Review Article

Esophageal gastrointestinal stromal tumors: a literature review

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Background and Objective: Gastrointestinal stromal tumors (GISTs) account for less than 1% of digestive tract tumors. The most common location of these tumors is the stomach, while the esophageal location is estimated to be between 0.7–5% of all GISTs, which explains the lack of specific guidelines and randomized trials. The objective of this review is to develop a revision of literature about clinicopathological features, diagnostic and treatment management.

Methods: We searched PubMed, Embase, Google Scholar and MEDLINE databases from 1998 to 2022 by using the keywords: "Esophageal gastrointestinal stromal tumor", "GIST", "GIST treatment", "GIST epidemiology", "GIST surgical treatment", "esophageal GIST management", "imatinib", "GIST clinicopathologic features". Additional literature was searched manually from references of related articles.

Key Content and Findings: GISTs arising from the interstitial cells of Cajal (ICC), are CD117 positive and are characterized by mutations in the c-kit genes or mutations of the platelet-derived growth factor receptor alpha. Their diagnosis is often challenging and it is difficult to distinguish themselves from other subepithelial lesions that arise from the esophagus, such as leiomyomas and leiomyosarcomas. The endoscopic ultrasound plays an important role in the identification of GISTs but the immunopathological assessment via fine needle aspiration biopsy during endoscopic ultrasound is substantial for the precise diagnosis. These tumors are potentially malignant and their goal standard treatment is based on radical surgery. Endoscopic management has also been described for smaller and low risk GISTs. Chemotherapy is based on tyrosine kinase inhibitors (TKIs) which have been described in metastatic, adjuvant and neoadjuvant settings.

Conclusions: Esophageal GISTs are a rare entity and their optimal management has not been yet defined and more data based on prospective studies or clinical trials are necessary.

Keywords: Gastrointestinal stromal tumors (GISTs); esophageal GIST; GIST treatment

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Introduction and epidemiology

Gastrointestinal stromal tumors (GISTs) are rare neoplasms, accounting for less than 1% of all the tumors that arise in the digestive tract (1). GISTs are mainly localized in the stomach (60–70%) and small intestine (20–30%), while esophageal GISTs present around 0.7% to 5% of all stromal tumors of the digestive tract (2,3). Because of the low incidence, the current literature focusing on esophageal GISTs is poor and based on case series and retrospective studies. Although GISTs typically affect elder people with an equal gender distribution (4), an esophageal localization is more often observed among young male patients (5,6). It is widely established that the gastrointestinal stromal tumors arise from the pacemaker cells of the gut, also known as the interstitial cells of Cajal (ICC) (7). As the ICC are more abundant in the distal tract of the esophagus, approximately 80% of esophageal GISTs arise in this location (8,9).

Table 1 The search strategy summary

Items	Specification
Date of search	10 September 2021–June 2022
Databases and other sources searched	PubMed, Embase, Google Scholar, MEDLINE
Search terms used	"Esophageal gastrointestinal stromal tumor", "GIST", "GIST treatment", "GIST epidemiology", "GIST surgical treatment", "esophageal GIST management", "imatinib", "GIST clinicopathologic features"
Timeframe	1998–June 2022
Inclusion and exclusion criteria	Articles not in English language have been excluded. Review articles, pooled series, retrospective studies, systematic reviews, meta-analysis, original articles and case reports have been included
Selection process	Three authors (CADP, SH, MCG) independetly reviewed the cited databases. Final decision about the included articles was taken after collegial discussion

Radical resection of the lesion is the treatment of choice for non-metastatic esophageal GISTs. Because surgery is burdened by high morbidity and mortality rate, in the last years minimally invasive and even endoscopic approaches have been developed. Moreover, the use of tyrosine kinase inhibitors (TKIs) has been described in various settings (neoadjuvant, adjuvant and metastatic) (10-12). This article offers a review on the current diagnostic and therapeutic management of the esophageal GISTs (*Table 1*). We present this article in accordance with the Narrative Reporting checklist (available at https://gist.amegroups.com/article/view/10.21037/gist-21-18/rc).

Clinical and pathological presentation

In about half of the cases, esophageal GISTs are asymptomatic lesions diagnosed accidentally during endoscopic and radiologic procedures (6,13). When symptomatic, the most common clinical manifestations are dysphagia (23–50% of cases), followed by chest pain (up to 15%) and gastrointestinal bleeding (up to 10%). Less frequent symptoms are cough, fatigue, dyspnea and weight loss (1,5,14).

Macroscopically, GISTs are exophytic, white and non-capsulated lesions of the digestive tract (15). Small tumors present mostly with a homogenous section surface and mucosa, whilst the large masses might be characterized by areas of necrosis and ulcerated mucosa (16). GISTs are pathologically classified into spindle cell, which is the most frequent subtype (up to 70% of cases), epithelioid cell and mixed cell types in about 20% and 10% of the cases respectively (17).

The immunopathologic presentation of GISTs, on the other hand, is very specific. The identification of the c-KIT mutations (18) allowed the discovery of a sensitive diagnostic marker and the use of targeted therapy with imatinib. KIT mutations are the most common gene alterations found in up to 75% of GISTs (19), followed by PDGFRA mutations in 10% of the cases (20) and KIT/PDGFRA wild-type GISTs in up to 10–15% (21).

Regarding the esophageal GIST mutation status, the most frequent KIT mutations is in exon 11, especially exon 11 deletions of codons 557 and 558, which has also been associated with recurrent disease (22).

Diagnosis

The diagnosis of esophageal GISTs is mainly based upon endoscopic evaluation with histologic confirmation. The typical endoscopic appearance is as a submucosal lesion which bulges into the gastrointestinal tract. The presence of mucosal alterations and ulcerations are more frequent in large lesions. Endoscopic ultrasonography (EUS) provides useful information, being esophageal GISTs usually hypoechoic, well-defined lesions originating from muscularis propria. The presence of lesions greater than 4 cm, mucosal ulcerations, irregular borders, internal inhomogeneity and the presence of enlarged lymph nodes are features correlated with high malignancy risk in terms of tumor recurrence (23).

Chest radiogram and esophagogram with oral contrast media have low sensibility and even lower specificity (24) while a computed tomography (CT) scan with oral and intravenous contrast media is usually performed to obtain a

precise localization of the lesion and an appropriate staging, and it is useful also to plan the treatment (25). GISTs appear as intramural masses isoattenuating to muscle and moderately enhancing (25). The use of fluorodeoxyglucose-positron emission tomography (FDG-PET) for GISTs is debatable since other benign lesions such as leiomyomas have been shown to have a ranged avidity for FDG uptake (26); however, FGD-PET might be useful to assess the response to chemotherapy and to detect disease recurrences (27).

Histologic confirmation is crucial for the definitive diagnosis of GISTs and its differential diagnosis from other submucosal tumors. EUS fine needle aspiration (EUS-FNA) has a diagnostic accuracy up to 100% for lesions greater than 4 cm while it reduces to 86–91% for lesions between 2–4 cm (28). EUS-FNB for small lesions reach an accuracy rate up to 87% (29). Deep biopsy via endoscopic submucosal dissection (ESD) has also been described especially for the diagnosis of small subepithelial lesions (30). GISTs are immunohistochemically positive for CD117/c-Kit in over 95% of cases, while other markers include CD34, SMA, DOG1, S-100 protein and Ki67 (31). KIT/PDGFRA wild type GISTs are tested for succinate dehydrogenase (SDH) deficiency and BRAF mutations amongst others (32).

Esophageal GISTs should be differentiated from other submucosal benign or malignant tumors such as leiomyoma, leiomyosarcoma, hemangioma, schwannoma and papillary epithelioma (3). Tumors with smooth muscle and neural sheath differentiation such as leiomyomas, leiomyosarcomas and schwannomas are usually the most frequent lesions that could be confounded with GISTs. EUS findings and histologic confirmation are the most useful tools for the differential diagnosis.

All the aforementioned lesions appear hypoechoic during an EUS exam. Leiomyomas usually show the same echogenicity compared to the proper muscle layer, meanwhile GISTs appear slightly more echogenic and schwannomas have an extremely lower echogenicity (33). The presence of irregular borders, heterogeneity and invasiveness of the adjacent tissues are signs of malignancy such as leiomyosarcomas or high malignant GISTs (34).

Histopathology and immunochemistry are important to make a distinction between these subepithelial lesions. Leiomyomas express smooth muscle markers but in contrast to GISTs they are negative for CD117 and anoctamin 1 (35). Leiomyosarcomas have similar features to leiomyomas but they show a high cell pleomorphism and mitotic rate (35).

Schwannomas on the other hand have a positivity for S100 protein and glial fibrillary acidic protein (GFAP) and are CD117 negative.

Treatment

Since the lasts World Health Organization (WHO) considers all GISTS malignant, regardless of site, mitosis number and dimensions (36), radical surgery with no dissection of clinically negative lymph nodes remains the mainstay for non-metastatic GISTs treatment (37). Tumor residual and tumor rupture are the main features associated with poor prognosis and higher recurrence rates (38). For lesions <2 cm clinical and instrumental follow up can be advised but patients should be thoroughly informed about the potential malignant risk that GISTs carry. However, specific guidelines regarding the esophageal GIST treatment are lacking because of their rarity (1).

The anatomical features of the esophagus and the lack of a serosal layer to confine the submucosal lesions, lead to a more complicated surgical management. In particular, wedge or segmental resections are unfeasible, differently from gastric GIST where these procedures are the treatment of choice (39).

Surgical tumor enucleation, avoiding extensive esophageal resection, should be considered for low to intermediate malignancy risk esophageal GISTs (tumors no larger than 5 cm and with <5 mitosis per 50 high power field) (9,40). When the procedure exposes to high risk of capsule rupture, enucleation should be avoided since this complication is associated with poor prognosis (41).

Tumor enucleation via video-assisted thoracoscopic surgery (VATS) has been shown to be feasible with clear advantages in a shorter hospital stay and lower morbidity rates (40). Perforation rate of the mucosal layer during enucleation for submucosal esophageal tumors was described in up to 23% of the cases, predominantly controlled endoscopically (42).

In case of high risk of capsule rupture, for GISTs larger than 5 cm and/or with malignancy features, esophagectomy is the only curative option. However, esophagectomy is a major surgery procedure, burdened by morbidity rates as high as 59% and with a 90-day mortality that in high volume center is still today of about 4.5% (43-46). The development of minimally invasive surgery, performed as minimally invasive esophagectomy (MIE) or robot-assisted minimally invasive esophagectomy (RAMIE), has shown beneficial outcomes in terms of blood loss, pain control and hospital stay in some retrospective series. However, no randomized controlled trials (RCTs) confirmed these

results, while a higher risk of anastomotic leak has been reported in studies focusing on MIE. Recent articles about mediastino-laparoscopic transhiatal esophagectomy for esophageal GISTs have shown that this hybrid technique could offer a feasible option in selected patients, but the evidence is only available in the form of case reports.

Since surgery, either tumor enucleation or esophagectomy, exposes the patient to considerable risks, the possibility of an endoscopic treatment for esophageal GIST has been recently examined (47). ESD has been described in small (<2 cm) and uniform hypoechoic GIST. However, the rate of associated complications such as perforation goes from 6.4% to 20% (48).

Endoscopic submucosal excavation (ESE), in which the endoscopist performs longitudinal incision instead of a circular incision, has shown to be feasible with a 95–100% rate of complete resection in upper GI submucosal tumors. However, perforation rate remains as high as 12.9–20% (49,50).

To limit the incidence of esophageal perforation, a different technique, called submucosal tunneling endoscopic resection (STER) has been developed. It combines characteristics of ESD and per-oral endoscopic myotomy (POEM), with a theoretically lower risk of incidence as it preserves the mucosal integrity around the lesion (51).

A retrospective study has shown a slight advantage of STER compared to ESE in terms of the patient's recovery and shorter hospital stay (50). Lastly, alternative endoscopic treatments, such as cryoablation, has been described for esophageal GIST (52,53), even though literature is limited to small case series. The use of TKIs after the identification of the mutation of the c-KIT in the human GISTs changed dramatically the management and the prognosis of gastrointestinal stromal tumors.

Imatinib was the first drug used as a first line treatment for metastatic and inoperable GISTs after a randomized trial showed a clinical benefit rate up to 83% (54). It has also been described a benefit from elective surgery for selected patients with metastatic GISTs who have a responsive disease or a focal resistance to TKIs (11).

Imatinib, used as an adjuvant treatment, has been shown to prevent recurrences and increase the survival rates (9) but no specific randomized trials have been made for esophageal GISTs in particular.

On the other hand, several studies in the form of case reports and case series have shown the advantage of the downsizing effect of the neoadjuvant therapy with TKIs before surgery for esophageal GISTs (55-57).

Since clinical response to TKIs is correlated to tumor genotype, the assessment of the tumor mutational status is necessary for a successful targeted therapy since different lines of therapy could be applied (58,59).

There are no specific guidelines about esophageal GISTs up to date therefore every patient diagnosed with an esophageal GIST should undergo a multidisciplinary evaluation.

Conclusions

The esophageal GISTs represent a rare entity and no specific guidelines have been developed. Randomized or prospective studies are necessary to decide their optimal management and more data are required to assess their precise prognosis.

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Footnote

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