Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and represent 1% to 2% of all gastrointestinal malignancies. They can occur anywhere throughout the gastrointestinal tract and are seen most commonly in the stomach (60%) and small bowel (30%). They constitute 2% of gastric malignancies and 14% of tumors found in the small intestine. Overall, they are rare tumors with an annual incidence of 3000 to 5000 cases per year.\(^1\)

The median age at presentation is 60 years with a slight male predominance. The most common symptoms at presentation are bleeding and abdominal pain. Other symptoms include dyspepsia and early satiety. GISTs are commonly found incidentally during radiologic imaging, endoscopy, and surgery.

Previously thought to be smooth muscle tumors in the class of leiomyomas and leiomyosarcomas, recent pathologic examination has noted mixed neural and myogenic features, leading them to be separately classified as GIST. They are thought to arise from the interstitial cells of Cajal, which are known as the pacemaker cells of the gut. GISTs are characterized by more than 95% being KIT (CD117)-positive. Most are composed of uniform spindle cells (70%), a small fraction are dominated by epithelioid cells, and the remaining tumors are a mix of spindle and epithelioid cells.\(^2\)

**DIAGNOSIS**

GISTs are often diagnosed after resection of an undiagnosed mass and pathologic examination. In Japan, where routine screening upper gastrointestinal endoscopy is performed, many are found in early stages. The recommended evaluation for
a gastrointestinal mass suspicious for a GIST includes CT of the chest, abdomen, and pelvis. On this imaging, the mass appears as well circumscribed and predominately extraluminal. Characteristically, GISTs have a heterogeneously enhancing soft-tissue rim surrounding a necrotic center. Other examinations to consider are positron emission testing, endoscopy, and endoscopic ultrasound (EUS). EUS has been particularly useful to evaluate these subepithelial lesions and for biopsy if necessary. Percutaneous biopsy is not recommended because of the risk of rupturing the tumor and seeding the peritoneal cavity. Tissue confirmation of diagnosis is recommended only if neoadjuvant imatinib is being considered because of unresectability, or if the differential of the mass includes lymphoma.

**STAGING OF GIST**

All GISTs are believed to have malignant potential except perhaps those smaller than 1 cm. Size and numbers of mitoses per 50 high-power fields (HPF) are the best prognostic indicators for determining the malignant potential of GISTs. Multiple staging systems for GISTs have been proposed. Besides size and mitoses, other proposed risk factors include site, evidence of tumor rupture, grade, and KIT mutational status. Using EUS, the characteristics of tumor size, extraluminal border, depth, and heterogeneity have been used to predict the malignant potential of GISTs. However, the criteria proposed by Miettinen and Lasota at the Air Force Institute of Pathology (AFIP) may be considered the current standard for prediction. Miettinen and colleagues reviewed more than 2000 GISTs from multiple anatomic sites, with long-term follow-up, and found size, number of mitoses, and anatomic location were the most important predictors of metastatic potential. A risk stratification system was developed using their findings classifying GISTs on a spectrum from no malignant potential to high. Overall, tumors 5 cm or smaller with five or fewer mitoses per 50 HPF in the gastric location have the least malignant potential, and intestinal GISTs greater than 5 cm with more than five mitoses have the greatest malignant potential. The new Union for International Cancer Control TNM staging system closely parallels the AFIP system. However, variability in reporting remains. Current studies support the need for a standardized approach to histopathologic evaluation and reporting of GIST specimens to improve risk classifications and subsequent treatment recommendations.

**IMMUNOPHENOTYPING AND GENE EXPRESSION PROFILING**

More than 95% of GISTs are positive for the tyrosine kinase receptor protein KIT, which is detected by the antibody CD117. Other common markers are CD34 (60%–70% of GISTs) and smooth muscle actin (SMA) (30%–40%). They are typically negative for desmin and S-100 (<5% positive). In contrast, leiomyomas and leiomyosarcomas are positive for SMA and desmin, and negative for KIT and CD34, which helps distinguish GISTs from other mesenchymal tumors. However, KIT positivity may be seen in metastatic melanoma, angiosarcomas, and other tumors, although other immunotyping often can determine the true histopathology. GISTs can be KIT-negative approximately 5% of the time, making diagnosis particularly challenging.

Because of the ubiquitous KIT positivity among GISTs, whether the level of expression of KIT or the presence of other proteins impacts prognosis is unknown. A retrospective study of 106 patients treated with imatinib mesylate found that expression of KIT, CD34, desmin, and S-100 had no prognostic significance in patients with GISTs.

Gene expression profiling of GISTs has shown that untreated tumors have a distinct homogeneous signature that clusters separately from other sarcomas. Signatures vary by anatomic site, with gastric GISTs having a similar signature to rectal, but small
intestinal GISTs appearing much different. The National Comprehensive Cancer Network (NCCN) GIST task force recently stated that gene profiling remains an investigational tool but may be useful in identifying molecular targets of tumor progression, predicting response to tyrosine kinase inhibitor therapy, and studying pathogenesis.

**MUTATIONS**

Activating mutations of exon 11 are the most common mutations of the KIT receptor gene. Others include exons 9, 13, and 17. Patients without KIT mutations often have mutations of the PDGFR-α receptor (PDGFR) gene that are strongly associated with gastric GISTs and epithelioid morphology. KIT and PDGFR mutations are mutually exclusive and found in 80% to 90% of adult GISTs. In the small cohort of patients who do not have KIT receptor mutations, PDGFR mutations are often found. Some of the high-risk intestinal GISTs that lack either the KIT and PDGFR mutation have been found to have a BRAF mutation. GISTs without a mutation in either the KIT or PDGFR genes are known as wild-type. The clinical significance of the variety of mutations found in GIST has prompted much investigation.

A recent study that evaluated the prognostic significance of these mutations in 127 patients after primary resection of localized GISTs found point mutations and insertions in KIT exon 11 had a statistically significant favorable prognosis, whereas deletions had a worse prognosis and exon 9 mutations had a poor prognosis on univariate analysis. However, on multivariate analysis these findings were not significant. Notably, exon 9 mutations are fairly specific to intestinal GISTs, which have a higher risk for progressive disease based on multiple factors.

The presence and type of KIT mutations have been found to predict response to tyrosine kinase inhibitors in recent multiinstitutional trials. Patients with exon 11 mutations have better objective response rate (63%–83.5%) and increased progression-free survival than those with exon 9 mutations (34%–48% objective response rate) or wild-type mutations (23%–37% objective response rate). However, for those with imatinib resistance or intolerance, GISTs with exon 9 or wild-type mutations had improved responses and progression-free survival to second-line sunitinib than those with exon 11 mutations.

**TREATMENT OF GIST**

Management of GIST requires a multidisciplinary team, including surgeons, medical oncologists, pathologists, and radiologists. Often GISTs are identified after resection of an undiagnosed gastrointestinal mass. Thus, surgeons must be aware of the basic tenets of primary surgical treatment.

The treatment of primary, localized GISTs is surgical resection with negative margins. The morbidity is low for tumors smaller than 10 cm confined to the primary organ, and these can often be removed by a wedge or segmental resection. Lymphadenectomy is not required because these tumors rarely metastasize to the lymph nodes. The most important technical point is to avoid rupture during removal, because it increases the risk of dissemination and recurrence. GISTs are soft, friable tumors and care should be taken when handling to prevent violating the pseudocapsule. A grossly negative margin is all that is required, because microscopically positive margins have not been shown to affect survival, and management should be individualized in terms of re-resection. GISTs located in the proximal stomach, especially on the greater curvature, may be amenable to wedge resection. For larger tumors, wedge resection might impact the capacitance function of the stomach and result in esophageal reflux. Surgical judgment and awareness of the gastrointestinal
problems associated with extensive proximal gastrectomy are required to distinguish when wedge resection can be used as an alternative to a more formal extensive gastrectomy. After primary resection, the 5-year disease-free survival is 96% for patients with low-risk features, 54% for intermediate-risk, and 20% for high-risk.\textsuperscript{4} The median time for recurrence is 19 to 25 months.\textsuperscript{1}

**LAPAROSCOPIC RESECTION OF GIST**

Because microscopically negative margins seem to be less important in determining survival and lymph node staging is unnecessary given the rarity of lymph node metastases, the role of laparoscopy in GIST surgery has increased. Previously, only GISTs less than 2 cm in diameter were considered safe for laparoscopy. Although no large prospective trials have been performed, several case series have defined the safety and feasibility of laparoscopic resection for gastric GISTs. In two series with an average tumor size of approximately 4 cm, the 5-year disease-free survivals were 92% and 96%, respectively.\textsuperscript{19,20} The laparoscopic approach significantly decreased length of stay and blood loss. No port site recurrences were seen. Although the patients in these studies were amenable to primary resection and overall had a low malignant potential, survival was determined by the same factors (size, mitoses) as open. Therefore, the goals of surgery for laparoscopy remain the same as those for open technique: grossly negative margins, removal of the tumor without rupture, avoidance of tumor manipulation, and following the principles of oncology. Use of a hand port is recommended as needed for larger tumors to allow for safe and intact removal, and an experienced endoscopist should be present for localization of intragastric lesions.\textsuperscript{19} Laparoscopic resection of GIST is technically feasible and can be safely performed.

**METASTATIC GIST**

In 20% to 30% of patients, GISTs have already developed metastases to the viscera or the peritoneum at presentation. The most common sites of synchronous metastases or subsequent recurrence are liver, peritoneum, or both. Metastases to the lung and bone occur late. Because of the multifocality and diffuse nature of recurrence, this stage of disease is not usually amenable to surgical resection. Historically, treatment with surgery alone for metastatic GIST was associated with poor survival. However, the treatment of metastatic GIST helped to develop the concept of targeted therapy.

**TYROSINE KINASE INHIBITOR THERAPY**

*Imatinib Mesylate*

In a disease that recurs in approximately 50% of patients within 5 years and chemotherapy is ineffective, the discovery of the mutation of the \textit{KIT} gene in 1998 and the subsequent development of imatinib mesylate, a receptor tyrosine kinase inhibitor, revolutionized the treatment of recurrent and metastatic GIST.\textsuperscript{21–23} Imatinib is a potent selective small molecular inhibitor of a family of structurally related tyrosine kinase signaling enzymes, including \textit{KIT}, the leukemia-specific \textit{BCR-ABL} chimera, and PDGFR\textit{A}.\textsuperscript{8} Imatinib has shown an 80% clinical benefit in phase II trials of patients with advanced or recurrent GIST. Progression-free survival of up to 20 to 24 months has been noted with doses of 400 mg/d.\textsuperscript{2,4} Phase III escalation trials of 800 mg/d did not show a benefit with higher doses of imatinib, except in patients with exon 9 \textit{KIT} mutations. Therefore, a standard dose of 400 mg/d of imatinib in recommended unless the exon 9 mutation exists, and then 800 mg/d is recommended.\textsuperscript{24} Primary resistance to imatinib can occur (ie, disease progression within 6 months of treatment). However,
secondary resistance (progression after 6 months after evidence of initial effectiveness) occurs more frequently, with an average time to progression of 20 months. It is believed to occur through development of a secondary acquired KIT mutation. Therefore, the development of other agents has been necessary.

**Sunitinib Malate**

The U.S. Food and Drug Administration approved sunitinib malate in 2006, another small molecule inhibitor of receptor tyrosine kinases that has been shown to be an effective second-line therapy for patients with GISTs. Sunitinib is believed to bind to different kinases thought to cause aberrant behavior of GIST, and has particular effectiveness in patients who have GISTs with the exon 9 mutation. In a randomized, placebo-controlled, double-blind study of patients with unresectable imatinib-resistant GIST, time to tumor progression improved from 6.4 weeks in the placebo arm to 27.3 weeks in the sunitinib group. Some findings also suggest that imatinib-resistant recurrent disease may respond better to sunitinib after cytoreductive surgery. As more is understood about the molecular biology of GISTs, new targeted therapies are being developed.

**ADJUVANT TREATMENT OF RESECTED GIST**

The benefit of imatinib mesylate in the adjuvant setting has been shown in phase III randomized controlled trials. The recently completed Z9000 and Z9001 trials conducted by the American College of Surgeons Oncology Group (ACOSOG) showed that imatinib provides benefit in patients with intermediate to high risk (nongastric and/or large tumors) that have KIT-positive GIST. A dose of 400 mg/d of imatinib for a year is the recommended treatment. However, controversy over the duration of therapy remains, with future trials being designed to answer this question.

**NEOADJUVANT TREATMENT OF GIST**

Several clinical trials have recently been completed evaluating the efficacy of imatinib in unresectable or marginally resectable disease. Although these studies involved small numbers of patients, tumor size reduction and improved respectability were observed. Despite the limited data, imatinib is the preferred initial treatment for patients with locally advanced unresectable disease. However, until more confirmatory work is performed, the use of imatinib in the neoadjuvant setting for radiographically resectable disease remains investigational and is not currently recommended.

**SURGICAL TREATMENT OF METASTATIC GIST**

Imatinib is the standard for treating recurrent or metastatic GIST. However, because it is associated with a median time to recurrence of less than 2 years, surgical resection in patients with residual disease has been considered. Some patients may benefit from surgical resection of remaining gross disease to improve progression-free survival and prevent secondary resistance, because remaining tumor harbor cells are capable of undergoing mutation and are the clones presumed resistant to therapy. Resection should include removal of all gross disease and may require multivisceral resection, omentectomy, and peritoneal stripping. Because liver metastases are often multicentric and not amenable to traditional segmental or lobar hepatectomy, radiofrequency ablation or hepatic embolization can be performed. Surgical therapy may be especially appropriate for patients who do not have access to clinical trials to receive further medical therapy.
PEDIATRIC GIST

Although rare in children, 1% to 2% of GISTs do occur in the pediatric population and are thought to be fundamentally different entities from adult GISTs. These GISTs typically lack KIT and PDGFRA mutations (wild-type GIST) and strongly express CD117. Pediatric wild-type GISTs have different characteristics from adult wild-type GISTS. A recent study suggested that defects in succinate dehydrogenase may be the impetus for oncogenesis in patients affected by pediatric GIST. Testing for germline mutations in succinate dehydrogenase has been recommended in this population.33 Pediatric GISTs, unlike adult sporadic GISTs, metastasize to the lymph nodes and are more commonly epithelioid. They are almost exclusively gastric in origin and, unlike adult GISTs, are more common in girls. Surgery with repeat resections for recurrence is the mainstay of therapy because response to tyrosine kinase inhibitor therapy may be limited. The NCCN GIST task force recommended that pediatric patients with GIST be referred to specialty centers or treated in the context of clinical trials, because of the unique nature of the tumors.8 The National Institutes of Health organized a consortium for pediatric GIST research (http://www.pediatricgist.cancer.gov/CPGR).

GIST ASSOCIATED WITH OTHER TUMORS AND SYNDROMES

A rare entity that resembles pediatric GIST but is more commonly found in women is known as Carney triad. Patients have multifocal gastric GISTs, paragangliomas, and pulmonary chondromas.34 The clinical course can be prolonged even in the face of lymph node or visceral metastases. Carney-Stratakis syndrome is characterized by the presence of a GIST and paragangliomas.

Inherited germline mutations in either KIT or PDGFRA produce familial GISTs. Associated clinical findings of hyperpigmentation and gastrointestinal dysfunction, such as dysphagia or irritable bowel syndrome, are commonly present. Age of onset is typically in the fifth decade and 90% of patients develop a GIST by 70 years of age. Most familial GISTs have favorable histologic features, and patients do not have a shortened survival if affected.35–37

GISTs are one of the malignancies seen in association with neurofibromatosis-1. Age at presentation is similar to that for adult sporadic GIST, but tumors are more commonly found in the small intestine. Imatinib seems to have limited effect in these patients, and many experience progression, with a median survival of 21 months.38

SUMMARY

GISTs are a unique class of mesenchymal tumors specifically identified within the past decade. Intense molecular and genetic study has been used to characterize these tumors and develop treatment strategies. Although the mainstay of treatment remains surgical resection, therapy targeted at the inhibition of tyrosine kinases has had dramatic results. Because of the rapid accumulation of information about the diagnosis and treatment of these tumors, the NCCN convened a GIST task force to provide updated recommendations in 2010. As understanding of these tumors advances, rapid changes in treatment recommendations will continue and should warrant regular updates in tumor management.

REFERENCES


