Review Article

Robotic/thoracoscopic approach to esophageal gastro-intestinal stromal tumor

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Abstract: Gastro-intestinal stromal tumor (GIST) of the esophagus are rare and account for only 1–2% of all GIST. As a result, there is a lack of clear guidelines regarding their optimal management. Previously mistaken for leiomyomas or leiomyosarcomas, it is relatively recently that their origin from the interstitial cells of Cajal was identified, when their expression of double expression C-Kit and CD34 was discovered. They are submucosal tumors, and their presentation is non-specific, with dysphagia being the most frequent symptoms. They appear as well defined iso or hypoattenuating round tumor with smooth sharp edges on computed tomography, and differ from leiomyoma by being fluorodeoxyglucose (FDG) avid on positron emission tomography. Surgical resection is the mainstay of treatment, however, indications and modality of resection are topic of debate. Due to high morbidity of esophagectomy, minimally invasive solutions are appealing. In this review, we propose a general overview of esophageal GIST, and a discussion the different surgical options.

Keywords: Gastro-intestinal stromal tumor (GIST); esophageal GIST; submucosal tumor; minimally invasive esophageal surgery; robotic esophageal surgery

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Introduction

Gastro-intestinal stromal tumor (GIST) is a rare subset of gastro-intestinal (GI) tumors of mesenchymal origin. They have an uneven distribution along the GI tract, with the stomach being the most common location and the esophagus being among the least frequent. They can cause vague GI symptoms, often are asymptomatic and are discovered incidentally. The complex anatomy of the esophagus poses a unique challenge for surgical management. Robotic surgery provides the surgeon with enhanced visualization and dexterity with the promise of reaching surgical sites that previously required maximal exposure. In this review we will describe the epidemiology, diagnostic testing, management and role of robotic surgery in the treatment of those tumors.

Historical data/epidemiology

GISTs are of relative recent discovery. In 1983, Mazur and Clark (1) re-examined 28 gastric wall tumors previously classified as leiomyomas or leiomyosarcomas using the neuroectoderm marker S-100. They found 8 of the tissue samples to be positive for S-100, and thus hypothesized a possible myenteric nervous system origin for these tumors which were previously believed to be smooth muscle. In their 1998 landmark paper, Hirota *et al.* described the association between the *C-Kit* gene mutation and GIST, which has since been exploited as a target for therapy against GIST. They were also behind the discovery of the

origin of GIST from the interstitial cells of Cajal (ICC) by uncovering their common double expression of C-Kit and CD34 (2).

Because of their recent history and the misclassification they suffered, the incidence and prevalence of GIST has probably been under-recognized. Different population based studies are available, Nilsson *et al.* in Sweden described an annual incidence of 14.5 per million and a prevalence of 129 per million (3), of which 59% were located in the stomach, 34% in the small bowel, 6% colorectal and the esophagus being a part of the 1% of the "other" location. In Northern Italy, Mucciarini *et al.* found comparable results with GIST found to represent 0.2% of all invasive cancer for an incidence of 14.2 per million (4), stomach being again the most common location with 62.9% esophageal GIST (E-GIST) representing 1.6% of the total. Using the US Cancer Statistics database for all 50 states, Patel and Benipal using the US Cancer Statistics database for all 50 states, who found an annual incidence of 7 per million, 65.1% being in the stomach, while the esophagus was not mentioned (5).

Looking specifically at E-GIST, according to reviews from Lott *et al.* and Feng *et al.* using pooled data analysis to extract 55 and 135 patients respectively from the literature and their own centers: the tumor affects predominantly males (60–65%) with 50% being younger than 60 years old in both series, with an overwhelming predilection for the lower third of the esophagus, with 80% to 92% occurring at this location (6,7). The predominance in the lower esophagus parallels the uneven distribution of ICC, from which they originate (8).

Presentation/management/classification

E-GIST present with a variety of GI symptoms mainly depending on size and location. The clinical presentation is not specific and can mimic other benign or malignant esophageal conditions. The most frequent complaint is dysphagia, present up to 53% of the patients, followed by bleeding, abdominal pain, weight loss, fatigue, nausea and respiratory symptoms (6,7). Of note, E-GIST are asymptomatic in approximately 25% of patient according to several series (3,4,6,9).

Imaging characteristics of E-GIST have only been formerly described recently. The first imaging series specific to E-GIST was from 2012 by Shinagare *et al.* and was limited to seven patients over a period to 10 years (10). E-GIST in this study were described on computed tomography (CT) as "*well defined*, *round*, *with smooth sharp edges*" and iso- or hypoattenuating compared with the muscle with mild enhancement on contrast CT. E-GIST are usually homogenous with heterogenicity being a sign of possible central necrosis. In this series, tumors were fluorodeoxyglucose (FDG) avid on positron emission tomography (PET-CT). Winant *et al.* found similar radiologic feature analyzing eight patients' data over an 18 years period; they included endoscopy findings revealing that all tumors were intramural with encroachment into the lumen, ulceration of the overlying mucosa was present in three patients (11). While this series demonstrated little differences compared to esophageal leiomyomas on CT and endoscopy, E-GIST had significant FDG avidity on PET-CT versus absence to mild avidity observed in esophageal leiomyoma.

GIST staging and classification have been established by the AJCC 8th edition guidelines. The guideline introduced the mitotic rate as a prognostic factor, with 5 mitoses per 5 high power field (HPF) considered a high mitotic rate (12). Gold *et al.* built a nomogram using 127 patients from their institution to predict recurrence-free survival (RFS) after complete resection, variable included were: mitotic rate (with breakpoint at 5 mitoses per HPF), size (as a non-linear continuous variable) and location (small bowel having the worst prognosis) (13). This nomogram was later validated in two other different cohorts, however subgroup analysis was not available and the exact number of E-GIST in those cohorts is unavailable, but represent less than 5% of the total.

General management

Workup often starts with a CT scan given the non-specific nature of the clinical presentation. CT scan is a necessary element of the management as it gives essential information for the management such as location, size, and local and distant extension. CT scan also provides a reliable means for follow-up during or after treatment. PET-CT are helpful in differentiating GIST from leiomyoma, but can also be used for surveillance (14), as a decrease in FDG avidity has been advocated as a sign of treatment response (15). The role of endoscopic ultrasound is debated for E-GIST, as it does not allow to differentiate them from other submucosal tumors, however it can in select cases help obtain biopsy via fine needle aspiration when a precise diagnosis is needed prior to resection (16).

Surgery is the mainstay of treatment for E-GIST and

will discussed in greater details in the next paragraph. According to the NCCN guidelines: it is reasonable to resect all GIST 2 cm or greater, however this cutoff is arbitrary as the growth rate and metastatic potential have not been well studied (17). The recent years have seen tremendous progress in adjuvant medical management of GIST with the use of tyrosine kinase inhibitors (TKIs), imatinib being the most studied of the available drugs. Adjuvant imatinib yielded a benefit in RFS at 1 year in a multicenter randomized controlled trial (18). Another study shows similar result with longer RFS and overall survival when the duration of Imatinib was extended to 3 years post resection (19). However, both studies included a low number of E-GISTs and therefore it is hard to conclude on a clear benefit for adjuvant TKIs therapy for E-GIST. A recent topic of interest is the role of Imatinib in patient with locally advanced disease or in organ preserving surgery in poorly positioned tumors, however due to the lack of strong evidence, the NCCN guideline recommends individualized decision making in specialized centers (17).

Surgical management

The classic guiding principles for the surgical resection of GISTs has been to prevent spillage and dissemination by leaving the tumor capsule intact and attaining a microscopically negative margin. Lymphadenectomy is not necessary as lymphatic invasion has not usually been described. More recently there has been an effort towards organ preservation and minimally invasive surgery while adhering to these surgical tenets. However, GISTs can be difficult to localize complicating potential resection. GISTs of the esophagus present a particular challenge due to the lack of a serosal layer and mesentery as well as the impossibility to perform wedge resection. The laparoscopic approach for GISTs of the stomach has shown good oncologic results and possibly lower recurrence rate compared to the open approach according to one meta-analysis as well as less peri-operative complications (20). The approach for E-GISTs, however, is still debated. The recent trend has been towards tumor enucleation in an attempt to avoid esophagectomy. Several case series have shown the feasibility of enucleation as compared to esophagectomy, however, due to the rarity of E-GIST, the number of cases is too low for a randomized control trial. Duffaud *et al.* published the results of nine E-GIST resections in France: four enucleations and five esophagectomies, patients were allocated to one of the resection modality at the discretion of a multidisciplinary team, they found that R0 resection was achieved with none of the enucleation but with 3 of the esophagectomies, they had two recurrences at a median follow-up of 24 months, both within the enucleation group (21). Those results are discordant from another French study by Robb *et al.*, who reviewed 16 patients with E-GIST, eight patients underwent Ivor-Lewis esophagectomy and eight patients underwent enucleation, including 5 thoracoscopically. This study too was not randomized and surgical management was decided by a multidisciplinary team. The patients who underwent esophagectomy had a larger average tumor size and half of them had mucosal ulceration. Two of those patients died during the index hospitalization. Out of the remaining six patients, the two with the largest tumors (100 and 250 mm) experienced recurrences. In the enucleation group, the largest tumor size was 65 mm, had no capsular violation, and none of the patient experienced recurrence or death at a median follow-up of 6.4 years (22). The latter study highlights the importance of patient selection and the feasibility of performing thoracoscopic enucleation with good oncologic results, which led them to recommend enucleation for tumors less than 65 mm and without ulceration. Those findings were similar to an earlier series of seven patients by Lee *et al.*, in which five patients underwent enucleation through thoracoscopic approach (2 of whom required conversion to open) and 2 underwent esophagectomy. Esophagectomy were performed for tumor greater than 100 mm and mucosal ulceration. There were two recurrence in this series, both occurred in patients who underwent esophagectomy at a median follow-up of 4.4 years, confirming again that thoracoscopic E-GIST enucleation is feasible and can exhibit good oncologic results (23). *Table 1* summarizes the findings of those studies.

Role of robotic surgery

The robotic approach to esophagectomy has been described by several authors (24,25), and was the object of a recent large review by Harbison *et al.* comparing outcomes of robotic assisted versus non-robotic minimally invasive esophagectomy for esophageal cancer using the NSQIP database. They found robotic esophagectomy to be feasible on a larger scale with outcome similar to the standard of care regarding adequacy of the oncologic resection and complications (26). But as discussed above, for E-GIST, enucleation should be the goal whenever possible. We

Table 1 Significant findings in the quoted series comparing enucleation to esophagectomy for E-GIST

Studies	Duffaud *et al.*, 2017 (21)	Robb *et al.*, 2015 (22)	Lee *et al.*, 2009 (23)
Number of patients	9	16	7
Age (years), median [range]	69 [36–81]	61 [24–88]	46 [39–68]
Tumor location	Not stated	6 tumors located in the proximal third, 9 in the middle third and 1 in the distal third of the esophagus	Distal third in all patients
Enucleation/ esophagectomy, n [%]	4 [44]/5 [56]	8 [50]/8 [50]	5 [71]/2 [29]
R0 resection, n [%]	Enucleation: 0; esophagectomy: 3 [60]	Enucleation: 6 [75]; esophagectomy: 5 [63]	Enucleation: 5 [100]; esophagectomy: 2 [100]
Lesion size, range in mm	Enucleation: 30–70; esophagectomy: 5–150	Enucleation: 18–65; esophagectomy: 55–250	40–170**
Complications	Non stated	2 deaths post-operative in the esophagectomy group; 2 pulmonary emboli**; 2 pneumonias**; 1 chylothorax**; 1 anastomotic leak**	Not stated
Median follow-up	24 months	6.4 years	4.4 years
Chemotherapy	Pre- and post-operative imatinib 2 patients	Adjuvant therapy with TKI* in 2 patients in the enucleation group and 2 esophagectomy groups. Neoadjuvant therapy in 2 patients in the esophagectomy group	1 patient had Imatinib after recurrence
	Post-operative only imatinib in 4 patients		1 patient had Imatinib, switched to Sunitinib due to progression
Recurrence	2 in enucleation group (50%) 0 in the esophagectomy group	No patients in the enucleation group	Both patients who underwent esophagectomy had recurrence
		2 patients in the esophagectomy group	

*, drug not specified; **, group in which the patients belong is not stated. E-GIST, esophageal gastro-intestinal stromal tumor; TKI, tyrosine kinase inhibitor.

believe that by the advantages that robotic surgery confers over open and non-robotic VATS, including the possibility of a more precise and delicate dissection in confined spaces due to the magnification of the camera and the wristed instruments, makes it an appealing solution for E-GIST enucleation. Unfortunately, no case of robotic E-GIST enucleation has been published to date. However, robotic enucleation for other submucosal esophageal tumors is gaining popularity and several case reports exists in the literature (27-35). All but 2 of those cases were leiomyomas, the remaining 2 were an esophageal lipoma and a schwannoma. No complications were reported, in particular no mucosal injury. DeUgarte *et al.* reported the largest leiomyoma to be resected robotically, measuring 7 cm × 7 cm × 5.5 cm. The authors noted that this tumor was almost encircling the esophagus and that the use of laparoscopic instrument may not have permitted the required circumferential dissection (30). Khalaileh *et al.* conducted a review of the literature on enucleation for esophageal leiomyoma, comparing open (n=49) versus laparoscopic (n=68) versus robotic (n=8) approaches in regards to complications: they found respectively 10.2%, 13.3% and 0 overall complications, and 6.1%, 5.6% and 0 mucosal injury (32). These reports attest the feasibility of robotic enucleation for submucosal tumors with good results, and should encourage attempt at GIST resection through this approach.

Description of the operative procedure for robotic enucleation of submucosal tumors

After review of preoperative imaging, either a right or left thoracic approach is chosen. Lower esophageal tumors may be approached from either side depending on the tumor's exact location. Mid to upper tumors are better approached through the right chest. Under general

anesthesia, endotracheal intubation using a double lumen tube is performed. The patient is positioned in a lateral decubitus position, a roll is placed under the axilla to help create space for trocar placement. Single lung ventilation is initiated. Three or four 8-mm robotic ports are then sequentially inserted in a similar pattern for a robotic esophagectomy. The chest is insufflated to 8 mmHg with CO_2. A 12-mm assistant port is inserted anteriorly just above the diaphragmatic insertion and will be the site of specimen extraction. The robot is docked to the ports and robotic instruments are inserted. The lung is retracted anteriorly exposing the esophagus. Utilizing bipolar cautery, the mediastinal pleura is divided longitudinally over the esophagus. The tumor is localized visually and with endoscopic guidance if needed. A myotomy is then created longitudinally over the mass, splitting the longitudinal fibers and dividing the inner circular layers with either hook cautery or the bipolar dissector. With the long bipolar cautery and Cadiere forceps, the tumor is dissected away from the surrounding tissues while keeping the tumor capsule and esophageal mucosa intact. Peritumoral tissue is grasped for retraction as grasping the tumor itself will risk rupture and spillage of cells. As the mucosa is approached blunt dissection is used in lieu of cautery with the use of gentle traction. Once the tumor is dissected free it can be removed using an endobag. The esophagus is then submerged in water and the esophagus is insufflated via upper endoscopy to uncover any potential mucosal injuries. Air and fluid are suctioned out and the myotomy is approximated using 4-0 absorbable horizontal mattress sutures Endoscopy is repeated to ensure the absence of stricture or full thickness suture. A pleural flap may be created for additional buttressing if desired. At this point, instruments are removed and the robot is undocked. Finally, a chest tube is placed and the lung is reinflated. Routine postoperative esophagram is not necessary but can be performed prior to resumption of diet if mucosal integrity is in question.

Conclusions

To date, the results of robotic assisted surgery for E-GIST have not been reported. However, the current trend toward minimally invasive enucleation in an effort to avoid esophagectomy and associated morbidity will surely assure a growing role for robotic surgery in the management of E-GIST.

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