to the time required for creating the submucosal tunnel between the submucosal and MP layer to expose the lesion in STER group and for occluding the gastric-wall defect by loop-and-clip closure technique. The overall complete resection rate and en bloc resection rate was 100% and 84.4%, respectively. There was no significant difference in en bloc resection rate and intraoperative bleeding among the three groups.
We have evaluated the predictors of en bloc resection, long operative time and intraoperative bleeding. Tumors with greater size and irregular shape and younger age (<60 years) were significant risk factors for piecemeal resection. Tumors with greater size and irregular shape were the significant contributors to piecemeal resection. Chen T. et al reported that STER provided a 90.6% en bloc resection rate for upper gastrointestinal SMTs [16]. However, in the present study, the en bloc resection rate in STER group was only 77.3%, which is lower than that in ESD group or EFTR group. In Chen’s study, the maximum size of the tumor was 5.0cm in diameter, since they considered that implementation of STER for SMTs with a long diameter ≤ 5.0cm and a transverse diameter ≤ 3.5cm could facilitate a high en bloc resection rate [6]. In the present study, the maximum tumor size was 9.0cm and the tumors with size larger than 4.0cm accounted for 31.8% of all tumors in STER group. Furthermore, the percentage of irregular shaped tumor in STER group was 63.6%, which was significantly higher than that in ESD and EFTR group. Tumors with large size and irregular shape would be difficult for endoscopists to successfully achieve en bloc resection by STER because of limited space and poor exposure of operative filed in the created submucosal tunnel. In addition, although some large lesions were resected intacty, it was difficult to remove them integrally from the submucosal tunnel due to the high risk of laceration of mucosa in the entrance of the tunnel[18][22]. Importantly, the vast majority of lesions that received piecemeal resection in the present study were leiomyomas. Similar to the previous studies, our data demonstrated that there was no residue or recurrence in lesions that received piecemeal resection during the follow-up period [16][23]. Interestingly, younger age (< 60 yrs) is one of the independent predictors of piecemeal resection. We considered that the unexpected result was mainly due to the significant negative correlation between tumor size and age.

Similarly, large size and irregular shape were independent predictors for procedures requiring a long operative time (≥ 60min). Previous study suggested that the maximum size of the lesion removed by STER should be less than 35 mm in diameter, since the large tumor size and narrow lumen in the submucosal tunnel may result in
limited operative field[24]. However, there was controversial opinion considering that
the improvement and maturity of STER technology made the resection of large-
size tumor become feasible. In the present study, the maximum size of lesion removed
successfully by STER is 90 mm with no recurrence during follow-up. Furthermore, for
resection of tumors at the EGJ, it is crucial to inject a small dose of indigo carmine into
the submucosa around the tumor location in order to aid in orientating the submucosal
tunnel, subsequently decreasing the procedure time. The risk of aspiration pneumonia,
deep venous thrombosis, and cardiorespiratory distress may increase because of the
long procedure time. Thus, it is necessary to fully evaluate the size and shape of the
tumor by EUS and radiological examination before the procedure. Tumors with greater
size and irregular shape were also independent predictors for intraoperative
bleeding. For irregular-shaped large tumors, extra care should be paid to fully expose
and pre-treat the blood vessels to prevent bleeding.

The current study has several limitations. First, this study is a single-center
retrospective study with a relatively small sample size, which may result in the
development between the approach of endoscopic resection and tumor size. Secondly, the
procedures of endoscopic resection were not performed by the same endoscopist.
Short follow-up period (range 6-26 mo) is the third limitation. Thus, a prospective,
large-scale, randomized controlled study with a long-term follow-up period is
necessary in the future to validate the results observed.

CONCLUSION
Endoscopic resection is effective and safe for SMTs in the MP layer at the EGJ. Tumors
with large size and irregular shape were independent predictors for piecemeal
resection, long operation time and intraoperative bleeding.

ARTICLE HIGHLIGHTS
Research background
Submucosal tumors (SMTs) from the esophagogastric junction (EGJ) is much more difficult to resect because of the sharp angle and narrow lumen of the EGJ. SMTs originating from the muscularis propria (MP) in EGJ, especially those grow extraluminally and adhere closely to the serosa, makes the endoscopic resection even more difficult.

Research motivation
Endoscopic resection approaches, including endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER) and endoscopic full-thickness resection (EFTR) have been widely used for the treatment of SMTs from the MP layer at the EGJ. Only limited studies have demonstrated the predictors associated with the difficulty of endoscopic resection.

Research objectives
The aim of this study was to investigate the predictors of difficult endoscopic resection for SMTs from the MP layer at the EGJ.

Research methods
A total of 90 patients with SMTs from the MP layer at the EGJ were included in the present study. The difficulty of endoscopic resection is measured by long procedure time, failure of en bloc resection and intraoperative bleeding. Clinicopathological, endoscopic and follow-up data were collected and analyzed. Statistical analysis of independent risks for piecemeal resection, long operative time, and intraoperative bleeding were assessed using univariate and multivariate analyses.

Research results
No adverse events that required therapeutic intervention occurred during or after the procedures. Surgical approach had no significant correlation with en bloc resection, long operative time and intraoperative bleeding. Large tumor size (≥ 30 mm) and
irregular shape of the tumor were independent predictors for piecemeal resection (OR 7.346, \(P = 0.032\) and OR 18.004, \(P = 0.029\), respectively), long operative time (\(\geq 60\) min) (OR 47.330, \(P = 0.000\) and OR 6.863, \(P = 0.034\), respectively) and intraoperative bleeding (OR 20.631, \(P = 0.002\) and OR 19.020, \(P = 0.021\), respectively).

**Research conclusions**

Endoscopic resection is an effective treatment for SMTs in the MP layer at the EGJ. Tumors with large size and irregular shape were independent predictors for difficult endoscopic resection.

**Research perspectives**

The current study may provide a useful reference for operators during endoscopic resection of SMTs originating from the MP layer at the EGJ in the future.
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