

A guide for the diagnosis and management of gastrointestinal stromal cell tumors

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Abstract | Gastrointestinal stromal cell tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract and are frequently detected on routine endoscopy. Although only ~10–30% of GISTs are clinically malignant, all may have some degree of malignant potential. Preoperative determination of malignancy risk can be estimated from tumor size and location, but reliable histopathologic criteria are not currently available. Given such biological uncertainty, accurate diagnosis is essential to differentiate these lesions from other truly benign, subepithelial tumors. Endoscopic ultrasound-guided fine-needle aspiration has emerged as an important procedure to secure a tissue diagnosis of a GIST. When encountering GISTs, gastroenterologists are faced with challenging management decisions, especially in the face of small, incidentally discovered lesions. The majority of localized GISTs are managed via surgical resection, although a select few may be observed using serial endoscopic ultrasound examinations. This Review provides a general overview of GISTs, with an emphasis on their endoscopic diagnosis, the management of localized disease, and the management of incidentally discovered GISTs.

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Introduction

Gastrointestinal stromal cell tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract and are thought to originate from the interstitial cells of Cajal, which regulate gastrointestinal motility. In the medical literature, GISTs have been confused with true smooth muscle neoplasms because of their similar appearance by light microscopy. In the past 10 years or so, immunohistochemical staining for the tyrosine kinase, c-kit (also known as CD117), has shown the presence of this receptor in approximately 95% of GISTs,¹ thereby allowing differentiation from other mesenchymal spindle-cell neoplasms. C-kit is a transmembrane receptor that is activated by the binding of *KIT* ligand—a stem cell factor. Approximately 75–80% of GISTs have *KIT* mutations, while 8% have mutations in the platelet-derived growth factor receptor, a polypeptide gene (*PDGFRA*) encoding a c-kit-homologous receptor tyrosine kinase.^{2,3} Mutations in these genes cause functional changes in the protein that lead to ligand-independent constitutional activation.

The clinical presentation of GISTs can range from symptomatic gastrointestinal bleeding or abdominal pain, to incidental discovery during an endoscopy performed for other reasons.⁴ Approximately 10–30% of GISTs are clinically malignant,⁵ but all GISTs are known to have some degree of malignant potential.⁴ Although tumor

size and location can afford an estimate of the preoperative malignancy risk,^{1,6} reliable preoperative histological tests to predict malignancy are not currently available. In addition, the majority of the available literature regarding prognosis provides a biased viewpoint, as most of the patients in the reported studies presented with clinical symptoms, large tumors, or metastatic GISTs.^{4,7–10} The above-mentioned difficulty in assessing GIST malignant potential and prognosis and the increasing incidence of the ‘incidental GIST’ pose particular challenges to gastroenterologists, who need to make management decisions after these lesions are discovered.

This article provides an overview of GIST diagnosis and treatment, with emphasis on endoscopic diagnosis, the management of localized disease, and the incidental GIST.

Epidemiology

Approximately 4,000–6,000 new cases of GIST are diagnosed in the US each year. The reported annual incidence is 11–14.5 cases per 1 million individuals, with a prevalence of approximately 129 cases per 1 million individuals.^{10,11} GISTs most commonly occur in the stomach (60–70% of cases), followed by the small intestine (20–30%), the colon and rectum (5%), and the esophagus (<5%).¹²

Histology

Histomorphologically, most GISTs are composed of spindle cells, although 20–30% are predominantly composed of epithelioid cells.¹³ Regardless of morphology, c-kit expression has emerged as the defining feature of

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Key points

- Gastrointestinal stromal cell tumors are the most common mesenchymal neoplasm of the gastrointestinal tract and are frequently discovered on routine endoscopy
- Approximately 10–30% of gastrointestinal stromal cell tumors are clinically malignant, but all such tumors may have some malignant potential
- Preoperative malignancy risk can be estimated from tumor size and location, but a set of reliable histologic criteria do not currently exist
- The diagnosis of a gastrointestinal stromal cell tumor can be suggested by esophagogastroduodenoscopy or endoscopic ultrasonography, but definitive diagnosis requires tissue acquisition via endoscopic ultrasound-guided fine-needle aspiration
- Complete surgical resection is the mainstay of treatment for localized disease, although, for a small subset of patients, surveillance via serial endoscopic ultrasound examinations can be undertaken
- Imatinib therapy is the treatment of choice for locally advanced and metastatic disease, and can also be used as neoadjuvant therapy before surgical resection

GIST.³ By contrast, other spindle-cell neoplasms of the gastrointestinal tract do not express c-kit.¹⁴ GISTs can also stain positive for the cell surface glycoprotein CD34 (60–70%), smooth muscle actin (30–40%), S100 protein (5%), and desmin (1–2%).¹⁴ Approximately 75–80% of GISTs display *KIT* mutations. Of the 20–25% of GISTs without *KIT* mutations, about one-third (8% of the total) display *PDGFRA* mutations.^{2,15}

Clinical presentation**Symptoms**

Approximately 70% of GISTs are clinically symptomatic.^{10,16} In one large cohort of patients with GISTs, the most common presenting symptom was gastrointestinal bleeding (53% of patients). Overt gastrointestinal bleeding occurred in 34% of patients, whereas anemia secondary to insidious bleeding was present in 19%.¹⁶ Other common presenting symptoms were abdominal pain or fullness (32%), or the presence of a palpable mass (13%). Site-specific symptoms include dysphagia for esophageal GISTs, and rare obstruction and/or perforation for colonic GISTs.

Incidental GIST

In large, population-based studies, 15–30% of patients with GISTs were asymptomatic; in these patients, GISTs were discovered incidentally.^{4,10,16} In these studies, incidental GIST discovery occurred mostly via surgical resection performed for other reasons or by postmortem examination. In the past 3 years or so, several studies have noted the existence of subclinical microscopic gastric GISTs.^{17–20} Agaimy *et al.* found that microscopic gastric GISTs were present in 22.5% of consecutive autopsies performed on patients aged 50 years or older.¹⁹ Kawanowa *et al.* reported microscopic GISTs in 35% of surgically resected whole stomachs removed because of gastric carcinoma.²⁰ Given that endoscopic examination is increasingly being used for

assessment of the upper gastrointestinal tract, the recognition of incidental subepithelial lesions during these procedures has significantly increased accordingly. One retrospective study reported a prevalence of subepithelial gastric masses of 0.36% during routine endoscopy.²¹ These studies suggest that GISTs are far more common than has previously been recognized.

Malignant potential

As mentioned earlier, approximately 10–30% of GISTs are clinically malignant, although the fact that all GISTs are considered to have some degree of malignant potential should be kept in mind. GISTs in the small intestine are more aggressive than those located in the stomach; malignant behavior is detected in approximately 40–50% of GISTs in the small intestine and in about 20–25% of gastric GISTs.¹ Few data are available on the behavior of GISTs located in unusual sites, such as the esophagus, colon, and rectum; however, in terms of prognosis, tumors in these sites should probably be assumed to have a similar risk profile to that of intestinal GISTs.¹ One of the most striking features of GISTs is their variable and unpredictable behavior. Large, presumed malignant GISTs can behave in a benign manner, whereas small, incidentally discovered GISTs can behave in a malignant fashion. Thus, GISTs are not classified as ‘benign’ or ‘malignant’, but are rather stratified by the clinical risk of malignancy associated with them (very low, low, moderate, or high), as determined by tumor size, location, and number of mitoses identified on surgical histology (Table 1).⁶ A preoperative estimate of risk can be made from tumor size and location, but a reliable set of preoperative histopathological criteria do not currently exist. Making a reliable diagnosis of GIST on initial discovery is particularly important because of the uncertainty regarding the behavior of these tumors. Differentiation from other subepithelial tumors is imperative, as the majority of these neoplasms are truly benign, and may be managed very differently from GIST.

Diagnostic tools**CT**

CT is usually the initial imaging modality used in patients who present with abdominal symptoms. One study that looked at the use of CT scans in evaluating suspected GISTs reported that small GISTs have sharp margins, an intraluminal growth pattern, and a homogenous density. By contrast, large lesions have irregular margins, extraluminal growth patterns, and inhomogenous density.²² Radiographic features that correlated with aggressive GISTs were calcification, ulceration, necrosis, cystic areas, fistula, metastases, ascites, and signs of infiltration.²² Unfortunately, the usefulness of CT in the evaluation of GIST is limited by the fact that smaller lesions cannot be easily analyzed. In addition, CT does not allow accurate evaluation of the gastrointestinal wall layers, a shortcoming that limits the usefulness of this technique for differential diagnosis. Thus, CT is mainly reserved for

Table 1 | Malignancy risk stratification of gastrointestinal stromal cell tumors by tumor size, mitotic count, and location

| Size | Mitotic count | Risk of progressive disease by location (%) ^a | | | |
|---------------|----------------|--|------------------------|---------------------|---------------------|
| | | Gastric | Jejunal/Ileal | Duodenal | Rectal |
| ≤2 cm | ≤5 per 50 HPFs | None (0) | None (0) | None (0) | None (0) |
| >2 cm, ≤5 cm | ≤5 per 50 HPFs | Very low (1.9) | Low (4.3) | Low (8.3) | Low (8.5) |
| >5 cm, ≤10 cm | ≤5 per 50 HPFs | Low (3.6) | Moderate (24) | (Insufficient data) | (Insufficient data) |
| >10 cm | ≤5 per 50 HPFs | Moderate (12) | High (52) | High (34) | High (57) |
| ≤2 cm | >5 per 50 HPFs | None (0) ^b | High (50) ^b | (Insufficient data) | High (54) |
| >2 cm, ≤5 cm | >5 per 50 HPFs | Moderate (16) | High (73) | High (50) | High (52) |
| >5 cm, ≤10 cm | >5 per 50 HPFs | High (55) | High (85) | (Insufficient data) | (Insufficient data) |
| >10 cm | >5 per 50 HPFs | High (86) | High (90) | High (86) | High (71) |

^aDefined as metastasis or tumor-related deaths. ^bDenotes tumor categories with very few patients. Abbreviation: HPFs, microscopic high-power field in tissue sections. Permission obtained from Elsevier © Miettinen, M. & Lasota, J. *Semin. Diagn. Pathol.* 23, 70–83 (2006).

the characterization of large GISTs or for the assessment of metastatic spread.

PET

GISTs are metabolically active, and thus take up the PET imaging agent ¹⁸F-fluorodeoxyglucose, a radio-labeled, synthetic analog of glucose. Traditionally, PET imaging has been mainly used to determine the stage of advanced disease, when planning surgery, and in assessing response to imatinib therapy. Serial PET scans have also become standard-of-care to monitor tumor response to therapy. A 2005 study of 10 patients with gastric GIST reported a significant correlation between ¹⁸F-fluorodeoxyglucose uptake and mitotic index but not tumor diameter.²³ These results led authors to suggest that ¹⁸F-fluorodeoxyglucose uptake is a predictor of the malignancy potential of a GIST.²³ However, before PET becomes a standard tool to characterize malignant risk before surgery, further studies will need to be performed to validate these findings.

Endoscopy

The majority of subepithelial gastrointestinal lesions are discovered on endoscopy. Typically, subepithelial lesions present as a bulge in the gastrointestinal tract, with smooth, intact, normal overlying mucosa. When encountering such formations, possible etiologies include mesenchymal tumors (GISTs, leiomyomas, leiomyosarcomas, glomus tumors, lipomas, liposarcomas, hemangiomas, neuromas, granular cell tumors), vascular structures (aneurysms, varices), cysts, pseudocysts, neoplasms of adjacent organs, and even extramural structures (in up to 30% of all cases presenting as subepithelial masses).^{24–28} Standard forceps are usually unsuitable for collecting adequate tissue samples for diagnosis because of the subepithelial location of these tumors. Some clinicians have advocated the use of stacked, or bite-on-bite biopsies, but the diagnostic yield of this approach is poor, in the range of 17–42%.^{29,30} Important imaging features that help narrow the differential diagnosis include lesion size, location, color, overlying mucosa,

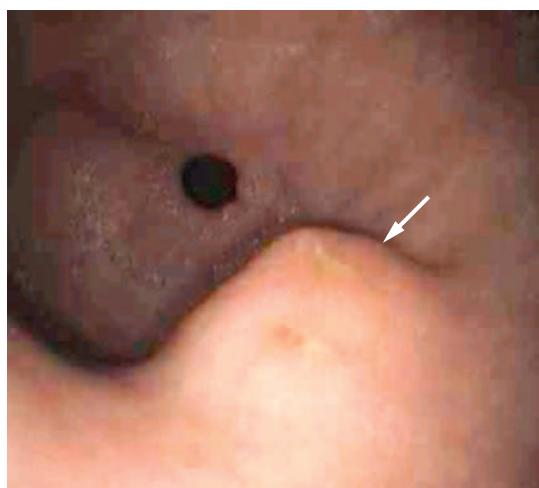


Figure 1 | Esophagogastroduodenoscopy image of a gastrointestinal stromal cell tumor showing a mass with smooth, intact, normal overlying mucosa. The arrow points to the tumor.

and compression characteristics. GISTs are the most common subepithelial gastrointestinal lesions, and they are usually characterized by an oval or smooth shape, normal overlying mucosa with occasional ulceration, location in the stomach or small intestine, and a firm consistency on compression (Figure 1). One prospective study compared the performance characteristics of endoscopy with those of endoscopic ultrasonography (EUS) in the diagnosis of gastrointestinal subepithelial masses.²⁴ Esophagogastroduodenoscopy (EGD) correlated well with EUS in determining the size of intramural lesions, but performed poorly in the determination of extramural lesion size. Diagnosis using EGD was correct in only 39% of cases. Given the poor accuracy and specificity of EGD, and the inability to obtain adequate tissue by using standard forceps biopsy, further evaluation of gastrointestinal subepithelial masses with EUS is, therefore, usually warranted following EGD to obtain an accurate diagnosis.

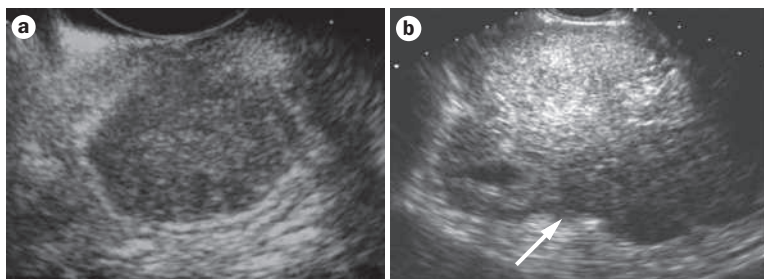


Figure 2 | Endoscopic ultrasonography images of gastrointestinal stromal cell tumors. **a** | The classic findings of a round, hypoechoic mass, located in the fourth sonographic layer. **b** | The high-risk features of a large mass with irregular borders (arrow).

EUS

EUS can help to further characterize subepithelial lesions by providing information regarding tumor size, shape, which gastrointestinal wall layer it originated from, tumor border, and internal composition. Classic EUS features of a GIST are a dark or hypoechoic appearance, a round to oval shape, and a location in the fourth sonographic wall layer, which corresponds to the muscularis propria (Figure 2a). The tumor border is usually smooth and well defined, although large or clinically malignant GISTs can display an irregular contour. The tissue can be heterogeneous or homogenous, and the masses can occasionally exhibit features of echogenic foci, cystic spaces, or ulceration. Leiomyomas may present with similar characteristics, but these tumors are predominantly located in the esophagus, and are rare in the stomach or small intestine.

Several trials have examined the ability of EUS to differentiate GISTs from other subepithelial tumors. Hunt *et al.* found that subepithelial tumors were more likely to be GISTs than c-kit-negative tumors when they were larger than 4 cm, or displayed ulcerations or cystic spaces. When using these criteria, the calculated diagnostic sensitivity for GIST was 64.7% and the specificity was 91.7%.³¹ This study also reported that subepithelial tumors located in the stomach or small intestine were GISTs in 80.0% of cases. Subepithelial tumors located in the esophagus were GISTs in only 11.1% of cases. If tumors located in the stomach or small intestine were considered to be GISTs, whereas tumors located in the esophagus were considered to be non-GISTs, the diagnostic sensitivity and specificity would be 94% and 67%, respectively.^{31,32} Brand *et al.* reported a sensitivity and specificity of 95% and 72%, respectively, for the simplified diagnostic criterion that “...all hypoechoic lesions not originating in the submucosa [are GISTs].”^{32,33} Okai *et al.* also suggested that the presence of a marginal halo and the finding of relatively high echogenicity (as compared with the surrounding proper muscle layer) on EUS might suggest the diagnosis of a GIST, but the sensitivity of these criteria was very low.³⁴

In spite of the promising studies described above, the usefulness of EUS imaging alone for the diagnosis of subepithelial masses has been called into question. EUS performs better than EGD in evaluating gastrointestinal

subepithelial lesions, but the diagnostic accuracy of EUS imaging alone has been shown to be as low as 43%.²⁴ In addition, studies have shown interobserver agreement to be poor, and the diagnostic accuracy to depend heavily on the experience of the endosonographer.³⁵

EUS to assess malignant potential

Despite limitations in the use of EUS imaging alone to make the diagnosis of a GIST, the characteristics of the subepithelial lesions as viewed via EUS can be used to assist in predicting malignant potential. Chak *et al.* found that features predictive of malignant submucosal tumors were diameter >4 cm, irregular extraluminal border, echogenic foci, and cystic spaces.³⁶ When the presence of at least two of the following three features were used as malignancy determinants—irregular border, echogenic foci, and cystic spaces—sensitivity ranged from 80% to 100%, depending on the endosonographer.³⁶ The likelihood of malignancy when all three features were absent was between 0% and 11%.³⁶ Palazzo *et al.* found that presence of an irregular extraluminal margin, cystic spaces, and lymph nodes with a malignant pattern were predictive of malignancy risk.³⁷ Presence of at least one of these three features as criterion for malignancy had a sensitivity of 91%, a specificity of 88%, and a positive predictive value of 83%. Brand *et al.* showed that using any two of the three following criteria for malignancy, heterogeneous echotexture, size >3 cm, and irregular margins, had a sensitivity of 80% and specificity of 77%.³³

A 2007 study by Jeon *et al.* examined exclusively c-kit-positive gastric GISTs and found that the EUS features of mass size >3 cm, irregular borders, mucosal ulceration, or a non-oval shape suggested the lesions were at high risk of malignancy.³⁸ Shah *et al.* performed a similar analysis and found that tumor size >5 cm, the presence of an irregular extraluminal border, local invasion, and heterogeneity were predictive of malignancy risk.³⁹

The above studies are retrospective and provide somewhat conflicting results that have not been validated in prospective series. An abstract by Nickl *et al.*⁴⁰ represents the only available report of a large, prospective study to date assessing EUS features predictive of malignancy risk in GISTs. This study found that size \geq 3 cm, surface ulceration, a nonoval shape, and the presence of irregular or indistinct margins were associated with high-risk lesions. Notably, echogenic foci and cystic spaces were not associated with malignant potential. Given that this study was only published as an abstract, we are left to draw our own conclusions from a conflicting body of literature. Large tumor size and irregular border have been associated with malignancy risk in the majority of studies, and thus they should be considered as indicators of malignancy when encountered (Figure 2b). Variables such as ulceration, cystic spaces, echogenic foci, and heterogeneity have proven less consistent than tumor size and irregular border in their ability to predict malignancy risk. Thus, the endosonographer should recognize that, although EUS imaging may aid in identifying malignant

potential, the predictive accuracy of this methodology has not been well defined.

EUS-guided fine-needle biopsy

As EUS imaging characteristics alone lack sufficient specificity and accuracy in the diagnosis of GIST, acquisition of tissue for histological analysis has become the standard-of-care. The options for sampling a GIST include jumbo forceps biopsy using the bite-on-bite technique, endoscopic submucosal resection, EUS-guided fine-needle aspiration, EUS-guided Tru-cut® (Allegiance Healthcare Corp., McGaw Park, IL) biopsy, laparoscopic or laparotomic excision, and percutaneous biopsy. Laparoscopic or laparotomic excision is the standard approach for lesions that are not amenable to endoscopic sampling.⁴¹ Percutaneous biopsy is not usually recommended because of the possible risk of tumor rupture and peritoneal spread. Forceps biopsy and endoscopic submucosal resection are not feasible sampling techniques because of their poor tissue yield and the risk of perforation,^{29,30} respectively. Current guidelines of the National Comprehensive Cancer Network,⁴² and of the American Gastroenterological Association⁴³ state that EUS-guided sampling of GIST tumors is the preferred sampling technique. This approach entails use of fine-needle aspiration or core biopsy, and usually relies on cytology. This strategy enables the collection of sufficient subepithelial tissue to provide a cytologic diagnosis of a 'spindle' or 'epithelioid' neoplasm (Figure 3), as well as to perform immunohistochemical staining for c-kit for definitive diagnosis (Figure 4).

EUS-guided fine-needle aspiration

EUS-guided fine-needle aspiration (EUS-FNA) has been proven to provide enough cytologic material for diagnosis, with many large studies supporting its use in sampling lymph nodes, the pancreas, and extraintestinal masses.^{44–50} Although these studies included only a small number of patients with GISTs, they were able to demonstrate that EUS-guided sampling was safe and effective in this setting. Several studies have assessed the efficacy of EUS-FNA for the diagnosis of subepithelial tumors. Ando *et al.* retrospectively examined 49 patients with subepithelial tumors originating in the fourth sonographic layer.⁵¹ The overall tissue yield of EUS-FNA in sampling subepithelial tumors was 91.8%, and the calculated sensitivity for the diagnosis of a GIST was 95%. The diagnostic accuracy of immunohistochemical analysis on EUS-FNA specimens was 91%, compared with 77% accuracy when EUS features alone were examined. Vandernoot *et al.* collected tissue samples from 62 intramural and extramural masses and reported a sensitivity, specificity, and diagnostic accuracy of EUS-FNA of 89%, 88%, and 89%, respectively.⁵² Akahoshi *et al.* reported biopsy data on 53 patients with subepithelial lesions undergoing EUS-FNA, and reported a diagnostic yield of 82% for this technique.⁵³ A 2009 retrospective study evaluated 38 surgically resected, histologically confirmed, c-kit-positive

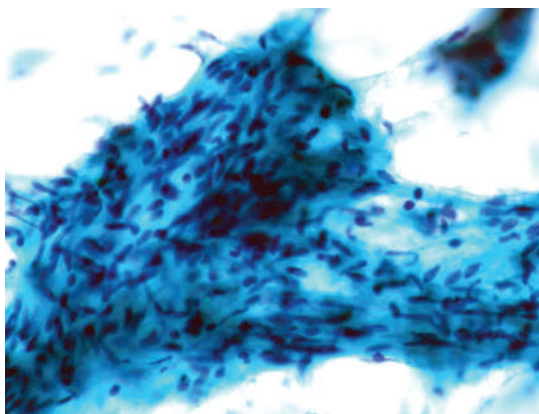


Figure 3 | Cytology smear showing spindle cells from a tissue sample collected by endoscopic ultrasonography-guided fine-needle aspiration.

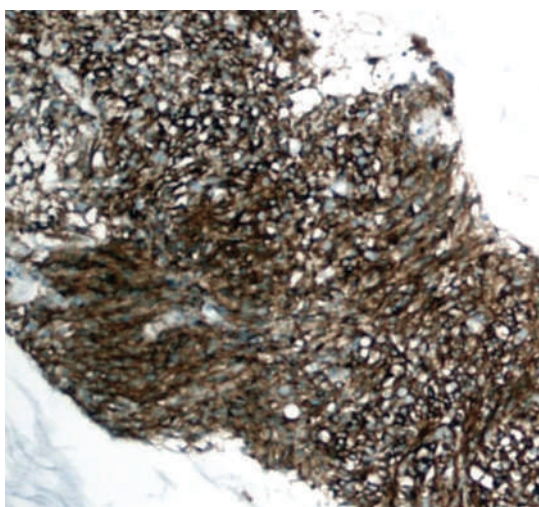


Figure 4 | Cell block specimen showing diffuse brown staining for c-kit immunohistochemistry from a tissue sample collected by endoscopic ultrasonography-guided fine-needle aspiration.

GISTs.⁵⁴ The diagnostic yield and sensitivity of preoperative EUS-FNA was found to be 78.4%. Notably, the presence of an onsite cytopathologist to immediately review the adequacy of samples has been shown to improve diagnostic yield and has proven to be cost-effective.^{55,56}

The use of EUS-FNA has its limitations, including its inability to determine malignant potential on cytological specimens, and an inadequate tissue yield in up to 33.3% of samples.⁵⁷ Nevertheless, the performance of EUS-FNA for the diagnosis of GIST compares favorably with other well-accepted indications of this procedure, such as sampling pancreatic lesions and lymph nodes. Presently, EUS-FNA has proven to be the most accurate and reliable method to secure a diagnosis of GIST. As performance of EUS-FNA is good, but not excellent, more studies are needed to further characterize alternative sampling techniques.

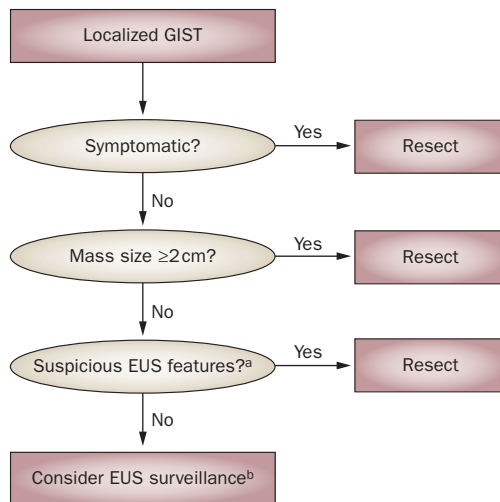


Figure 5 | Proposed algorithm for the management of localized gastrointestinal stromal cell tumors. ^aPossible high-risk endoscopic ultrasonography features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity. ^bEndoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits. Abbreviations: EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal cell tumor.

EUS-guided Tru-cut® biopsy

EUS-guided core needle biopsy using a 19-gauge Tru-cut® needle has been proposed to overcome some of the limitations of EUS-FNA. The Tru-cut® needle is a spring-loaded device that yields an actual core of tissue rather than individual cells or small groups of cells. The use of tissue cores enables immunohistochemical staining, as well as affording the theoretical benefit of preoperative assessment of malignancy risk. The device functions well in the esophagus, rectum, and stomach. However, given that it relies on triggering a spring-loaded cutting sheath, its use is limited in the fundus, antrum, and duodenal bulb, because of the echoendoscope angulation interfering with its deployment.⁵⁸ Preliminary reports that have examined the diagnostic accuracy of Tru-cut® biopsies have been promising, in particular regarding its use in the diagnosis of subepithelial lesions.^{58–60} In this subgroup of lesions, implementation of EUS-guided Tru-cut® biopsy provided an accurate tissue diagnosis in 80% of patients, compared with a diagnostic accuracy of 20% achieved using EUS-FNA.⁶⁰ However, the number of GISTs in these studies was extremely small, totaling five in one study⁶⁰ and two in the other.⁵⁹ In addition, one follow-up study failed to demonstrate a significant difference in accuracy between the two modalities, and reported mediastinitis and bleeding to be complications associated with Tru-cut® biopsy.⁶¹ Technical problems with Tru-cut® deployment were also reported.⁶¹ Other studies have provided conflicting results.^{62–64}

Given anatomical limitations, the risk of complications, and conflicting results reported by studies performed to

date, EUS-guided Tru-cut® biopsy is usually reserved for collecting samples from lesions that cannot be adequately sampled by EUS-FNA and that are in a location suitable for Tru-cut® deployment.

Fine-needle biopsy predictors of malignancy

Several factors have been studied in an effort to provide preoperative cytologic risk assessment. One study showed that the presence of mitoses in specimens collected by fine-needle aspiration were associated with malignant GISTs.⁵¹ However, mitoses are seldom seen on smears. The same study also found that a high Ki-67 labeling index, a protein marker of cell proliferation, was significantly associated with malignant lesions. However, large, prospective studies have not been performed to validate the usefulness of this marker. Since 2001, *KIT* and *PDGFRA* mutation analysis has been proven possible using EUS-guided cell block specimens.^{65–67} As *KIT* mutation analysis has prognostic importance and can be predictive of response to treatment,^{68–72} its preoperative determination may help to guide the approach to treatment in locally advanced and metastatic disease. The clinical role of such testing is currently being investigated.

Management of GISTs

Localized GISTs

The management of localized GISTs remains controversial, as no prospective studies addressing this subject have been published. Some experts recommend surgical removal of all GISTs, regardless of their size, because of the uncertainty surrounding the issue of their malignant potential. However, as the incidental discovery of GISTs on routine endoscopy is increasingly frequent, the resection of all neoplasms may not be feasible. Figure 5 illustrates an algorithmic approach we propose to aid in the management of localized GISTs.

Surgical resection

In the majority of cases, resection is the primary treatment for localized GISTs. The primary goal of surgery is complete tumor removal with clear resection margins. Avoidance of tumor rupture is imperative, as its occurrence has been shown to be associated with a high risk of intra-abdominal dissemination and a poor prognosis.⁷³ Routine lymphadenectomy does not seem necessary as nodal metastasis is rare.⁹ The location of the lesion dictates the type of surgery that should be performed. In cases of esophageal, small intestinal, and rectal GISTs, wedge resections are not usually feasible, and thus wide resections are the surgery of choice.⁷⁴ As GISTs are most commonly found in the stomach, we will focus on the surgical approach to GISTs in this location. Gastric wedge resection is the procedure performed most frequently, and we recommend it as the treatment of choice. However, in some cases, tumor size and location may be an indication for an extensive surgery, including partial or total gastrectomy. In the past few years, laparoscopic wedge resection, which is less invasive than

the traditional technique, has been studied, and it has demonstrated promising results with regard to efficacy, safety profile, and length of hospitalization.^{75–82} Short and long-term outcome in these studies have been equivalent to the open surgical approach. Guidelines suggest that laparoscopic wedge resection may be used for tumors ≤ 5 cm.⁷³ When planning the surgical removal of a GIST, the choice between an open gastric wedge resection and a laparoscopic wedge resection should be made by the individual surgeon, and it is usually based on personal experience and institutional preference.

Following complete resection, guidelines of the National Comprehensive Cancer Network suggest abdominal and pelvic CT scan surveillance every 3–6 months for 3–5 years, and annually thereafter.⁷³ Less frequent surveillance than this may be acceptable for small tumors (< 2 cm).

EUS surveillance

Although the majority of GISTs should be resected, for a small subset of patients, EUS surveillance may be the best option. No large, prospective studies have assessed the safety of EUS surveillance for patients with GISTs; however, one small case series reported the follow-up of 25 subepithelial tumors over a mean period of 19 months. This study found that 24 of 25 lesions (96%) remained stable with regard to size and EUS features. One lesion in this study increased in diameter from 30 mm to 38 mm and became irregular and nonhomogenous during follow-up. This lesion was subsequently identified as a GIST of high malignant potential at resection.^{43,83} Guidelines differ slightly in their recommendations regarding the use of EUS surveillance in this setting. The American Gastroenterological Association recommends removal of all GISTs with diameter ≥ 3 cm, as well as tumors < 3 cm with concerning endosonographic features (for example, an irregular border, presence of cystic spaces, echogenic foci, heterogeneity).⁴³ The National Comprehensive Cancer Network recommends removal of all GISTs with size ≥ 2 cm,⁷³ whereas the European Society for Medical Oncology recommends removal of all GISTs > 2 cm.⁴¹ All guidelines recognize that the management of small, incidentally discovered GISTs remains controversial. Taken together, these guidelines suggest that surveillance is probably a safe approach for the management of the asymptomatic patient with an incidentally discovered small GIST (< 2 cm), which does not display suspicious endosonographic features.⁴³ Although an irregular border is, aside from size, the only high-risk feature recognized for GISTs by the majority of available studies, additional features, such as cystic spaces, ulcerations, echogenic foci, and heterogeneity have been shown to be predictive of high risk in some patient series.^{33,36–40} Thus, the presence of any of the above characteristics should probably suggest a surgical approach and preclude EUS surveillance as a primary management strategy. Monitoring with EUS should also be considered for elderly patients with significant comorbidities and a high surgical risk.

Given the dearth of data on the safety and limitations of an EUS surveillance strategy, a thorough discussion with the patient regarding the possible malignant potential of all GISTs, as well as the risks and benefits of serial examinations versus surgical resection, should be undertaken before proceeding with this approach. When opting for EUS surveillance, the gastroenterologist should be aware that compliance with serial examinations has been shown to be low. The study by Nickl and colleagues demonstrated that only 50% of patients completed even one follow-up surveillance examination.⁴⁰

Optimal timing of surveillance has not been investigated, and the frequency of EUS examination should, therefore, be selected on a case by case basis. The most common frequency selected is 1 year,⁸⁴ although more frequent surveillance may be necessary depending on the clinical scenario.

Endoscopic resection

Endoscopic resection of GISTs, which are located in the muscularis propria, is rarely implemented because of an inability to obtain a complete resection, and because implementation of this procedure is associated with a high rate of complications (for example, bleeding and perforation). Several small case series have studied varying techniques, including endoscopic submucosal resection, endoscopic submucosal dissection, endoscopic band ligation, and endoscopic enucleation using an insulated-tip electro-surgical knife.^{85–88} Efficacy and complication rates varied in these studies, and follow-up was limited. The uncertainty associated with the adequacy of resection, and the high complication rates associated with these procedures, means they do not have a role in the management of GIST.

Locally advanced or metastatic GISTs

An in-depth discussion on the management of locally advanced and metastatic GISTs is beyond the scope of this article. However, since 2000, treatment options have been changed substantially by the development of imatinib mesylate, a selective inhibitor of certain tyrosine kinases, including c-kit and the platelet-derived growth factor receptor, α polypeptide.^{89,90} In the setting of locally advanced or metastatic GISTs, patients should be referred to an oncologist for discussion regarding initiation of imatinib therapy.⁸⁹ In the case of localized, large GISTs that are initially considered unresectable, neoadjuvant imatinib therapy may be implemented for 6–12 months before surgery to increase the chance of complete resection and to decrease morbidity.⁴¹ Imatinib may also be useful as an adjuvant therapy after surgery.⁴¹ In a 2006 study, sunitinib, another tyrosine kinase inhibitor, has been shown to be useful in patients with advanced GIST after failure of imatinib therapy.⁹¹ Imaging can be used to monitor response to tyrosine kinase inhibitor therapy. Performing a CT scan, and possibly a PET scan, is recommended within 3 months of initiating therapy,⁷³ and serially thereafter with the frequency of scans dictated by the response to treatment.

Conclusions

The diagnosis and management of GISTs represent a unique challenge to gastroenterologists. This Review has attempted to provide an overview of GISTs, with an emphasis on the endoscopic diagnosis and the management of localized disease. As large, prospective studies have not been performed to help guide GIST management, the diagnostic and therapeutic approach to the small, incidental GIST is mostly empirical and extrapolated from small case series. Future studies will need to focus on alternative sampling methods to provide core tissue, the preoperative determination of malignancy risk, and the role of minimally invasive endoscopic therapeutic interventions.

Review criteria

PubMed was searched using the terms “gastrointestinal stromal tumor”, “gastrointestinal stromal cell tumor”, “GIST”, “stromal cell tumor”, “submucosal tumor”, “subepithelial tumor”, “endoscopic ultrasound”, “endoscopic ultrasonography”, “EUS”, “endoscopic ultrasound-guided fine-needle aspiration”, “fine-needle aspiration”, “Tru-cut® biopsy”, and “endoscopic submucosal resection”, both alone and in combination. Original articles, reviews, practical guidelines, letters, editorials, and their reference lists were considered. There were no language restrictions. Emphasis was placed on randomized, controlled trials, and reviews were cited in areas where there were no marked updates.

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