Gastrointestinal Stromal Tumors—Diagnosis and Management: A Brief Review

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ABSTRACT
Gastrointestinal stromal tumors (GISTs) are rare but are the most common mesenchymal tumor in the gastrointestinal tract. They arise from a precursor cell in the myenteric plexus, and most tumors express a characteristic CD117 antigen, which is part of a tyrosine kinase receptor. This finding has led to the development of novel chemotherapeutic agents targeted at these receptors and has revolutionized the treatment of these tumors, which had been historically disappointing. Surgery is recommended for tumors >2 cm in size and even has a role in metastatic disease. The approach to tumors <2 cm in size is more controversial, as these lesions tend to be less aggressive, but the true malignant potential of GISTs can only be determined by surgical resection and histologic evaluation.

INTRODUCTION
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract. However, they only constitute approximately 1% of all primary GI tumors. They may occur anywhere in the GI tract from esophagus to anus, and rarely in the omentum and mesentery adjacent to the GI tract. GISTs are most commonly found in the stomach (60%–70%) and small intestine (20%–30%). Colorectal (5%) and esophageal (5%) tumors are less often encountered.

The neoplastic GIST cells appear to originate from a precursor cell lineage in the myenteric plexus which also differentiates into the interstitial cells of Cajal.

EPIDEMIOLOGY
Older epidemiologic data, such as that from the National Cancer Institute’s Surveillance, Epidemiology, and End Results registry, may be inaccurate because of misclassification of GISTs as smooth muscle tumors. Nevertheless, the data suggest the incidence of GISTs to be about 10 to 20 cases per million per year. However, the incidence of very small subcentimeter GISTs may be much higher. Two small studies demonstrated the presence of microscopic GISTs in resected stomachs in up to 35% of patients. This finding has led some experts to believe that most small GISTs do not progress to a clinically relevant size with malignant potential.

Symptomatic GISTs typically do not occur before the 6th decade of life, and asymptomatic tumors may go completely undetected until autopsy, if at all. There may be a small male predominance. Up to 30% of GISTs may be malignant at the time of diagnosis.

PATHOGENESIS AND HISTOLOGY
Morphologically, GISTs can range in size from a diameter of a few millimeters to extremely large masses measuring more than 30 cm. They generally appear as a single, well-circumscribed submucosal mass but may also form polyoid serosal or mucosal masses. Multiple tumors at different sites in the GI tract should raise a suspicion of familial GISTs.

GISTs are histologically defined as spindle cell, epithelioid, or sometimes pleomorphic tumors arising from the GI stroma/mesenchyma. The differential diagnosis of these stromal tumors is broad and includes leiomyoma, leiomyosarcoma, malignant melanoma, schwannoma, malignant peripheral nerve sheath tumor, desmoid tumor, inflammatory myofibroblastic tumor, solitary fibrous tumor, sarcomatoid carcinoma, neuroendocrine carcinoma, and angiosarcoma. GISTs, however, have a characteristic immunohistochemical pattern in that almost all (95%) express the CD117 antigen, which is part of the c-kit tyrosine kinase receptor. Most other GI mesenchymal tumors are negative for CD117, although some sarcomas (angiosarcomas, Ewing’s sarcoma), seminomas, and metastatic melanoma and small cell lung carcinoma can also be immunopositive for c-
A small percentage of GISTs (~5%) will not stain for CD117 (c-kit). The diagnosis of GIST in these cases is more challenging, and clinical factors such as tumor location and morphology are strongly considered. In addition, some GISTs also stain positive for other markers such as CD34 (60%–70%) and smooth muscle actin (30%–40%). Finally, gene mutation analysis can assist in the diagnosis, as about 80% of GISTs have a mutation in the KIT tyrosine kinase gene, and a smaller subset (5%–7%) will have a mutation in the platelet-derived growth factor (PDGFRA) tyrosine kinase gene.\(^\text{14,18,20-25}\)

**CLINICAL PRESENTATION**

GISTs are often incidentally detected during endoscopic or radiographic studies or during surgery for other conditions.\(^\text{1}\) Symptomatic esophageal GISTs usually present with dysphagia or as a mediastinal tumor.\(^\text{26}\) Symptomatic gastric and small bowel GISTs usually present with nonspecific complaints such as early satiety and bloating. Occasionally they can ulcerate and bleed, or grow large enough to cause pain or obstruction.\(^\text{17,27,28}\) Symptomatic colorectal GISTs may present with lower GI bleeding, perforation, pain, or obstruction. An externally palpable mass may rarely be present with malignant GISTs.\(^\text{1}\) Paraneoplastic production of insulin-like growth factor II leading to severe hypoglycemia has been described in rare cases.\(^\text{29}\)

The most common location of metastatic GIST is in the liver and peritoneum. Lung metastases are rare, although this is the most common site of metastatic disease for other soft tissue mesenchymal tumors.\(^\text{20,30,31}\)

GISTs may also present as part of a rare syndrome in young women named “Carney’s triad,” which includes primarily gastric GISTs, paraganglioma, and pulmonary chondroma. The GISTs in this syndrome can exhibit different behavior from other GISTs in that they can be quite indolent even after metastasizing.\(^\text{32}\) Another distinct autosomal dominant familial syndrome consisting of multicentric paragangliomas and multifocal GIST tumors has also been seen in young men and women.\(^\text{33}\)

**DIAGNOSIS**

As mentioned previously, GISTs are often incidentally found during investigation for unrelated problems. Contrast-enhanced computed tomography (CT) (or occasionally magnetic resonance imaging) is the imaging modality of choice to further evaluate an abdominal mass or nonspecific abdominal symptoms. GISTs usually appear as hyperdense enhancing solid mass lesions with IV contrast. Occasionally they may appear heterogeneous if there is necrosis, hemorrhage, or degeneration within a very large tumor.\(^\text{14,34}\)

When a small tumor is found on endoscopy, CT should be used to determine extent of the primary lesion or presence of metastases.\(^\text{14}\)

FDG (\(^{18}\)fluoro-deoxy-glucose)-positron emission tomography (PET) scan can add information on tumor metabolic activity, which can be of value since changes in activity often precede anatomic changes on CT. Combined PET/CT allows for matching and fusing any abnormal FDG activity to an anatomic finding. FDG-PET may be quite valuable in detecting unapparent metastases or an otherwise unknown primary site, and for assessing response to chemotherapy. For the patient with a large mass who is at high risk of metastases (Table 1), FDG-PET scan is recommended for staging. FDG-PET can also be used to determine whether tumor growth seen on CT is from actual tumor progression, which would likely have increased metabolic activity, or from tumor hemorrhage/edema.\(^\text{14}\)

Endoscopically, GISTs, like other subepithelial masses in the GI tract, generally have normal-appearing mucosa overlying the lesion. They usually appear smooth with tapered margins along the edges of the lesion (Figures 1 and 2). Changing patient position and air insufflation/deflation can help the endoscopist to distinguish if the mass is from external compression.\(^\text{36}\) GIST size is important in management; however, endoscopic visualization generally underestimates tumor size.\(^\text{37-39}\) Cold biopsy forceps can be used to estimate the size of the lesion, although this is usually underestimated by visual inspection alone.\(^\text{37-39}\) Forceps can also be used to obtain biopsy specimens and determine mass mobility and consistency. Gentle pressure with the closed forceps does not reveal a “pillow sign,” which is a soft indentation of the wall commonly associated with lipomas. Unfortunately, endoscopic biopsies usually do not obtain sufficient tissue for definitive diagnosis.\(^\text{36,40}\)

Radiologic imaging and routine endoscopic visualization have significant limitations in correctly diagnosing a GIST. These modalities cannot identify the different histologic layers of the bowel wall, and therefore are limited in their ability to differentiate between different causes of intramural masses.\(^\text{36}\) Furthermore, a recent study reported that the sensitivity and specificity of correctly distinguishing an intramural lesion from extramural compression with endoscopy alone was 87% and 29%, respectively.\(^\text{41}\)

Ultimately, endoscopic ultrasound is the most accurate method of reaching a specific diagnosis of a subepithelial lesion. For the purposes of this article, focus will be placed specifically on endoscopic ultrasound (EUS) diagnosis of GISTs only. Sonograph-
GISTs most commonly arise from the hypoechoic 4th layer of the gastrointestinal tract, which is the level of the muscularis propria. Rarely they can arise from the muscularis mucosa (2nd layer) (Figures 3 and 4). They are usually homogeneous with well-defined margins, although liquefaction necrosis, connective tissue deposition, and cystic or hyaline degeneration can change the appearance.\textsuperscript{37,42,43}

Because the differential diagnosis of a hypoechoic submucosal mass arising from the muscularis propria is broad, a definitive diagnosis of GIST can only be made histologically. Endoscopic biopsy with cold forceps typically is not helpful as usually only mucosal (not submucosal) specimens are obtained. However, EUS-guided fine needle aspiration (EUS-FNA) with a 22-gauge needle or core needle biopsy using a 19-gauge Trucut needle can target the lesion to secure a specimen for cytologic or core tissue examination, respectively. As mentioned, GISTs usually express unique immunohistochemical markers such as CD-117 (kit) and CD34, among others. Subsequently, multiple studies have established that GISTs can be reliably diagnosed using both cytomorphologic and immunohistochemical staining features of cytologic material or core tissue specimens obtained at EUS-FNA.\textsuperscript{44–56}

<table>
<thead>
<tr>
<th>Group</th>
<th>Tumor Parameters</th>
<th>% of Patients with Progressive Disease During Long-term Follow Up and Characterization of Risk for Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤2 cm</td>
<td>≤5 per 50 HPFs 0 none 0 none 0 none 0 none</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2 ≤ 5 cm</td>
<td>≤5 per 50 HPFs 1.9 very low 4.3 low 8.3 low 8.5% low</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;5 ≤ 10 cm</td>
<td>≤5 per 50 HPFs 3.6 low 24 moderate</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;10 cm</td>
<td>≤5 per 50 HPFs 12 moderate 52 high 34 high;† 57† high;‡</td>
</tr>
<tr>
<td>4</td>
<td>≤2 cm</td>
<td>&gt;5 per 50 HPFs 0† 50† 5 54 high</td>
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<tr>
<td>5</td>
<td>&gt;2 ≤ 5 cm</td>
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</tr>
<tr>
<td>6a</td>
<td>&gt;5 ≤ 10 cm</td>
<td>&gt;5 per 50 HPFs 55 high 85 high</td>
</tr>
<tr>
<td>6b</td>
<td>&gt;10 cm</td>
<td>&gt;5 per 50 HPFs 86 high 90 high 86 high;‡ 71 high;‡</td>
</tr>
</tbody>
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\textsuperscript{*} Based on previously published long-term follow-up studies on 1055 gastric, 629 small intestine, 144 duodenal, and 111 rectal GISTs.\textsuperscript{12,15,18,30}

\textsuperscript{†} Denotes tumor categories with very small numbers of cases.

\textsuperscript{‡} Groups 3a and 3b or 6a and 6b are combined in duodenal and rectal GISTs because of small number of cases.

\textsuperscript{†} No tumors of such category were included in the study. Note that small intestinal and other intestinal GISTs show a markedly worse prognosis in many mitosis and size categories than gastric GISTs.

Table 1. Risk Stratification of Primary GISTs (Reprinted with permission from Miettinen, M. Gastrointestinal stromal tumors: Pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23:70–83.)\textsuperscript{35}

Figure 1. Endoscopic appearance of a gastric GIST in the antrum.

Figure 2. Endoscopic appearance of a gastric GIST in the fundus.
The general consensus is that essentially all GISTs have malignant potential.\textsuperscript{1,57,58} CT or endosonographic features of increased malignancy risk include tumor size exceeding 3 cm and irregular margins. There is less agreement among experts on the prognostic value of other features, including echogetic foci, cystic spaces, non-oval shape, heterogeneous echotexture, exophytic development, and ulcerated overlying mucosa. Tumors associated with enlarged lymph nodes are also more likely to be malignant.\textsuperscript{6,42,59} However, CT or sonographic features alone are usually not sufficient to assess malignancy risk. Mitotic index of a GIST is an integral part of risk assessment. In fact, size and mitotic count of a tumor were the foundation for a consensus approach to risk stratification of GISTs published in 2002.\textsuperscript{14,18} Unfortunately, cytology obtained by FNA is insufficient to evaluate mitotic count, so tissue obtained via surgical resection is required.\textsuperscript{56}

In addition to size and mitotic count, anatomic location of the tumor factors into risk stratification. In general, nongastric primary location is a risk factor for poorer disease-free survival. Some studies have shown that in the stomach, the most common site for GISTs, benign tumors outnumber malignant ones by up to 5 to 1. On the other hand, most esophageal and colonic GISTs are malignant.\textsuperscript{1,3,5,58,60–63} Table 1 summarizes the risk of progressive disease, defined as metastases or tumor-related death, of GISTs with regard to size, location, and mitotic index.\textsuperscript{35}

**MANAGEMENT**

A recent guideline publication by the National Comprehensive Cancer Network suggests that all localized, nonmetastatic GISTs ≥2 cm in size should be resected.\textsuperscript{14,35} In general, the goal of surgery is segmental resection with an intact pseudocapsule and negative resective margins. Peritumor resection is associated with a higher risk of local recurrence when compared with segmental resection.\textsuperscript{14,64} Thorough exploration of the abdomen for evidence of metastases (especially the liver and peritoneal surfaces) is essential, and careful handling of the tumor is necessary to avoid rupture. Routine lymph node resection is not necessary because nodal metastases are uncommon.\textsuperscript{14,65}

The management of smaller GISTs (<2 cm) is more controversial. The growth rate and metastatic potential of these tumors remains unknown. Endoscopic resection of small GISTs has been reported although risk of positive margins and tumor spillage render this approach contentious.\textsuperscript{66} Laparoscopic resection has been described for gastric GISTs with good results, but data on this surgical approach for tumors in other locations are limited.\textsuperscript{14,67,68} Asymptomatic small lesions with benign endosonographic features may be followed with surveillance; however, a strategy for such surveillance has not been established, and as mentioned, the malignant potential of smaller tumors is not truly known.

Prior to 2001, complete resection of primary GISTs was not possible in approximately 50% of patients, resulting in a median survival of only 1 to 2 years.\textsuperscript{27} Standard cytotoxic chemotherapy regimens have shown significantly dire response rates (0%–5%) for unresectable or metastatic disease.\textsuperscript{57–72} Treatment of these tumors was revolutionized, however, by the subsequent finding that mutational activation of KIT or PDGFRA stimulated their growth. This led to the development of specific small molecule inhibitors of tyrosine kinase such as imatinib mesylate (Gleevec) and sunitinib malate. Two major phase III trials have shown, in patients with unresectable or metastatic
GIST, response rates of about 50% and 1-year progression-free survival and overall survival rates of about 70% and 85%, respectively, with imatinib.\textsuperscript{73,74} The results of these studies led to the 2001 FDA approval of imatinib mesylate for first-line use with metastatic or unresectable GISTs.\textsuperscript{75} Recent long-term results have shown that nearly 50% of patients with advanced GISTs treated with imatinib survived for more than 5 years.\textsuperscript{76} Patients who are intolerant or resistant to imatinib may respond to sunitinib malate (Sutent), which is also an oral tyrosine kinase inhibitor that is less specific than imatinib. Sunitinib was FDA approved in January 2006 as second-line use in patients with advanced GIST.\textsuperscript{14}

In addition to primary therapy for unresectable and metastatic disease, imatinib mesylate is also recommended as neoadjuvant therapy for both large tumors and poorly positioned small GISTs that may be considered marginally resectable on technical grounds.\textsuperscript{14,77–82} For primary localized resectable GISTs, standard of care is surgery followed by postoperative radiologic surveillance.\textsuperscript{14} Unfortunately, previous studies have shown that only about 50% of all patients with localized resectable GISTs remain free of recurrence after 5 years, despite complete tumor resection.\textsuperscript{27,83–85} Several large studies have recently been launched to evaluate the efficacy of adjuvant imatinib for tumor recurrence. Preliminary reports from a phase III trial conducted by the American College of Surgeons Oncology Group are encouraging. In patients with a completely resected GIST at least 3 cm in maximal diameter who received 1 year of adjuvant imatinib vs. placebo, the recurrence rate was only 3% vs. 17% after a median of 14 months.\textsuperscript{94} Surgery may also have a role in recurrent or metastatic disease in patients with stable disease or with limited disease progression on tyrosine kinase inhibitors (TKI) (imatinib or sunitinib). Data from several studies have led the National Comprehensive Cancer Network to recommend surgery for 1) disease that is stable or shrinking on TKI therapy when complete gross resection is possible; 2) isolated areas of progressive disease on TKI therapy after initial response (indicative of secondary drug resistance), while other sites of disease remain stable (limited disease progression); or 3) emergencies including hemorrhage, perforation, obstruction, or abscess. Patients with widespread or diffuse disease progression on TKI therapy (generalized disease progression) should have their imatinib dose increased, have their TKI switched to sunitinib, or be enrolled in clinical trials.\textsuperscript{14} In patients with isolated liver metastases, but multifocal bilobar disease precluding hepatic resection, hepatic artery chemoembolization may also have some therapeutic benefit.\textsuperscript{95–97}

REFERENCES

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