Endoscopic resection of upper GI extraluminal tumors (with videos)

Li-Yun Ma, MD,[1,*] Zu-Qiang Liu, MD,[1,*] Lu Yao, MD,[1] Mei-Dong Xu, MD,[1] Shi-Yao Chen, MD,[1] Yun-Shi Zhong, MD,[1] Yi-Qun Zhang, MD,[1] Wei-Feng Chen, MD,[1] Li-Li Ma, MD,[1] Wen-Zheng Qin, MD,[1] Jian-Wei Hu, MD,[1] Ming-Yan Cai, MD, FASGE,[1] Li-Qing Yao, MD,[1] Quan-Lin Li, MD,[1,2] Ping-Hong Zhou, MD FASGE[1,2]

Shanghai, China

Background and Aims: Endoscopic resection is a feasible treatment for GI extraluminal tumors but remains a challenging procedure with limited data. In this study, we assessed the safety and efficacy of endoscopic resection for extraluminal tumors in the upper GI tract.

Methods: From May 2016 to December 2021, 109 patients undergoing endoscopic resection for extraluminal tumors in the upper GI tract were retrospectively included. Clinicopathologic characteristics, procedure-related parameters, adverse events (AEs), and follow-up outcomes were analyzed.

Results: The en-bloc tumor resection rate was 94.5% and en-bloc retrieval rate 86.2%. Statistical analysis revealed tumor size $\geq$3.0 cm and irregular shape as significant risk factors for piecemeal extraction. Resection time and suture time were 46.8 $\pm$ 33.6 minutes and 20.6 $\pm$ 20.1 minutes, respectively. Large tumor size was significantly associated with a longer procedure duration. Five patients (4.6%) experienced major AEs, including recurrent laryngeal nerve injury, hydrothorax, major bleeding, local peritonitis, duodenal leakage, and repeat endoscopic surgery for tumor extraction. Minor AEs occurred in 13 patients (11.9%). Irregular tumor shape and tumor location (duodenum) were significantly associated with AE occurrence. Mean postoperative hospital stay was 4.7 $\pm$ 3.3 days. No recurrence or metastasis was observed during the mean follow-up period of 31.8 $\pm$ 15.2 months.

Conclusions: Endoscopic resection is a safe and feasible therapeutic approach for upper GI extraluminal tumors. Tumor size, shape, and location impact the difficulty and safety of the procedure. Endoscopic resection of duodenal tumors is also feasible but associated with an increased risk of AEs compared with tumors in other locations. (Gastrointest Endosc 2022;96:752-63.)

(footnotes appear on last page of article)

Upper GI submucosal tumors (SMTs) are typically covered by normal mucosal layers and detected by endoscopy or CT, after which the layers are determined by EUS. Some SMTs originate from the muscularis propria or serosa and present with a predominantly extraluminal growth pattern, whereas others originate from extraluminal tissues (eg, mediastinum, omentum, and mesentery) and externally compress the lumen.[1] These extraluminal or predominantly extraluminal tumors tend to be more aggressive than more common SMTs.[1,2] Thus, complete resection is required for curative treatment.[1]

This video can be viewed directly from the GIE website or by using the QR code and your mobile device. Download a free QR code scanner by searching "QR Scanner" in your mobile device's app store.

Traditionally, laparoscopic wedge resection with a linear stapler has been the standard therapy for the management of upper GI extraluminal SMTs. Neither lymphadenectomy nor wide resection margins are required routinely because most SMTs, including GI stromal tumors (GISTs), rarely metastasize to regional lymph nodes.[3,4] Although laparoscopic surgery is generally more convenient than open surgery, lesions near the esophagogastric junction (EGJ) or pyloric ring are difficult to perform using laparoscopic methods because of the anatomic structure.[1,4,5]

With the advance of endoscopic techniques, endoscopic surgery including endoscopic full-thickness resection (EFTR) and submucosal tunneling endoscopic resection (STER) may provide minimally invasive approaches for the safe resection of extraluminal tumors. Several studies have reported cases of endoscopic resection of extraluminal SMTs.[1,6,7] However, these procedures remain challenging because of the difficulty of operation and the high risk of perforation or infection. Currently, limited data are available regarding the safety and efficacy of these procedures. Notably, more than 100 cases of endoscopic resections for extraluminal tumors have been performed at our center since 2016. Therefore, we assessed the safety and efficacy of the procedures to fill this knowledge gap.

METHODS

Patients

We retrospectively reviewed the medical records of 110 consecutive patients who underwent endoscopic surgery for extraluminal tumors at Zhongshan Hospital, Fudan University, Shanghai, China between May 2016 and December 2021. One hundred nine patients with extraluminal tumors underwent endoscopic resection, and 1 patient was terminated after full-thickness myotomy. The terminated patient had a 2.5-cm completely extraluminal tumor in the greater curvature of the stomach. The tumor was densely adhered to the peritoneal tissue and could not be dissected under endoscopy because of a partial gastrectomy 2 years earlier. For safety, the patient was converted to open surgery and was discharged uneventfully on postoperative day 6. The remaining 109 patients were included in this study for further analysis (Fig. 1).

SMTs were initially diagnosed by endoscopy, EUS, and CT, whereas EUS-FNA biopsy sampling was not performed on tumors that had been planned for resection. Extraluminal tumors were defined as tumors originating from surrounding tissues, or SMTs with >50% exophytic tumor growth. Patients were selected for endoscopic procedures if they met the following inclusion criteria: tumor predominantly located outside the GI lining (>50%) or originating from the surrounding tissues, such as the mediastinum, omentum, and mesentery, based on CT and EUS examinations and confirmed during surgery; tumor closely adjacent to the GI wall; tumor cross-sectional diameter of $\leq$5.0 cm; and no evidence of metastatic lesions detected by chest and abdominal CT. SMTs <2 cm were also resected if patients indicated a preference for resection over surveillance. Exclusion criteria were cardiopulmonary diseases that contraindicated general anesthesia or coagulation disorders.

The study and procedures were conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki. This study was approved by the Ethics Committee of Zhongshan Hospital (B2021-864), and informed consent was obtained from all patients for all procedures and interventions.

Endoscopic equipment and accessories

All procedures were performed using a standard single-channel endoscope (GIF-Q260J; Olympus Optical Co, Ltd, Tokyo, Japan) with a transparent cap (D-201-11804; Olympus Optical Co, Ltd) attached to the tip of the endoscope to obtain better visualization. Other equipment included a T-type hybrid knife (Erbe, Tuebingen, Germany), insulated-tip knife (KD-611L; Olympus Optical Co, Ltd), hook knife (KD-620LR; Olympus Optical Co, Ltd), hemostatic forceps (FD-410LR; Olympus Optical Co, Ltd), high-frequency electrosurgical generator (VIO 200D; Erbe), argon plasma coagulation system (APC 300; Erbe), snare (SD-230U-20; Olympus Optical Co, Ltd), CO_2 insufflator (Olympus Optical Co, Ltd), and EUS machine (GF-UE260-AL5; Olympus Optical Co, Ltd).

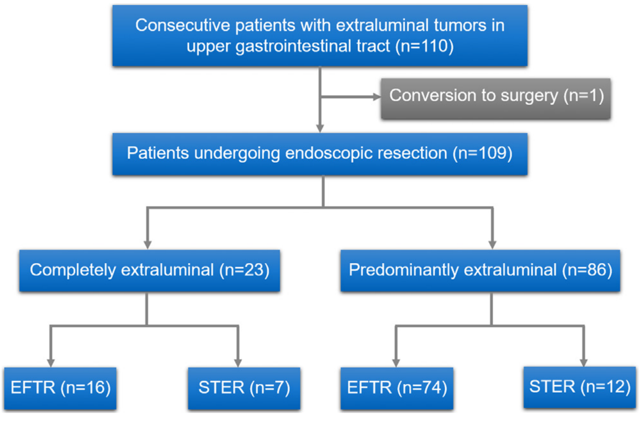

Figure 1. Flowchart of patients and lesions. *EFTR*, Endoscopic full-thickness resection; *STER*, submucosal tunneling endoscopic resection.

Procedures

All procedures were performed by 15 endoscopists with experience in more than 100 cases of advanced endoscopic surgeries, including STER, EFTR, and peroral endoscopic myotomy. The operators were classified into 3 levels based on their endoscopic resection experience, including junior endoscopists (with over 5 years of experience), intermediate endoscopists (with over 8 years of experience), and senior endoscopists (with over 12 years of experience). The junior endoscopists performed the procedures under the surveillance of senior endoscopists. All patients were under general anesthesia with endotracheal intubation. Prophylactic intravenous antibiotics were administered 30 minutes before the procedure. CO_2 was used routinely during the operating procedure. A 20-gauge needle was inserted into the right lower quadrant to relieve intraoperative pneumoperitoneum when necessary. After the procedure, a nasogastric tube was placed for decompression and active monitoring of bleeding.

STER procedure

STER was chosen for patients with tumors located at the lower esophagus, gastric cardia, or greater curvature of the stomach. The procedure was performed in several steps, as previously reported[1,8] (Fig. 2A and Fig. 3). After injecting a mixture of normal saline solution, indigo carmine, and epinephrine into the submucosa, a 2-cm longitudinal mucosal incision was made 3 to 5 cm above the tumor site. A submucosal tunnel was created toward the tumor location between the mucosal and muscular layers. Full-thickness myotomy was then performed above the estimated tumor location. The tumor and surrounding connective tissue were carefully resected, ensuring that the tumor capsule remained intact. The tumor was subsequently extracted using a snare or retrieval basket. Large tumors that were difficult to pass through the submucosal tunnel or cardia were subjected to piecemeal retrieval using a snare or hook knife. The Effect 1-4-1 (effect 1, cutting width 4, cutting time interval 1) mode with the most electric cutting components and the least electric coagulation components was recommended. Repeat endoscopic retrieval on the next day when the tumor was partly softened by gastric acid was also feasible in the interest of safety. After careful hemostasis in the tunnel and tumor sites, the mucosal incision was closed using several hemostatic clips in a zipper fashion, with or without nylon rope to avoid mucosal leakage. A gentle suction could be performed to bring the mucosa close to the submucosa before releasing the clips (Video 1, available online at www.giejournal.org).

EFTR procedure

EFTR was selected for patients with tumors located near the gastric fundus (Fig. 2B and Fig. 4), antrum, lesser curvature of the stomach, or duodenum (Fig. 2C and Fig. 5), because submucosal tunneling is not feasible for these anatomic locations.[9] EFTR was performed as previously described and included several steps.[4] The border of the lesion was marked with several dots according to the tumor compression on the GI wall as well as EUS and CT results. After submucosal injection of a mixture containing saline solution, indigo carmine, and epinephrine, the mucosal and submucosal layers surrounding the lesion were cut. Full-thickness myotomy was then performed, followed by gradual intentional perforation. Next, the tumor was carefully dissected from the surrounding muscularis propria, serosa, or omentum. Dental floss traction was used if needed to stabilize the movable tumor. The tumor was extracted by either a snare or retrieval basket. The mucosal incision could be enlarged to extract the extraluminal tumors smoothly. Piecemeal resection in the peritoneal cavity was avoided to prevent tumor implantation and metastasis. The piecemeal methods were the same as above. The defect was closed using nylon rope and clips after careful hemostasis. Biogel was used as needed to promote incision healing and reduce the risk of leakage where needed (Videos 2 and 3, available online at www.giejournal.org).

Postoperative management

Prophylactic antibiotics were administered for the first 48 hours postoperatively if no adverse events (AEs) were observed. If the patient reported chest or abdominal pain, thorac or abdominal CT was performed to determine the occurrence of hydrothorax, pneumothorax, seroperitoneum, or pneumoperitoneum. All patients remained fasting for the first 24 hours after surgery. A liquid diet was permitted on postoperative day 2, and oral intake was gradually increased to a normal diet over the next 2 weeks if no adverse symptoms (eg, fever, dyspnea, chest pain, abdominal pain) occurred.

Histopathology

Surgical specimens were fixed in 10% formalin solution, embedded with paraffin, and sectioned for pathologic examination following standard procedures. Hematoxylin and eosin and immunohistochemical staining were carried out to determine the characteristic of the tumors. For GISTs, the number of mitotic figures per 50 high-power fields was counted. Risk classification was performed according to the revised National Institutes of Health grading system reported by Joensuu.[10]

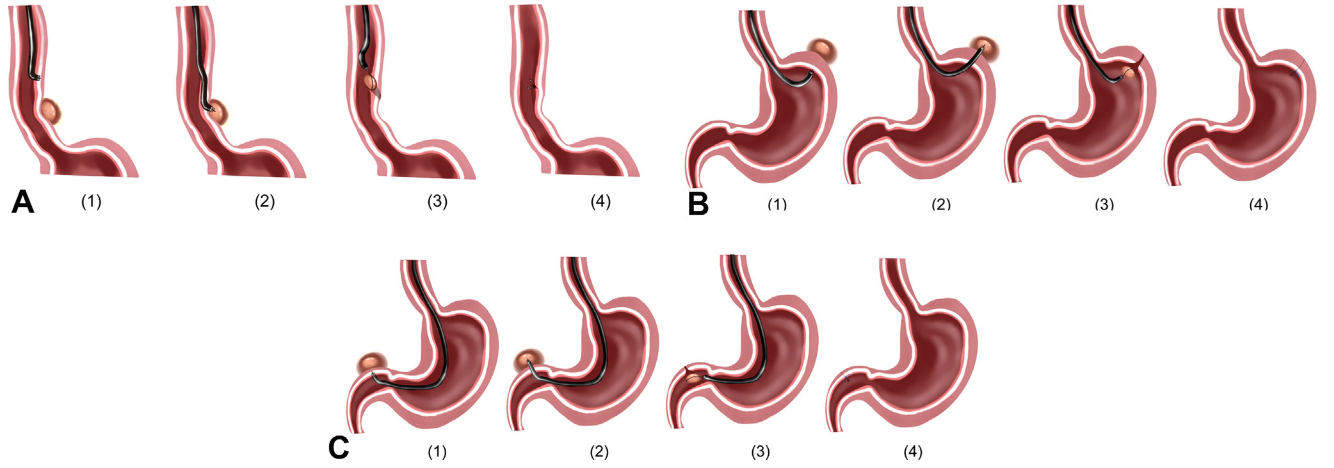

Figure 2. Endoscopic surgery for extraluminal tumors. **A,** Submucosal tunneling endoscopic resection of esophageal extraluminal tumors: *(1)* mucosal incision, *(2)* submucosal tunneling and full-thickness myotomy, *(3)* tumor dissection and retrieval, and *(4)* tunnel closure. **B,** Endoscopic full-thickness resection of gastric extraluminal tumors: *(1)* mucosal incision, *(2)* full-thickness myotomy, *(3)* tumor dissection and retrieval, and *(4)* defect closure. **C,** Endoscopic full-thickness resection of duodenal predominant extraluminal tumors: *(1)* mucosal incision, *(2)* full-thickness myotomy, *(3)* tumor dissection and retrieval, and *(4)* defect closure.

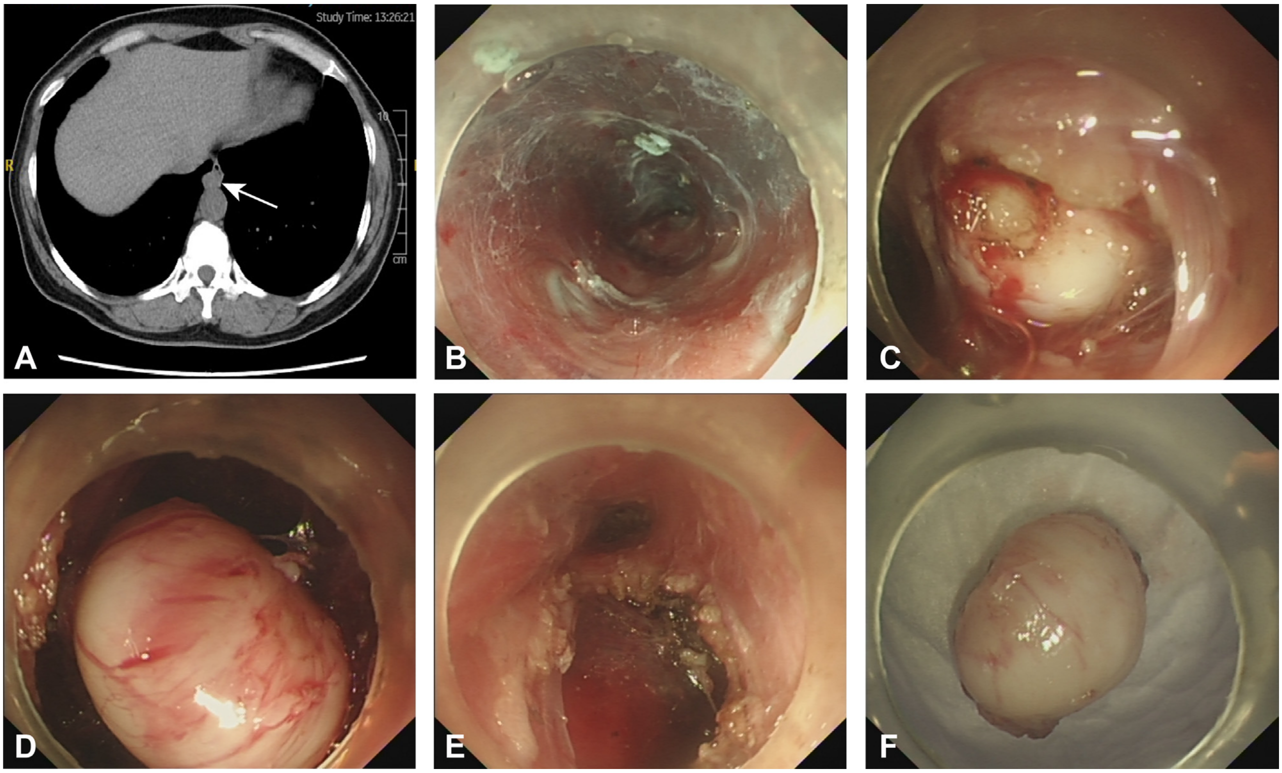

Figure 3. Submucosal tunneling endoscopic resection of an esophageal extraluminal tumor. **A,** CT showing the location of the extraluminal tumor near the cardia (*arrow*). **B,** Established submucosal tunnel 5 cm proximal to the tumor site. **C,** Exposed tumor after full-thickness myotomy. **D,** Tumor dissection. **E,** Endoscopic view in the submucosal tunnel after tumor removal. **F,** Resected tumor.

Outcome definitions

Resection time was defined as the time from mucosal incision to tumor removal. Suture time was defined as the time from attaching the first clips to complete closure of the mucosal defect. The tumor shape was considered "regular" if it was oval or globular. Complete en-bloc resection was defined as resection of the tumor with the capsule intact. En-bloc retrieval was defined as the complete retrieval of an en-bloc tumor with an intact tumor capsule through the oral cavity.[1] Tumor size was determined by measuring both the longest and shortest diameters on the final retrieved specimen.

AEs were assessed according to the American Society for Gastrointestinal Endoscopy lexicon of endoscopic AEs[11] and the Clavien-Dindo grading system.[12] AEs grading "moderate" to "fatal" by American Society for Gastrointestinal Endoscopy grading or "III to IV" by Clavien-Dindo grading were defined as major AEs, which were associated with an altered clinical course. Major AEs potentially related to our procedures included pneumothorax, hydrothorax, abdominal cavity, or procedure area effusion requiring therapeutic intervention; major bleeding (>200 mL); repeat endoscopy for an AE; leakage; and nerve injury.[13] Minor AEs included mild mucosal injuries that were repaired during the procedure, without any severe consequences, and inconsequential febrile episode (>38.5°C) that resolved in 3 days with antibiotic treatment.[14]

A small amount of effusion in the thorax or abdomen or a small volume of CO_2 in the thorax, mediastinum, subcutis, or abdomen can be spontaneously absorbed, resulting in minimal clinical impacts or symptoms. Thus, these minor technical AEs were not defined as AEs in this study.[13] Moreover, perforation at the resection site was expected, not accidental, and was likewise not classified as an AE.

Follow-up

Patients were assessed by standard endoscopy and CT at 3, 6, and 12 months after the procedure to evaluate wound healing and detect the presence of residual tumor or recurrence. Subsequently, patients were followed yearly.

Data collection and statistical analysis

Data including patient demographics, preoperative EUS and CT results, procedure-related information, tumor histology, postoperative examination results, AEs, length of hospital stay, and follow-up results were collected. Commercial software (IBM SPSS Statistics 20; SPSS Inc, Chicago, Ill, USA) was used for statistical analysis, with $P < .05$ taken to be statistically significant. The results are expressed as mean ± standard deviation or number (percentage), except where otherwise indicated. The odds ratio (OR)

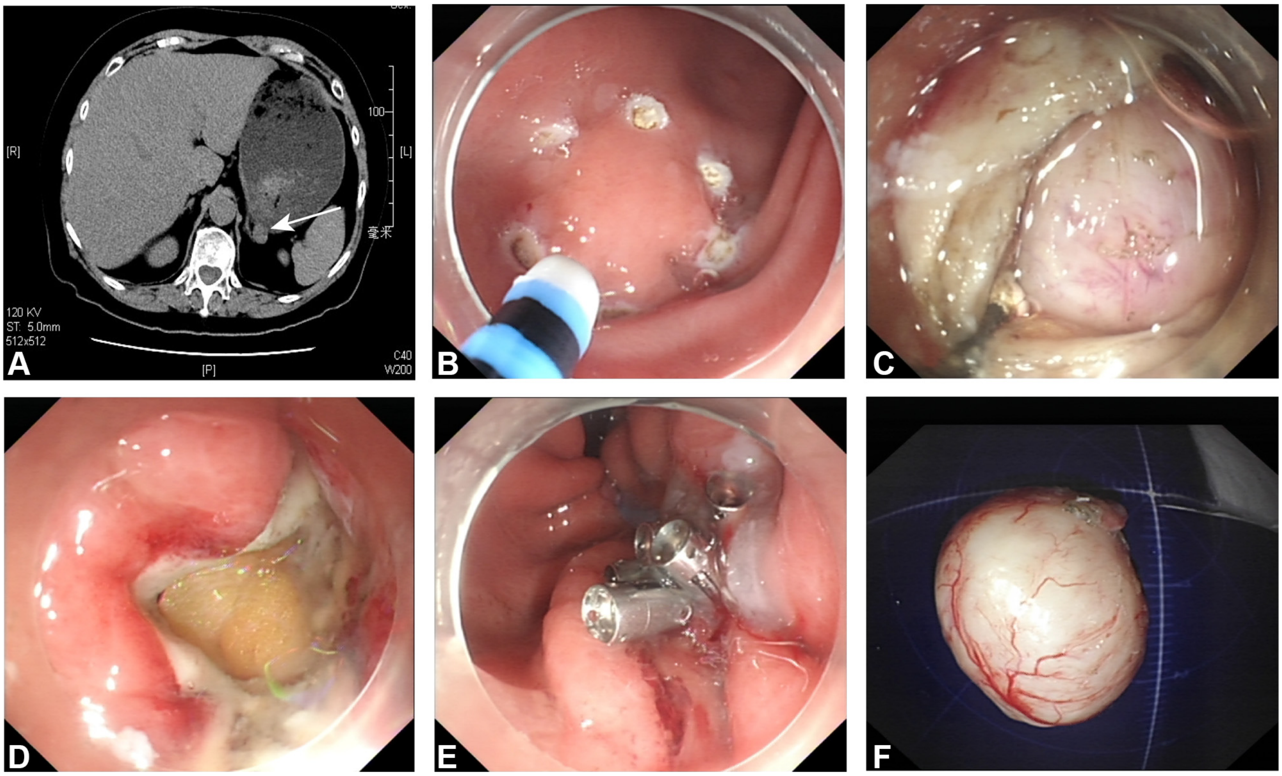

Figure 4. Endoscopic full-thickness resection of a gastric extraluminal tumor. **A,** CT showing the location of the extraluminal tumor at the fundus of the stomach (*arrow*). **B,** Prior incision of the mucosal and submucosal layers surrounding the lesion. **C,** Tumor exposure after full-thickness myotomy. **D,** Endoscopic view after tumor removal. **E,** Closure of the mucosal entry using nylon rope and clips. **F,** Resected tumor.

and 95% confidence interval (CI) were reported for significant variables identified by the multivariate analysis.

RESULTS

Clinicopathologic characteristics

One hundred nine patients with completely (23 [21.1%]) or predominantly (86 [78.9%]) extraluminal tumors in the upper GI tract were included in this study (Table 1). One patient was terminated after full-thickness myotomy because of extensive postoperative adhesions (Fig. 1). Mean patient age was 57.0 ± 11.0 years (range, 25-82) and the male-to-female ratio was 51:58. Mean tumor size was 2.5 ± 1.1 cm (range, 1.0-6.0), including 69 tumors (63.3%) with regular shapes. The 23 completely extraluminal tumors consisted of 6 (5.5%) in the posterior mediastinum and 17 (15.6%) in the abdominal cavity. The 86 predominantly extraluminal tumors included 6 (5.5%) in the esophagus, 5 (4.6%) in the EGJ, 66 (60.6%) in the stomach, and 9 (8.3%) in the duodenum.

Tumor histopathology results revealed 75 GISTs (68.8%), 16 schwannomas (14.7%), 10 leiomyomas (9.2%), 4 clarifying fibrous tumors (3.7%), 1 granular cell tumor (.9%), 1 solitary fibrous tumor (.9%), 1 neuroendocrine tumor (.9%), and 1 ectopic pancreas (.9%). Risk classification of the 75 GISTs according to the National Institutes of Health grading system[10] resulted in 37 tumors (33.9%) categorized as very low risk, 28 (25.7%) as low risk, 6 (5.5%) as intermediate risk , and 4 (3.7%) as high risk.

Procedure-related results

Among the 109 patients, 19 (17.4%) underwent STER and 90 (82.6%) underwent EFTR (Table 1). Twenty-eight incisions were closed using metal clips, and 81 incisions were closed using nylon rope and metal clips. The en-bloc resection rate was 94.5%, and the en-bloc retrieval rate was 86.2%. Fifteen tumors were removed in a piecemeal fashion, including 5 leiomyomas, 8 GISTs, 1 schwannoma, and 1 ectopic pancreas. Five leiomyomas were removed with piecemeal resection in the submucosal tunnel during STER, whereas the other tumors were removed piecemeal in the GI lumen after complete closure of mucosal incisions. Table 2 shows risk factors associated with piecemeal retrieval. Based on logistic regression analysis, tumor size ≥3.0 cm (OR, 26.273; 95% CI, 2.420-285.249; P = .007) and irregular shape (OR, 6.849; 95% CI, 1.101-42.597; P = .039) were significant risk factors for piecemeal retrieval. Other clinicopathologic characteristics (eg, age, sex, tumor location, and resection method) had no significant effects on piecemeal retrieval.

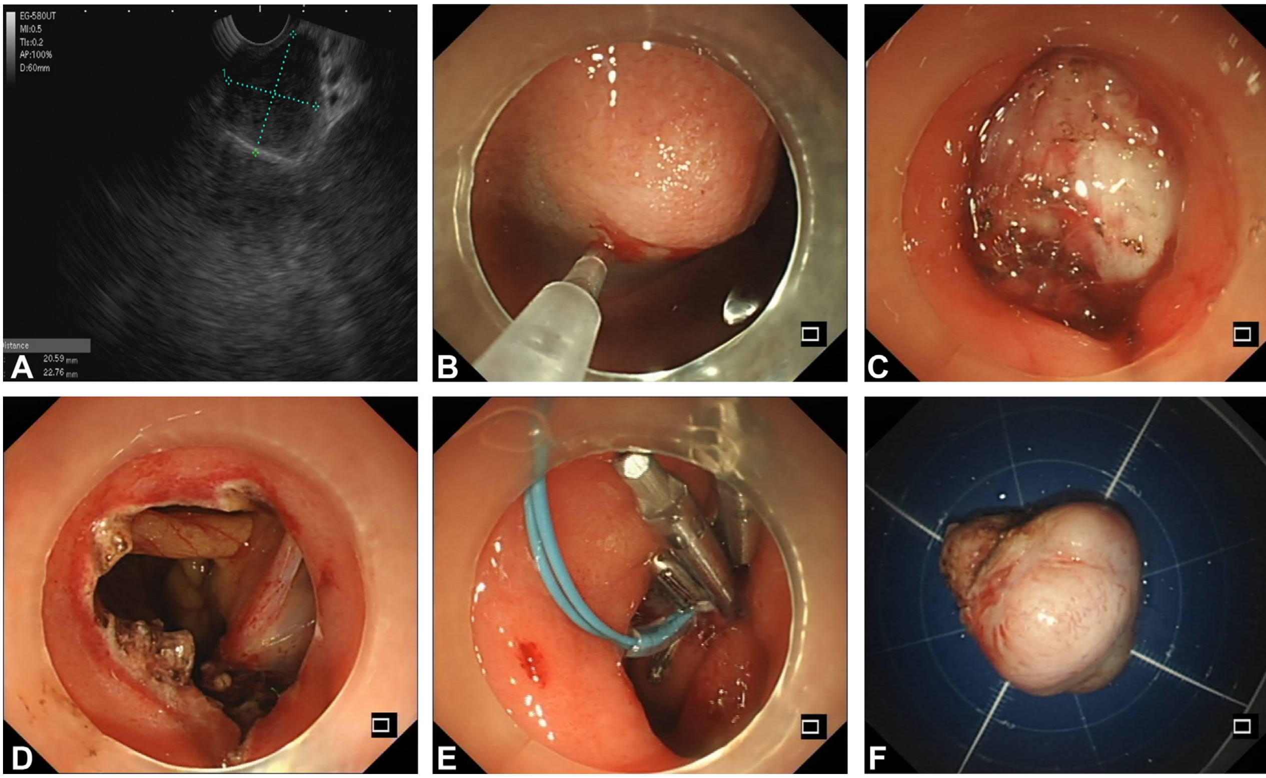

Figure 5. Endoscopic full-thickness resection of a duodenal predominantly extraluminal tumor. **A,** EUS view of the tumor. **B,** Incision into the mucosa. **C,** Tumor exposure after full-thickness myotomy. **D,** Endoscopic view after tumor removal. **E,** Closure of the mucosal entry using nylon rope and clips. **F,** Resected tumor.

The mean procedure time was 67.4 ± 42.8 minutes (range, 14-270) (Table 1). Specifically, the resection time and suture time were 46.8 ± 33.6 minutes and 20.6 ± 20.1 minutes, respectively. According to univariate and multivariate analysis, tumor size ≥3.0 cm (OR, 7.651; 95% CI, 2.583-22.665; $P < .001$) was a significant independent risk factor for prolonged procedure time (≥60 minutes) (Table 3). Other clinicopathologic characteristics (eg, age, sex, tumor location, growth pattern) were not significantly associated with a long procedure time.

AEs and follow-up

In this study, 5 patients (4.6%) had major AEs and 13 (11.9%) had minor AEs (Table 1). Major AEs included 1 case of left recurrent laryngeal nerve injury (.9%), 1 case of hydrothorax and repeat endoscopy to extract the tumor (.9%), 1 case of major bleeding and repeat endoscopy to extract the tumor (.9%), 1 case of duodenal leakage (.9%), and 1 case of localized peritonitis (.9%). Two tumors were left in the stomach because of their large size and difficulty in piecemeal retrieval. Considering that long operation time may increase the incidence of AEs, 2 tumors were extracted using an endoscope on the next day when the resected tumors were partly softened by gastric acid (Supplementary Table 1, available online at www.giejournal.org). The patient with left recurrent laryngeal nerve injury developed hoarseness and choking on postoperative day 1, and an immediate endoscopy inspection showed that the left side of the vocal cord was fixed. The pathologic findings of the schwannoma suggested that it was a mediastinal schwannoma originating from left recurrent laryngeal nerve. The symptoms were relieved by function compensatory after 4 months.

Details of these major AEs are described in Supplementary Table 1. Four cases (4.4%) of major AEs occurred in patients who underwent EFTR and 1 case (5.3%) occurred in a patient who underwent STER (Supplementary Table 2, available online at www.giejournal.org). Two cases of major AEs were located at the duodenum (Supplementary Table 3, available online at www.giejournal.org). No obvious difference in major AEs was found between predominantly (4.7%) and completely (4.3%) extraluminal tumors (Supplementary Table 4, available online at www.giejournal.org). Major AEs were slightly higher in the junior endoscopist group (10.0%) than in the intermediate (4.3%) and senior (3.9%) groups (Supplementary Table 5, available online at www.giejournal.org).

Minor AEs included 6 cases of mild mucosal injury (5.5%) and 7 inconsequential febrile episodes (6.4%). All mild mucosal injuries occurred during STER and

TABLE 1. Clinicopathologic characteristics of 109 patients with upper GI extraluminal tumors treated by endoscopic surgery

Characteristics	Values
Age, y	57.0 ± 11.0
Sex, male/female	51/58
Tumor size, cm	2.5 ± 1.1
Shape (regular)	69 (63.3)
Positions	
Predominantly extraluminal	86 (78.9)
Esophagus	6 (5.5)
Esophagogastric junction	5 (4.6)
Stomach	66 (60.6)
Duodenum	9 (8.3)
Completely extraluminal	23 (21.1)
Mediastinum	6 (5.5)
Abdomen	17 (15.6)
Histopathology	
GI stromal tumor	75 (68.8)
Very low risk	37 (33.9)
Low risk	28 (25.7)
Intermediate risk	6 (5.5)
High risk	4 (3.7)
Schwannoma	16 (14.7)
Leiomyoma	10 (9.2)
Clarifying fibrous tumor	4 (3.7)
Granular cell tumor	1 (.9)
Solitary fibrous tumor	1 (.9)
Neuroendocrine tumor	1 (.9)
Ectopic pancreas	1 (.9)
Procedure	
Submucosal tunneling endoscopic resection	19 (17.4)
Endoscopic full-thickness resection	90 (82.6)
Closure methods	
Metal clips	28 (25.7)
Metal clips and nylon rope	81 (74.3)
En-bloc resection	103 (94.5)
En-bloc retrieval	94 (86.2)
Procedure time, min	67.4 ± 42.8
Resection time, min	46.8 ± 33.6
Suture time, min	20.6 ± 20.1
Major adverse events	5 (4.6)
Recurrent laryngeal nerve injury	1 (.9)
Pneumothorax/hydrothorax	1 (.9)
Major bleeding	1 (.9)
Localized peritonitis	1 (.9)
Duodenal leakage	1 (.9)
Repeat endoscopy for tumor extraction	2 (1.8)
Minor adverse events	13 (11.9)
Mild mucosal injury	6 (5.5)
Inconsequential febrile episode (>38.5°C)	7 (6.4)
Peak postoperative temperature (°C)	37.6 ± .7
Postoperative hospital stay, days	4.7 ± 3.3
Follow-up, mo	31.8 ± 15.2
Recurrence	0
Metastasis	0

Values are mean ± standard deviation or n (%) unless otherwise defined.

were successfully repaired during the procedure, whereas all inconsequential febrile episodes occurred after EFTR (Supplementary Table 2). Peak postoperative temperature was 37.6 ± .7°C (range, 36.4-40.1). All AEs were treated successfully, and no procedure-related deaths occurred. Mean postoperative hospital stay was 4.7 ± 3.3 days (range, 2-33) (Table 1).

Based on logistic regression analysis of risk factors for AEs, tumors with an irregular shape (OR, 7.267; 95% CI, 1.556-33.948; P = .012) and tumors located in the duodenum (OR, 28.008; 95% CI, 3.041-257.913; P = .003) were associated with the occurrence of AEs (Table 4). Other clinicopathologic characteristics were not significantly associated with AEs.

Among 109 patients, 14 were lost to follow-up, and the mean follow-up period of 95 patients was 31.8 ± 15.2 months (range, 4-64). Imatinib is recommended for postresection treatment of intermediate- and high-risk GISTs. All 4 patients diagnosed with a high-risk GIST and 5 of 6 patients diagnosed with an intermediate-risk GIST received imatinib treatment and routine follow-up. The remaining patient with intermediate-risk GIST was followed with regular CT and endoscopy, and no tumor recurrence or metastasis was reported. Mean follow-up periods of intermediate- and high-risk GISTs were 31.7 ± 15.2 and 34.0 ± 11.2 months, respectively. No residual, recurrent, or metastatic lesions were detected in any patient during follow-up (Table 1).

DISCUSSION

With improvements in endoscopic resection techniques, intraprocedural perforation can be safely managed by experienced endoscopists. Intentional perforation provides access for removal of extraluminal lesions.[15] Natural orifice transluminal endoscopic surgery has been an outstanding improvement in endoscopic surgery over the past decades. The combination of natural orifice transluminal endoscopic surgery with STER or EFTR has

TABLE 2. Association of clinicopathologic characteristics of 109 patients with upper GI extraluminal tumors with piecemeal extraction

Factors	Univariate analysis Odds ratio (95% CI), *P* value	Multivariate analysis Odds ratio (95% CI), *P* value
Age		
<60 y (n = 61)	1 (reference)	1 (reference)
≥60 y (n = 48)	1.131 (.379-3.375), .825	1.682 (.268-10.569), .535
Sex		
Male (n = 51)	1 (reference)	1 (reference)
Female (n = 58)	.387 (.123-1.220), .105	.831 (.163-4.242), .824
Tumor size		
<3 cm (n = 71)	1 (reference)	1 (reference)
≥3 cm (n = 38)	40.833 (5.096-327.194), .000	26.273 (2.420-285.249), .007
Shape		
Regular (n = 69)	1 (reference)	1 (reference)
Irregular (n = 40)	16.130 (3.409-76.321), .000	6.849 (1.101-42.597), .039
Positions		
Stomach (n = 83)	1 (reference)	1 (reference)
Esophagus and esophagogastric junction (n = 17)	3.906 (1.094-13.947), .036	.289 (.009-9.736), .489
Duodenum (n = 9)	2.679 (.474-15.144), .265	3.774 (.272-52.277), .322
Growth pattern		
Predominantly extraluminal (n = 86)	1 (reference)	1 (reference)
Completely extraluminal (n = 23)	.234 (.029-1.879), .172	.081 (.004-1.739), .108
Method		
Endoscopic full-thickness resection (n = 90)	1 (reference)	1 (reference)
Submucosal tunneling endoscopic resection (n = 19)	4.154 (1.267-13.619), .019	14.730 (.610-355.513), .098

CI, Confidence interval.

made endoscopic resection of extraluminal tumors feasible.[1,6-8]

In 2016, our team first reported transesophageal endoscopic resection of a mediastinal tumor.[6] Since then, we have performed endoscopic resection for several extraluminal tumors. Subsequently, our team prospectively enrolled 8 patients who received STER for SMTs with a predominantly extraluminal growth pattern or extra-GI tumors, demonstrating that STER is a safe and effective approach for achieving curative resection of extraluminal tumors.[1] However, these reports included few patients, and limited data are available regarding the safety and efficacy of these procedures. Here, we retrospectively reviewed data from 109 patients who received endoscopic surgery for upper GI extraluminal tumors at our center. We analyzed the procedure-related parameters and AE outcomes, providing real-world evidence to help inform clinical decision-making and treatment strategies.

Our study showed that endoscopic procedures, including STER and EFTR, represent safe and effective therapeutic approaches for upper GI extraluminal tumors, resulting in an overall en-bloc resection rate of 94.5% and an en-bloc retrieval rate of 86.2%.[3] One hundred nine patients underwent successful endoscopic resection, and 1 patient was converted to surgery. Five patients suffered had major AEs and were successfully cured with interventional treatment (Supplementary Table 1). Moreover, our findings indicated that large tumor size and irregular tumor shape were significantly associated with piecemeal retrieval, which aligned with the results of prior studies.[13,16] Procedure duration was closely associated with large tumor size, whereas AE incidence was associated with irregular tumor shape and duodenal tumor location. No local recurrence or distant metastasis was observed in any patient during the follow-up period.

Since first introduced in early 2011, STER has become the preferred treatment for upper GI SMTs located in the esophagus, EGJ, or greater curvature of the stomach. The STER approach allows for the meticulous dissection of SMTs under direct visual observation while maintaining mucosal integrity, which reduces the risk of GI wall perforation and tumor capsule injury.[3,13] The longitudinal submucosal tunnel allows easy placement of clips to close the incision.[17] Indeed, the incidence of perforation-related major AEs among patients who underwent STER is lower than those who underwent EFTR (Supplementary Table 2). However,

TABLE 3. Association of clinicopathologic characteristics of 109 patients with upper GI extraluminal tumors with long procedure time (≥60 min)

Factors	Univariate analysis Odds ratio (95% CI), *P* value	Multivariate analysis Odds ratio (95% CI), *P* value
Age		
<60 y (n = 61)	1 (reference)	1 (reference)
≥60 y (n = 48)	1.488 (.696-3.182), .305	1.042 (.410-2.649), .932
Sex		
Male (n = 51)	1 (reference)	1 (reference)
Female (n = 58)	.535 (.250-1.147), .108	.600 (.234-1.536), .287
Tumor size		
<3 cm (n = 71)	1 (reference)	1 (reference)
≥3 cm (n = 38)	7.826 (3.104-19.733), .000	7.651 (2.583-22.665), .000
Shape		
Regular (n = 69)	1 (reference)	1 (reference)
Irregular (n = 40)	3.435 (1.511-7.811), .003	2.016 (.760-5.343), .159
Positions		
Stomach (n = 83)	1 (reference)	1 (reference)
Esophagus and esophagogastric junction (n = 17)	1.152 (.405-3.277), .790	.226 (.034-1.489), .122
Duodenum (n = 9)	.512 (.120-2.186), .366	.292 (.049-1.744), .177
Growth pattern		
Predominantly extraluminal (n = 86)	1 (reference)	1 (reference)
Completely extraluminal (n = 23)	.769 (.305-1.943), .579	.944 (.312-2.854), .918
Method		
Endoscopic full-thickness resection (n = 90)	1 (reference)	1 (reference)
Submucosal tunneling endoscopic resection (n = 19)	1.571 (.578-4.274), .376	1.864 (.398-8.721), .429

CI, Confidence interval.

mucosal injury is common, and the en-bloc retrieval rate is lower during STER procedures. It is technically difficult and time-consuming to resect and extract extraluminal tumors in the limited space of the established submucosal tunnel (Supplementary Table 2).[13]

In our study, 2 of 9 patients with duodenal tumors developed major AEs (Supplementary Table 3), and duodenal location was identified as a significant risk factor for AEs in the regression analysis. Actually, several severe AEs (eg, perforation, bleeding, leakage) have been reported to occur frequently in the duodenum both during and after endoscopic treatment.[18] Anatomic features of the duodenum (eg, narrow lumen, thin wall, poor operability of endoscopes in this location, and high degree of fibrillization of the submucosal layer) serve to increase the difficulty of endoscopic resection of duodenal SMTs, especially extraluminal tumors.[19,20] Therefore, endoscopic resection of extraluminal SMTs localized to the duodenum requires extra consideration and caution.

Endoscopic resection offers several advantages over traditional surgery. First, endoscopic techniques use a natural orifice to access the tumors, instead of a skin incision, which may contribute to less postoperative pain, faster recovery, and better cosmetic outcomes.[1,21] In fact, endoscopic approaches lead to less blood loss and shorter procedure time and postoperative hospital stay, compared with open or laparoscopic resection.[22-25] Second, endoscopic resection has comparable or lower rates of AEs than laparoscopic or open surgery. AEs such as bleeding, leakage, and intra-abdominal infection of endoscopic resection are comparable with those of laparoscopic surgery. Most importantly, the incidence of GI dysfunction is significantly lower than that of open or laparoscopic surgery, although tumor size was also reported to be smaller than that of traditional surgery.[23,24,26]

When used for stomach surgery, endoscopic procedures can overcome difficulties associated with laparoscopy at some locations, such as the EGJ and posterior wall of the gastric fundus.[27-29] These difficult sites for laparoscopy can be achieved by endoscopic techniques through establishing a submucosal tunnel in the lower esophagus or through direct full-thickness myotomy in the fundus of the stomach. Endoscopic resection is also feasible for tumors along the lesser and greater curvatures of the stomach because the omentum serves as a barrier that prevents gas from escaping after intentional perforation and also reduces the likelihood of leakage after closing the defect with nylon rope and clips.[3]

TABLE 4. Association of the clinicopathologic characteristics of 109 patients with upper GI extraluminal tumors with adverse events

Factors	Univariate analysis Odds ratio (95% CI), *P* value	Multivariate analysis Odds ratio (95% CI), *P* value
Age		
<60 y (n = 61)	1 (reference)	1 (reference)
≥60 y (n = 48)	.578 (.484-3.672), .578	4.105 (.817-20.627), .086
Sex		
Male (n = 51)	1 (reference)	1 (reference)
Female (n = 58)	.499 (.177-1.404), .188	1.888 (.457-7.795), .380
Tumor size		
<3 cm (n = 71)	1 (reference)	1 (reference)
≥3 cm (n = 38)	5.000 (1.697-14.729), .004	1.537 (.340-6.946), .576
Shape		
Regular (n = 69)	1 (reference)	1 (reference)
Irregular (n = 40)	8.750 (2.634-29.070), .000	7.267 (1.556-33.948), .012
Positions		
Stomach (n = 83)	1 (reference)	1 (reference)
Esophagus and esophagogastric junction (n = 17)	7.600 (2.204-26.206), .001	9.158 (.791-106.012), .076
Duodenum (n = 9)	8.686 (1.889-39.943), .005	28.008 (3.041-257.913), .003
Growth pattern		
Predominantly extraluminal (n = 86)	1 (reference)	1 (reference)
Completely extraluminal (n = 23)	.710 (.187-2.699), .615	.367 (.048-2.815), .335
Method		
Endoscopic full-thickness resection (n = 90)	1 (reference)	1 (reference)
Submucosal tunneling endoscopic resection (n = 19)	4.189 (1.359-12.911), .013	1.691 (.199-14.376), .631
Procedure time		
<60 min (n = 56)	1 (reference)	1 (reference)
≥60 min (n = 53)	2.439 (.842-7.064), .100	1.318 (.306-5.682), .711

CI, Confidence interval.

However, several concerns and limitations remain to be settled with regard to endoscopic resection of extraluminal tumors. The most pressing concern remains the effective management of intentional perforation. Gas-related events are common after perforation. Timely decompression using peritoneal puncture is necessary when intraoperative pneumoperitoneum occurs. A 20-gauge needle filled with normal saline solution was inserted into the right lower quadrant to relieve the pneumoperitoneum, and it was removed when the defect was completely closed and no further gas was released from the needle.[4] CO_2 insufflation helps to accelerate absorption and decrease postoperative pain.[13,14]

Meanwhile, perforation is often accompanied by the development of leakages and infection. Prophylactic intravenous antibiotics administrated 30 minutes before STER or EFTR is recommended. Sterile saline solution was used to rinse the cavity before any incision. Prophylactic antibiotics should also be administrated for the first approximately 48 hours postoperatively because of the increased risk of infection after full-thickness myotomy of the GI wall.[30] Notably, complete closure of the full-thickness defect is the most important step to avoid infection and leakages. Metal clips alone are effective for the closure of the mucosal entrance of the submucosal tunnel or lesions ≤2 cm with a high success rate.[31] Purse-string suture with nylon rope and clips has been proven to be reliable for defects larger than 2 cm.[5] Moreover, biogel is also useful to promote incision healing and reduce the risk of leakage.[32] Our results shows that these closure methods are feasible and reliable for full-thickness perforation, with only 1 patient developing duodenal leakage. Continued exploration for optimal endoscopic suturing techniques is required for further development of therapeutic endoscopy for extraluminal tumors.

In addition, en-bloc retrieval of tumors under endoscopy is difficult, especially for tumors larger than 3 cm. According to incomplete statistics, the en-bloc retrieval rate in our study is slightly lower than that in open (83%-100%) or laparoscopic surgery (84%-100%).[24,26] However, the risk of recurrence or metastasis did not increase during our follow-up period, which may benefit from the small tumor size, piecemeal extraction in the lumen, and adjuvant therapies. Improvement of the en-bloc retrieval rate under endoscopy is essential for further application of endoscopic resection.

These procedures are very technically demanding and should be performed by experienced operators in advanced endoscopic surgery. We recommend operators who perform this novel technique should undergo training with at least 100 cases of STER, EFTR, and peroral endoscopic myotomy, based on the known learning curve for peroral endoscopic myotomy.[33] In our study, junior endoscopists with over 100 cases of experience in advanced endoscopic surgery successfully completed the resection of relatively small tumors under the supervision of senior endoscopist. Although the procedure time was longer than intermediate and senior endoscopists, the rate of AEs was acceptable. Senior endoscopists have the shortest procedure time but a higher rate of minor AEs because of the large tumor size and difficult locations such as the duodenum (Supplementary Table 5). As more experience is gained, the overall procedure time tends to decrease and stabilize (Supplementary Fig. 1, available online at www.giejournal.org). Thus, these procedures may represent promising alternatives for extraluminal tumor resection. Preoperative examinations, such as CT and EUS, should be performed to determine the tumor size, shape, location, and relationship to the GI wall, vasculature, and other important structures.[8] Procedural details should be discussed prudently with experienced endoscopists and surgeons before the operation. Meanwhile, an experienced surgical team should be available as backup if conversion to surgery is required.

In summary, our data suggest that endoscopic resection of upper GI extraluminal tumors is feasible, safe, and effective. Endoscopic approaches represent another less-invasive alternatives for extraluminal tumor resection, which may reduce postoperative pain and functional impairment, resulting in faster recovery than traditional surgery. Tumor size, shape, and location impact the difficulty and safety of these procedures. Endoscopic resection of tumors in the duodenum is also feasible but associated with a relatively higher risk of AEs. To our knowledge, this represents the first comprehensive study evaluating the safety and efficacy of endoscopic resection of extraluminal tumors. Further large-scale prospective studies are necessary to fully assess the efficacy and safety of this novel technique, compared with conventional treatments.

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Abbreviations: AE, adverse events; CI, confidence interval; EFTR, endoscopic full-thickness resection; EGJ, esophagogastric junction; GI, gastrointestinal; GIST, GI stromal tumor; OR, odds ratio; SMT, submucosal tumor; STER, submucosal tunneling endoscopic resection.

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*Drs. Li-Yun Ma and Zu-Qiang Liu contributed equally to this article.

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Current affiliations: Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai, China (1), Shanghai Collaborative Innovation Center of Endoscopy, Shanghai, China (2).

Reprint requests: Quan-Lin Li, MD, or Ping-Hong Zhou, MD, FASGE, Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, 180 FengLin Rd, Shanghai 200032, China.

If you would like to chat with an author of this article, you may contact Dr Li at li.quanlin@zs-hospital.sh.cn or Dr Zhou at zhou.pinghong@zs-hospital.sh.cn.

SUPPLEMENTARY TABLE 1. Details of major adverse events

Patient no.	Sex	Age (y)	Tumor location	Size (cm)	Shape	Procedure time (min)	Adverse events	Treatment	Postoperative hospital stay (days)
1	M	66	Esophagus	4.0 × 2.0	Irregular	50	Left recurrent laryngeal nerve injury	Rehabilitation treatment	3
2	M	64	Stomach	3.0 × 2.5	Regular	270	Repeat endoscopy Hydrothorax	Retrieval of tumor under repeat endoscopy; thoracic drainage; antibiotics	15
3	F	61	Stomach	3.5 × 3.5	Irregular	120	Major bleeding (300 mL) Repeat endoscopy	Hemocoagulase Retrieval of tumor under repeat endoscopy	3
4	M	51	Duodenum	2.5 × 2.0	Regular	43	Duodenal leakage	Endoscopic abscess cavity debridement Antibiotics	33
5	M	48	Duodenum	4.0 × 2.5	Irregular	83	Localized peritonitis	Peritoneal drainage Antibiotics	10

SUPPLEMENTARY TABLE 2. Clinical characteristics and outcomes of 109 patients with upper GI extraluminal tumors between the EFTR and STER groups

	EFTR (n = 90)	STER (n = 19)
Age, y	57.6 ± 10.3	54.4 ± 13.9
Sex, male/female	40/50	11/8
Tumor size, cm	2.4 ± 1.0	3.2 ± 1.3
Shape (regular)	61 (67.8)	8 (42.1)
Position		
Esophagus	2 (2.2)	10 (52.6)
Esophagogastric junction	2 (2.2)	3 (15.8)
Stomach	77 (85.6)	6 (31.6)
Duodenum	9 (10.0)	0
Growth pattern		
Predominantly extraluminal	74 (82.2)	12 (63.2)
Completely extraluminal	16 (17.8)	7 (36.8)
Procedure		
En-bloc resection	86 (95.6)	17 (89.5)
En-bloc retrieval	81 (90.0)	13 (68.4)
Closure methods		
Metal clips	11 (12.2)	17 (89.5)
Metal clips and nylon rope	79 (87.8)	2 (10.5)
Procedure time, min	65.6 ± 42.5	75.6 ± 44.4
Resection time, min	43.9 ± 32.2	60.4 ± 37.5
Suture time, min	21.7 ± 21.6	15.2 ± 9.3
Adverse events	11 (12.2)	7 (36.8)
Major adverse events	4 (4.4)	1 (5.3)
Recurrent laryngeal nerve injury	0	1 (5.3)
Pneumothorax/hydrothorax	1 (1.1)	0
Major bleeding	1 (1.1)	0
Localized peritonitis	1 (1.1)	0
Duodenal leakage	1 (1.1)	0
Repeat endoscopy for tumor extraction	2 (2.2)	0
Minor adverse events	7 (7.8)	6 (31.6)
Mild mucosal injury	0	6 (31.6)
Inconsequential febrile episode	7 (7.8)	0
Peak postoperative temperature, °C	37.6 ± .7	37.4 ± .5
Postoperative hospital stay, days	4.8 ± 3.6	4.1 ± 1.7
Follow-up, mo	32.1 ± 14.2	30.6 ± 20.1

Values are mean ± standard deviation or n (%) unless otherwise defined.
EFTR, Endoscopic full-thickness resection; *STER*, submucosal tunneling endoscopic resection.

SUPPLEMENTARY TABLE 3. Clinical characteristics and outcomes of 109 patients with upper GI extraluminal tumors among different locations

	Esophagus (n = 12)	Esophagogastric junction (n = 5)	Stomach (n = 83)	Duodenum (n = 9)
Age, y	48.1 ± 12.5	51.6 ± 8.3	59.2 ± 10.3	52.1 ± 9.9
Sex, male/female	10/2	2/3	32/51	7/2
Tumor size, cm	3.5 ± 1.4	3.3 ± 1.4	2.4 ± 1.0	2.5 ± .8
Shape (regular)	4 (33.3)	3 (60.0)	57 (68.7)	5 (55.6)
Growth pattern				
Predominantly extraluminal	6 (50.0)	5 (100.0)	66 (79.5)	9 (100.0)
Completely extraluminal	6 (50.0)	0	17 (20.5)	0
Procedure				
En-bloc resection	11 (91.7)	5 (100.0)	80 (96.4)	7 (77.8)
En-bloc retrieval	8 (66.7)	4 (80.0)	75 (90.4)	7 (77.8)
Closure methods				
Metal clips	10 (83.3)	3 (60.0)	15 (18.1)	0
Nylon rope and metal clips	2 (16.7)	2 (40.0)	68 (81.9)	9 (100.0)
Procedure time, min	83.2 ± 53.0	73.4 ± 37.8	65.9 ± 43.2	56.7 ± 20.2
Resection time, min	65.6 ± 45.7	59.0 ± 33.2	44.2 ± 32.6	38.9 ± 13.4
Suture time, min	17.6 ± 14.3	14.4 ± 6.4	21.7 ± 22.1	14.4 ± 6.4
Adverse events	5 (41.7)	2 (40.0)	7 (8.4)	4 (44.4)
Major adverse events	1 (8.3)	0	2 (2.4)	2 (22.2)
Recurrent laryngeal nerve injury	1 (8.3)	0	0	0
Pneumothorax/hydrothorax	0	0	1 (1.2)	0
Major bleeding	0	0	1 (1.2)	0
Localized peritonitis	0	0	0	1 (11.1)
Duodenal leakage	0	0	0	1 (11.1)
Repeat endoscopy for tumor extraction	0	0	1 (1.2)	0
Minor adverse events	4 (33.3)	2 (40.0)	5 (6.0)	2 (22.2)
Mild mucosal injury	4 (33.3)	1 (20.0)	1 (1.2)	0
Inconsequential febrile episode	0	1 (20.0)	4 (4.8)	2 (22.2)
Peak postoperative temperature, °C	37.6 ± .6	37.4 ± .7	37.5 ± .6	38.3 ± 1.0
Postoperative hospital stay, days	4.6 ± 2.1	4.0 ± 1.4	4.3 ± 1.8	9.1 ± 9.2
Follow-up, mo	31.1 ± 20.1	44.3 ± 21.1	31.7 ± 14.5	27.4 ± 10.5

Values are mean ± standard deviation or n (%) unless otherwise defined.

SUPPLEMENTARY TABLE 4. Clinical characteristics and outcomes of 109 patients with upper GI extraluminal tumors between different growth patterns

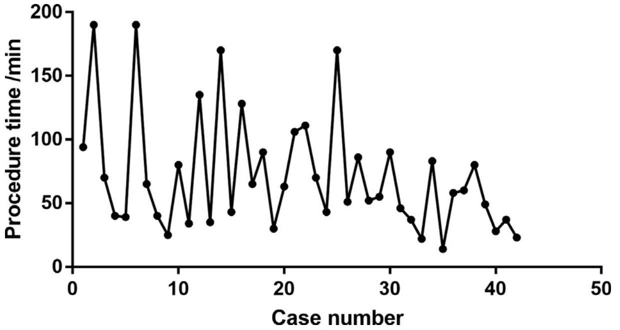
	Predominantly extraluminal (n = 86)	Completely extraluminal (n = 23)
Age, y	57.1 ± 11.0	56.6 ± 11.5
Sex, male/female	45/41	6/17
Tumor size, cm	2.5 ± 1.1	2.5 ± 1.2
Shape (regular)	53 (61.6)	16 (69.6)
Procedure		
En-bloc resection	80 (93.0)	23 (100.0)
En-bloc retrieval	72 (83.7)	22 (95.7)
Closure methods		
Metal clips	19 (22.1)	9 (39.1)
Nylon rope and metal clips	67 (77.9)	14 (60.9)
Procedure time, min	69.9 ± 43.9	57.7 ± 37.5
Resection time, min	47.7 ± 34.2	43.2 ± 31.8
Suture time, min	22.2 ± 21.8	14.4 ± 10.2
Adverse events	15 (17.4)	3 (13.0)
Major adverse events	4 (4.7)	1 (4.3)
Recurrent laryngeal nerve injury	0	1 (4.3)
Pneumothorax/hydrothorax	1 (1.2)	0
Major bleeding	1 (1.2)	0
Localized peritonitis	1 (1.2)	0
Duodenal leakage	1 (1.2)	0
Repeat endoscopy for tumor extraction	2 (2.4)	0
Minor adverse events	11 (12.8)	2 (8.7)
Mild mucosal injury	4 (4.7)	2 (8.7)
Inconsequential febrile episode	7 (8.1)	0
Peak postoperative temperature, °C	37.6 ± .7	37.6 ± .5
Postoperative hospital stay, days	4.8 ± 3.7	4.4 ± 1.5
Follow-up, mo	32.1 ± 14.5	31.0 ± 17.9

Values are mean ± standard deviation or n (%) unless otherwise defined.

SUPPLEMENTARY TABLE 5. Clinical characteristics and outcomes of 109 patients with upper GI extraluminal tumors among different operators

	Junior	Intermediate	Senior
No. of patients	10	23	76
Age, y	57.1 ± 12.7	56.7 ± 12.3	57.1 ± 10.5
Sex, male/female	3/7	7/16	41/35
Tumor size, cm	2.0 ± .6	2.4 ± 1.2	2.7 ± 1.1
Shape (regular)	8 (80.0)	14 (60.9)	47 (61.8)
Position			
Esophagus	1 (10.0)	1 (4.3)	10 (13.2)
Esophagogastric junction	0	1 (4.3)	4 (5.3)
Stomach	9 (90.0)	21 (91.3)	53 (69.7)
Duodenum	0	0	9 (11.8)
Growth pattern			
Predominantly extraluminal	6 (60.0)	18 (78.3)	62 (81.6)
Completely extraluminal	4 (40.0)	5 (21.7)	14 (18.4)
Procedure			
Submucosal tunneling endoscopic resection	2 (20.0)	5 (21.7)	12 (15.8)
Endoscopic full-thickness resection	8 (80.0)	18 (78.3)	64 (84.2)
En-bloc resection	10 (100.0)	22 (95.7)	71 (93.4)
En-bloc retrieval	9 (90.0)	20 (87.0)	65 (85.5)
Closure methods			
Metal clips	2 (20.0)	5 (21.7)	21 (27.6)
Nylon rope and metal clips	8 (80.0)	18 (78.3)	55 (72.4)
Procedure time, min	78.3 ± 69.5	70.7 ± 39.2	64.9 ± 39.7
Resection time, min	58.6 ± 68.6	48.8 ± 26.3	44.6 ± 28.9
Suture time, min	19.7 ± 8.1	21.8 ± 27.6	20.3 ± 18.8
Adverse events	2 (20.0)	1 (4.3)	15 (19.7)
Major adverse events	1 (10.0)	1 (4.3)	3 (3.9)
Recurrent laryngeal nerve injury	0	0	1 (1.3)
Pneumothorax/hydrothorax	1 (10.0)	0	0
Major bleeding	0	1 (4.3)	0
Localized peritonitis	0	0	1 (1.3)
Duodenal leakage	0	0	1 (1.3)
Repeat endoscopy for tumor extraction	1 (10.0)	1 (4.3)	0
Minor adverse events	1 (10.0)	0	12 (15.8)
Mild mucosal injury	0	0	6 (7.9)
Inconsequential febrile episode	1 (10.0)	0	6 (7.9)
Peak postoperative temperature, °C	37.6 ± .9	37.5 ± .6	37.6 ± .7
Postoperative hospital stay, days	5.6 ± 4.0	4.1 ± 1.2	4.8 ± 3.6
Follow-up, mo	28.0 ± 17.8	26.1 ± 11.8	34.0 ± 15.4

Values are mean ± standard deviation or n (%) unless otherwise defined. Junior endoscopists, >5 years of experience; intermediate endoscopists, >8 years of experience; senior endoscopists, >12 years of experience.



Supplementary Figure 1. Procedure times of 42 consecutive patients performed by a single endoscopist.