Review Article

Indications and limits of minimally invasive treatment of esophageal gastrointestinal stromal tumor: a narrative review

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Abstract: Esophageal gastrointestinal stromal tumor (GIST) is a rare neoplasm that arises from interstitial cells of Cajal that typically requires surgical resection due to its potential for aggressive behavior. These tumors can affect any site of the digestive tract, from the esophagus to the rectum. Though they arise from the submucosal layer, they can ulcerate through the mucosa or form pedunculated masses. Esophageal GIST generally has a worse outcome compared to tumors arising in the stomach. The preoperative evaluation includes imaging and endoscopic ultrasound (EUS) to obtain a tissue biopsy. For large, locally advanced, or metastatic tumors, neoadjuvant tyrosine kinase inhibitor therapy should be strongly considered. Tumor genotyping can help identify imatinib non-responders or those requiring a higher dose. Due to the rarity of regional nodal metastasis, surgical options include esophagectomy, tumor enucleation, and submucosal tunneling endoscopic resection (STER). Given a high risk of postoperative morbidity, esophagectomy should be avoided in favor of the less invasive enucleation or endoscopic resection. Thoracoscopic/laparoscopic and robotic-assisted enucleation and STER are minimally invasive operative approaches that appear to be safe with adequate oncologic outcomes based on currently available evidence. Adjuvant therapy should be considered for high-risk tumors, though the optimal duration of therapy remains under investigation.

Keywords: Gastrointestinal stromal tumor (GIST); esophagus; minimally invasive surgery; imatinib; endoscopic resection

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract with an annual incidence of 7 to 11 per million (1,2). Esophageal GIST, on the other hand, is an exceedingly rare tumor that comprises less than 1% of all GISTs (3). Esophageal GIST arises from the interstitial pacemaker cells of Cajal, are positive for c-KIT (CD117) or CD34, and the majority originate at the esophagogastric junction (3,4). Given its rarity, clinicopathological and outcomes data are limited to case reports and case series (5).

While standard treatment of localized GIST consists of surgical resection with negative margins without routine regional lymphadenectomy, surgical management of esophageal GIST remains a challenge due to esophageal

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anatomy with lack of tumor confinement by a serosal layer and the tenuous esophageal blood supply. Unlike gastric or intestinal GIST which is amendable to segmental or resection without need for intestinal anastomosis, esophageal GIST resection is limited to esophagectomy or tumor enucleation. Given the rarity of esophageal GISTs, there are currently no clear consensus recommendations or guidelines concerning optimal surgical management (4).

Given the morbidity of a laparotomy and/or thoracotomy, a minimally invasive surgical (MIS) approach is an attractive option in the surgical management of esophageal GIST. MIS approaches include endoscopic, laparoscopic, and robotic approaches and can be utilized for enucleation, esophagectomy, and submucosal tunneling endoscopic resection (STER). This paper reviews the current literature regarding the work-up and management of esophageal GIST in the context of an MIS approach. The literature search using PubMed included retrospective, prospective, and randomized controlled studies published in the English language between 2000 and 2020. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/ls-20-121).

Clinical work-up

GISTs account for 25% of stromal esophageal tumors according to a study by Miettinen *et al.* that included a cohort of patients with mesenchymal tumors of the esophagus (6). The median age at presentation for esophageal GIST is 61 years old, and esophageal GIST appears to be more common in males with a two-fold predominance (3). Patients most commonly present with symptoms at the time of diagnosis, and a quarter are diagnosed incidentally (3). The most common symptoms include dysphagia (39–53%), weight loss (20%), bleeding (8–12%), chest or abdominal pain (8–15%), and nausea (6%) (3,7). Secondary to the relative abundance of interstitial cells of Cajal along the esophagus, the most common distribution for esophageal GIST is the lower esophagus (81%), middle esophagus (16%), and proximal esophagus (3%), respectively (8). In one large series including 91 patients, the average tumor size on CT imaging was 7.9±5.4 cm (8). Compared to gastric GIST, esophageal GIST has a significantly larger mean tumor size (8.0 *vs.* 5.1 cm, P<0.001), a higher mean mitotic rate per 50 high power field (HPF) (13.4 *vs.* 8.0, P=0.005), higher odds of high-risk classification [odds ratio (OR) =4.53, 95% CI, 2.41–8.52], worse disease-specific survival [hazard ratio (HR) =0.158, 95% confidence interval (CI), 0.087–0.288], worse disease-free survival (HR =0.466, 95% CI, 0.241–0.901), and worse overall survival (HR =0.481, 95% CI, 0.294–0.785) (3).

Esophageal GIST appears as a submucosal lesion on imaging. When an esophageal submucosal mass is identified, the differential includes both benign and malignant tumors including leiomyoma, lipoma, hemangioma, schwannoma, leiomyosarcoma, and papillary epithelioma (9,10). Imaging, with options including computed tomography (CT), magnetic resonance imaging (MRI), ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET), endoscopic ultrasound (EUS), and contrast-enhanced EUS, can aid in making a diagnosis, measuring the tumor, and determining if there is local invasion or distant metastasis present (4,10). However, it can be difficult to distinguish leiomyoma from GIST prior to resection due to a similar appearance on CT, MRI, and EUS. In these cases, contrast-enhanced EUS or EUS-fine needle aspiration (EUS-FNA) can be performed to help differentiate between leiomyoma and GIST prior to surgical resection.

CT

As with GISTs in other portions of the gastrointestinal tract, small GISTs are most commonly intramural, and larger tumors may have an exophytic appearance with areas of necrosis (6,11). CT, which should be contrast-enhanced, may show an intraluminal, intramural, or exophytic mass that is hypodense with varying density and patchy enhancement on contrast-enhanced images (12). The mass may be homogenous or heterogeneous secondary to necrosis or calcification (*Figure 1*). CT allows for measurement of the mass, determination if there is local invasion into adjacent structures, and evaluation of distant metastatic disease to the liver or peritoneum, all necessary information in determining resectability and the appropriate operative approach. Metastatic lesions have a similar appearance to the primary tumor and can be heterogeneous due to necrosis, hemorrhage, or cystic degeneration (13,14). CT is also most often used for surveillance following neoadjuvant systemic therapy to assess tumor response or after surgical resection to detect disease recurrence.

MRI

On contrast-enhanced MRI, the solid portions of GISTs have low signal intensity on T1-weighted images and intermediate-to-high signal intensity on T2-weighted

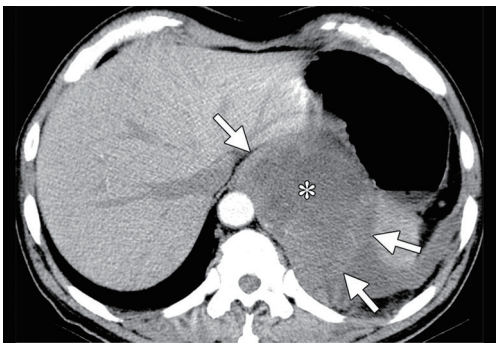

Figure 1 Esophageal GIST in a 65-year-old man with a several-month history of dysphagia and weight loss. Axial contrast-enhanced CT image shows a large distal esophageal mass (arrows) with central low attenuation secondary to necrosis (*). From Lewis RB *et al*. "From the radiologic pathology archives: Esophageal neoplasms: Radiologic-pathologic correlation". *Radiographics*. 2013;33:1083-108 (11). GIST, gastrointestinal stromal tumor.

images and demonstrate enhancement after gadolinium administration. The marked tissue hypersignal visualized on T2-weighted images are strongly correlated with a diagnosis of a GIST (13,15). Similar to CT, MRI allows for measurement of the tumor, detection of locally advanced GIST, and evaluation of liver metastasis.

FDG-PET

While FDG-PET does not necessarily differentiate leiomyomas from GISTs, the maximum standardized uptake value (SUVmax) appears to correlate with the risk of malignancy for GISTs. In a study of 26 patients who underwent preoperative FDG-PET followed by surgical resection of a gastric GIST, there was a significant correlation between SUVmax and various risk factors for malignancy including Ki-67 index (r=0.854), tumor size (r=0.888), and mitotic count (r=0.791) (16). Using a receiver-operating characteristic (ROC) curve, the authors derived a cut-off SUVmax value of 3.94 to characterize patients as "low-risk" and "high-risk" for malignancy. The sensitivity and specificity for this cut-off value was 85.7% and 94.7%, respectively. FDG-PET may have a role in assessing the response to neoadjuvant therapy (17).

EUS-FNA

Given nearly identical appearances on CT, MRI, and EUS, it can be nearly impossible to distinguish between a benign leiomyoma and a potentially malignant GIST on imaging. However, EUS allows for measurement and characterization of tumor size, shape, and relationship with the layers of the esophageal wall (4,18). In addition, EUS-FNA is the gold standard in obtaining a tissue diagnosis to differentiate the two tumors and can be utilized for mutational analysis if the tissue material is adequate. It is recommended that a 19-gauge needle is used for obtaining a histological sample, the mitotic index, and appropriate immunostaining of CD-117 and CD-34 (10). It appears that the diagnostic rate of an adequate specimen is directly related to the size of the lesion. In a study of 53 patients assessing the proportion of patients with an adequate specimen based on tumor size, 71% had an adequate specimen for a tumor size <20 mm, 86% for a tumor size of 20–40 mm, and 100% for a tumor size of >40 mm (19). Especially for large tumors, a tissue diagnosis is required in order to administer neoadjuvant systemic therapy in order to attempt organ- or function-preserving surgical resection, help avoid tumor rupture, reduce the risk of postoperative morbidity, and increase the likelihood of an MIS approach (20). While historically there has been some concern that preoperative biopsy may seed tumor, compromise oncologic resection, or increase postoperative morbidity, there does not appear to be any evidence of adverse outcomes associated with a preoperative biopsy (21).

Contrast-enhanced EUS

A newer modality that has promise in differentiating between a benign leiomyoma and potentially malignant GIST is contrast-enhanced EUS. In a retrospective study by Pesenti *et al.* that included 14 patients, the authors used the contrast agent SonoVue® (Bracco Imaging, Milan, Italy) to evaluate whether contrast-enhanced EUS could differentiate between benign and malignant subepithelial lesions of the stomach or esophagus (10). A final diagnosis was made based upon pathological studies. They observed that all 5 GISTs demonstrated enhancement in the early (after several seconds) and late phases (>30 seconds), whereas none of the other lesions showed enhancement except for one leiomyoma which demonstrated heterogeneous enhancement. While the findings are promising, the authors concluded that future studies with a larger number of patients are required to confirm these findings.

Neoadjuvant therapy

For larger tumors, imatinib, a tyrosine kinase inhibitor,

can be utilized in the neoadjuvant setting to downsize the tumor and improve the likelihood of organ preservation and an MIS approach. National Comprehensive Cancer Network (NCCN) guidelines currently recommend consideration of neoadjuvant systemic therapy for locally advanced esophageal GIST or if multi-visceral resection would be required to resect all gross disease (22). Tumor genotyping should be performed for all patients who are considered candidates for neoadjuvant therapy. If an exon 9 *KIT* mutation is identified, higher daily dosing of 800 mg per day of imatinib should be considered as opposed to the standard 400 mg per day of imatinib. This recommendation is based on a randomized EORTC (European Organization for Research and Treatment of Cancer) phase III trial in which patients who expressed an exon 9 mutant KIT protein and received an initial daily dose of 800 mg of imatinib had significantly improved progression-free survival (HR =0.39, 95% CI, 0.22–0.71) compared to those who expressed an exon 9 *KIT* mutation and received an initial daily dose of 400 mg of imatinib (23).

To date, there have been three prospective phase II studies performed for neoadjuvant imatinib. Given the rarity of esophageal GIST, neither of the studies included a significant number of patients with primary esophageal GIST. Therefore, application of study findings to patients with esophageal GIST are largely extrapolated from the study of patients with gastric or small bowel GIST. The multicenter Radiation Therapy Oncology Group (RTOG) 0132/American College of Radiology Imaging Network (ACRIN) 6665 trial analyzed 52 patients with KIT-positive GIST with either a primary GIST ≥5 cm or a resectable recurrent or metastatic GIST ≥2 cm. The patients received preoperative imatinib (600 mg per day for 8–12 weeks) followed by adjuvant imatinib for 2 years following surgery. For those with a primary GIST, the response by Response Evaluation Criteria in Solid Tumors (RECIST) was 7% partial, 83% stable, and 10% unknown (24). With a median follow-up of 4.9 years for surviving patients with primary GIST, 5-year progression-free survival was 57%, and 5-year overall survival was 77% (25).

An additional phase II trial was performed in Asia in which 56 patients with gastric GISTs ≥10 cm received 400 mg per day of neoadjuvant imatinib for six to nine months prior to surgical resection (26). The response rate by RECIST was 62% (95% CI, 48–75%), and the R0 resection rate was 91% (95% CI, 79–97%). After a median follow-up of 32 months, the 2-year progression-free survival rate was 89%, and the overall survival rate was 98%. Overall, the treatment was well-tolerated with grade 3–4 neutropenia and rash occurring in 8% and 9% of patients, respectively, and there were no treatment-related deaths.

With respect to evaluation of response to neoadjuvant therapy, NCCN guidelines recommend contrast-enhanced abdominal/pelvic CT, MRI or FDG-PET (22). Irrespective of tumor size and location, a rational interval to re-image patients is 8–12 weeks after initiating neoadjuvant imatinib. A single-institution randomized phase II trial showed that even a short course of neoadjuvant imatinib is associated with evidence of radiographic and histologic response. In this trial, nineteen patients were randomized to receive either 3, 5, or 7 days of neoadjuvant imatinib (27). Approximately 70% of patients had radiographic evidence of response via FDG-PET or contrast-enhanced CT scan. The preoperative duration of imatinib was also associated with the degree of tumor cell apoptosis via terminal deoxynucleotidyl transferase dUTP nick end labeling assay. The best response to neoadjuvant imatinib generally occurs at 28 weeks, and a plateau response is observed at 34 weeks, suggesting that treatment beyond 28–34 weeks may not provide any benefit (28). Collaboration between the medical oncologist and surgeon is recommended to determine the timing of surgical resection following a major response as tumors can develop resistance and progress to the point of unresectability without close follow-up. Imatinib can be stopped immediately before surgery and resumed as soon as the patient is able tolerate oral medications. Other tyrosine kinase inhibitors, such as sunitinib, regorafenib, and avapritinib, should be discontinued at least one week prior to surgery and can be restarted after postoperative recovery (22).

Operative approach and techniques

For esophagectomy and enucleation, operative approaches include open (laparotomy/thoracotomy), laparoscopic and/or thoracoscopic, and robotic approaches. Ivor-Lewis, transhiatal, or three-incision McKeown esophagectomy can be performed for esophageal GIST through an open, video-assisted thoracoscopic surgery (VATS), or robotic-assisted approach. Given the rarity of submucosal tumors requiring esophagectomy, there are currently little outcome data available regarding operative approach for esophageal GISTs, and most studies comparing outcomes by operative approach have been performed for epithelial esophageal cancer. In a retrospective single-institution study by Ahmadi *et al.* that included 210 patients, the authors observed that those who underwent a combined laparoscopic and

thoracoscopic Ivor-Lewis esophagectomy had less median intraoperative blood loss (321 *vs.* 657 mL, P<0.01), shorter median length of stay (10 *vs.* 14 days, P<0.01), and lower risk of an adverse event requiring reoperation or admission to the intensive care unit (21% *vs.* 34%, P<0.01) (29). In comparing a VATS to a robotic approach, Harbison *et al.* utilized the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) to evaluate short-term outcomes (30). Across 725 minimally invasive cases, there was no significant difference in 30-day morbidity or mortality between VATS and robotic approaches. Given adequate surgeon experience, a minimally invasive VATS or robotic approach appears to be the preferred operative approach when an esophagectomy is required.

Compared to esophagectomy, tumor enucleation is the favored procedure when feasible due to lower postoperative morbidity. Enucleation can also be performed through open, VATS, or robotic-assisted approaches. While there are currently no studies evaluating the association between operative approach and outcomes for enucleation of an esophageal GIST, results can be extrapolated from the literature for esophageal leiomyoma (31). In a study by Khalaileh *et al.*, the authors performed a systematic review comparing outcomes among open thoracotomy, thoracoscopic/laparoscopic, and robotic enucleation of esophageal leiomyoma (32). Across 32 studies and 125 total patients, a minimally invasive approach was associated with longer mean operative time (open: 117.4 minutes, thoracoscopic/laparoscopic: 141.4 minutes, robotic: 151.3 minutes). However, both thoracoscopic/laparoscopic and robotic approaches had a shorter mean hospital length of stay (open: 9.2 days, thoracoscopic/laparoscopic: 6.3 days, robotic: 5.7 days) and a lower rate of mucosal injury (open: 6.1%, thoracoscopic/laparoscopic: 5.6%, robotic: 0%) compared to an open approach.

An MIS approach has steadily replaced the traditional open thoracotomy for tumor enucleation since 1992 (33). VATS is used for tumors located in the upper and middle thoracic esophagus, and VATS or laparoscopic approaches are utilized for tumors in the lower third of the esophagus. A robotic approach can be used for tumors of any location. For tumors in the upper and middle esophagus, an approach through the right chest is typically preferred unless the tumor "leans" toward the left side of the chest. For tumors in the lower esophagus or esophagogastric junction, a left transthoracic or transabdominal approach is preferred. If a transthoracic approach is utilized, the patient is placed in the lateral decubitus position, and a double-lumen endotracheal tube is placed in order to selectively ventilate the contralateral lung (34). Absolute contraindications to a VATS or transthoracic robotic approach are an inability to achieve adequate working space in the chest or if the patient cannot tolerate single-lung ventilation due to pulmonary disease or previous pulmonary resection, and a relative contraindication is prior thoracic surgery in which severe adhesions are encountered in the chest cavity.

For VATS enucleation, general anesthesia with double lumen intubation is performed. The patient is then placed in a right or left lateral decubitus position with 15° frontal incline. Three or four 10 mm trocar ports are placed into the pleural cavity with location depending on the tumor site. After the tumor is identified thoracoscopically or via transillumination by endoscopy, the mediastinal pleura overlying the tumor is incised longitudinally with hook cautery. The esophagus is then mobilized circumferentially, and the muscle overlying the tumor is split longitudinally. A retracting suture may be placed over the mass to facilitate dissection between the mass and the submucosal layer. After successful resection of the mass and removal of the tumor from the chest, the esophagus is submerged under water, and the esophagus is insufflated via an endoscope or nasogastric tube to confirm that the mucosa is intact. The muscle layer is then re-approximated with an absorbable suture, and a thoracostomy tube is placed through one of the ports (33). A video of a VATS enucleation of an esophageal GIST is provided on the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) website (https://www.sages.org/video/thoracoscopic-enucleation-of-an-esophageal-gastrointestinal-stromal-tumor/) (35).

For robotic-assisted enucleation, a double lumen endotracheal tube is placed, the patient is placed in the lateral decubitus position with a roll positioned under the axilla, and single-lung ventilation is performed. Three or four 8-mm ports are placed, and the chest is insufflated with carbon dioxide. A 12-mm assistant port is typically placed anteriorly above the diaphragmatic insertion. The robot is docked, and the lung is retracted anteriorly to expose the esophagus. Similar to a VATS approach, the mediastinal pleura is divided longitudinally overlying the esophagus, and a myotomy is performed longitudinally over the mass with division of the longitudinal and inner circular muscle fibers with hook cautery or a bipolar dissector. The tumor is then dissected away while ensuring that the tumor pseudocapsule and esophageal mucosa remain intact. Care should be taken not to directly grasp the tumor as it may result in tumor

rupture. In addition, blunt dissection should be performed near the mucosa to avoid injury. Once dissected free, the tumor is placed in an endoscopic retrieval bag and removed from the chest cavity through the assistant port site. The esophagus is submerged under water and insufflated with an endoscope to evaluate for a mucosal injury. The myotomy is then closed using a 4-0 absorbable horizontal mattress suture. The robot is then undocked, a thoracostomy tube is placed, and the lung is re-inflated (31). A video of a robotic-assisted enucleation of an esophageal leiomyoma is provided on the SAGES website (https://www.sages.org/video/robotic-enucleation-of-giant-esophageal-leiomyoma/) (36).

STER is a newer minimally invasive technique that was first described by Xu *et al.* in 2012 for resection of submucosal tumors originating from the muscularis propria layer of the upper gastrointestinal tract (37,38). The mucosa flap that is created acts as a safety valve to prevent luminal content extravasation into the chest or abdomen. Absolute contraindications for STER include severe comorbidity and tumor involvement or direct proximity to extraluminal vessels, and relative contraindications include tumors greater than 3 to 4 cm in the shortest diameter due to an inability to retract the tumor from the mouth or greater than 5 cm in the longest diameter due to a higher risk of aggressive tumor behavior (39). After endotracheal intubation, using a standard gastroscope, a fluid cushion is created with an injection needle 5 cm proximal to the tumor. A longitudinal 2 cm mucosal incision is then made using a hook knife at the esophageal mucosa. A tunnel is then created between the submucosal and muscular layers using a hook or hybrid knife 1 to 2 cm beyond the tumor. Resection of the tumor is then performed using an insulated-tip, hook, or hybrid knife. Special care to safely resect the tumor completely and without violation of the tumor pseudocapsule or unnecessary injury to the esophageal adventitia must be utilized. Occasionally a dual-channel gastroscope is necessary for the use of a grasping forceps to retrieve the specimen into the submucosal tunnel. After tumor resection, the submucosal tunnel is lavaged with normal saline if the adventitia remains intact. Argon plasma coagulation or hot biopsy forceps are used for hemostasis in the submucosal tunnel, and the mucosal incision site is closed with 4 to 6 hemostatic clips (37). A video of a STER of an esophageal leiomyoma is provided on the SAGES website (https://www.sages.org/video/submucosal-tunneling-endoscopic-resection-of-an-esophageal-leiomyoma/) (40).

Choice of procedure

Surgical options include the highly invasive esophagectomy and the much less invasive tumor enucleation and the newer technique of STER. Given that esophagectomy is associated with a complication rate as high as 68% and a perioperative mortality rate as high as 13%, its use in the management of small esophageal GISTs with low risk features is questionable (41). NCCN guidelines state that surgical resection should be achieved with minimal morbidity, and complex multi-visceral resection should be avoided (22). However, there has been concern that tumor enucleation and STER could compromise oncologic outcomes as a result of incomplete tumor resection or increased risk of disruption of the tumor pseudocapsule (21). As there is clear evidence that tumor rupture is associated with an increased risk of disease recurrence, a more aggressive resection is warranted whenever there is concern for possible rupture of the tumor pseudocapsule (42,43).

Several case reports and case series have been published regarding surgical resection of esophageal GIST (*Table 1*) (5,21,44-51). In the largest series to date, Robb *et al.* evaluated outcomes across 16 patients who underwent tumor enucleation or esophagectomy for an esophageal GIST (21). Of the 8 patients who underwent enucleation, 5 were completed thoracoscopically, 1 underwent thoracoscopic-to-open conversion due to the tumor involving a large circumference of the esophageal wall, 1 was performed laparoscopically, and 1 was performed via planned thoracotomy. Of the 8 patients who underwent esophagectomy, 7 had a two-field operation with an open laparotomy and thoracotomy, and 1 underwent 3-field esophagectomy with a cervical anastomosis. Compared to esophagectomy, tumor enucleation was associated with significantly shorter median operative time (110 *vs.* 400 minutes, P=0.025) and hospital length of stay (5.5 *vs.* 11.5 days, P=0.013), and the severe postoperative complication rate was lower for enucleation (25% *vs.* 50%). The largest tumor that was resected via enucleation was 6.5 cm, and the median size of enucleated tumors was 4 cm (range, 1.8–6.5 cm). Esophagectomy was performed for larger tumors (median size =8.5 cm, range, 5.5–25 cm). Of those who underwent tumor enucleation, there were no breaches of the tumor pseudocapsule at resection, disease recurrences, or deaths after a median follow-up of 6.4 years. The authors also observed that mucosal ulceration observed on preoperative endoscopy was associated with larger tumor size and higher mitotic index. Given the association between

Table 1 Case reports and series regarding esophageal GIST resection by esophagectomy or enucleation

Study	Number of patients	Operation	Operative approach	Recurrence
Robb *et al.* (21)	16	8 esophagectomy, 8 enucleation	6 MIS, 10 open	Esophagectomy: 2 (25%); enucleation: 0 (0%)
Duffaud *et al.* (5)	9	5 esophagectomy, 4 enucleation	Not reported	Esophagectomy: 0 (0%); enucleation: 2 (50%)
Jiang *et al.* (44)	8	5 esophagectomy, 3 enucleation	8 open	Esophagectomy: 4 (80%); enucleation: 0 (0%)
Lee *et al.* (45)	7	2 esophagectomy, 5 enucleation	3 MIS, 4 open	Esophagectomy: 1 (50%); enucleation: 0 (0%)
von Rahden *et al.* (46)	4	4 enucleation	2 MIS, 2 open	0 (0%)
Blum *et al.* (47)	4	2 full thickness excision, 2 enucleation	1 MIS, 3 open	Full thickness excision: 1 (50%); enucleation: 1 (50%)
Koide *et al.* (48)	1	1 enucleation	1 MIS	Not stated
Chang *et al.* (49)	1	1 enucleation	1 open	Enucleation: 0 (0%)
Huang *et al.* (50)	1	1 enucleation	1 MIS	Enucleation: 0 (0%)
Yamada *et al.* (51)	1	1 enucleation	1 MIS	Not stated

GIST, gastrointestinal stromal tumor; MIS, minimally invasive surgery.

mucosal ulceration and more aggressive tumors, the authors suggest that enucleation should be performed for tumors that do not exhibit mucosal ulceration and are less than 6.5 cm in diameter, and esophagectomy should be performed for tumors that have mucosal ulceration or are greater than 9 cm in diameter. Robb *et al.* proposed a management algorithm based on tumor size and ulceration status (21).

In addition to enucleation, another less invasive approach is STER. STER is a newly developed endoscopic approach to resecting submucosal tumors originating from the muscularis propria layer of the esophagus. In a retrospective study that included 180 patients with upper gastrointestinal submucosal tumors of which 167 were of esophageal or esophagogastric origin and 28 were GISTs, Chen *et al.* analyzed outcomes following STER (52). *En bloc* resection was successful in 90.6% of cases, and the complication rate was 8.3%. Significant risk factors for piecemeal resection were irregular tumor shape and tumor size ≥3 cm. Though the median procedure time was 45 minutes (range, 15–200 minutes) the median duration of hospitalization was 3.2 days. After a median follow-up 36 months, none of the patients experienced a local recurrence or distant metastasis. The authors concluded that STER is appropriate for submucosal tumors with an axial diameter ≤5 cm and a transverse diameter ≤3.5 cm.

In another large series of patients that included 165 patients, Du et al evaluated the effectiveness and safety of STER for submucosal tumors (38). The primary study outcomes were rates of *en bloc* resection, complete resection, complications, and recurrence. Of note, only 3 patients had a GIST (1.8%), and most of the tumors were leiomyomas (5.2%). Across the 106 esophageal submucosal tumors, the *en bloc* resection rate was 81.1%, and the complication rate was 19.8%. Gas-related complications and fever were the most common complications, and mucosal injury occurred in 2.8% of patients. In this series the median procedure time was 46 minutes and the mean hospitalization time was 7 days. There were no disease recurrences during follow-up. However, given the small number of patients with a GIST included in the study cohort, these findings should be interpreted with caution.

Tumor rupture is associated with an increased risk of recurrence and decreased overall survival (53-55). In a retrospective review of 242 patients, rupture events occurred in 103 patients. The 5-year recurrence-free survival of patients with macroscopic tumor rupture was 37% versus 96% for patients with no defect. Early reports of the endoscopic series may not be mature enough to provide meaningful data regarding the risk for tumor recurrence with piecemeal resection in cases when the mediastinum is entered. Additionally, there is no data as to whether this

scenario should impact recommendations to administer adjuvant therapy. Understanding these outcomes will be dependent on accurate descriptions of the tumor pseudocapsule by the surgeon and the pathologist, and a consensus definition has been recently proposed (56).

Conclusions

Esophageal GIST is an infrequent tumor with a potential for aggressive behavior. Initial work-up should include CT or MRI imaging to characterize the tumor and EUS-FNA to obtain a tissue diagnosis. Patients with larger or locally advanced tumors that may require esophagectomy or multi-visceral resection should undergo neoadjuvant systemic therapy with a tyrosine kinase inhibitor. If possible, esophagectomy should be avoided due to a high risk of postoperative morbidity, and VATS or robotic enucleation or STER are feasible minimally invasive options based on current case series in the literature. In order to better understand the long-term consequences of piecemeal resection, adoption of standardized terminology to describe the status of the tumor pseudocapsule is important.

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Footnote

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