Colorectal Gastrointestinal Stromal Tumors: A Brief Review

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are rare lesions that constitute the majority of mesenchymal tumors in the gastrointestinal tract. Within the colon and rectum, they represent 0.1% of all cancers. They can present with a variety of symptoms but are often asymptomatic. Although many lesions may be benign, up to half of patients develop recurrent disease within a few years. Almost all GISTs contain a mutation in the c-kit tyrosine kinase that leads to its constitutive activation and results in cell proliferation. This discovery has led to the immunostaining of the c-kit antigen (CD117) to distinguish GISTs from other malignancies. Radiologic examinations can be helpful in initial diagnosis and staging. Surgery is the best treatment for cure, but recent advances have led to the use of imatinib mesylate, a tyrosine kinase inhibitor, to treat metastatic or unresectable disease, or both. There are currently many clinical trials available to help treat GISTs.

KEYWORDS: Gastrointestinal stromal tumors, colon cancer, imatinib mesylate, CD117/c-kit, surgery

Objectives: Upon completion of this article, the reader should be able to summarize the diagnosis and management of colorectal gastrointestinal stromal tumors.

Gastrointestinal stromal tumors (GISTs) are extremely rare, constituting less than 1% of all gastrointestinal (GI) malignancies.¹ These tumors are even more unusual within the spectrum of colorectal lesions, making up about 0.1% of colon and rectal tumors. Even though they are so rare, they are still the most common mesenchymal tumor of the GI tract.² They were first described by Stout, who thought that they originated from smooth muscle cells.³ Later studies utilizing electron microscopy revealed that these tumors rarely share the same ultrastructural characteristics with smooth muscle.⁴ Mazur and Clark described immunohistochemical staining differences between stromal tumors

and smooth muscle cells and suggested that most of these tumors resemble cells of nerve sheath origin.^{4,5} It was around this time that the term gastrointestinal stromal tumor was first introduced, and since then the category has come to include most tumors that were initially described as leiomyoma, cellular leiomyoma, leiomyoblastoma, and leiomyosarcomas.^{5,6} In one study reviewing over 200 GISTs collected over 20 years, two thirds of the cases were initially described as smooth muscle tumors.⁷

Recent work has described the interstitial cells of Cajal (ICCs) as the progenitors of GISTs because of shared markers, including CD117 (c-kit), a tyrosine

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kinase.⁸⁻¹⁰ In 2001, the National Institutes of Health formed a GIST Workshop to create consensus guidelines for the diagnosis of these tumors.¹¹ One result is that positive CD117 expression has become a major diagnostic criterion for GISTs because it indicates the presence of this tyrosine kinase. Many groups are evaluating their previously diagnosed mesenchymal tumors for the presence of CD117. Miettinen et al in 2001 looked at 144 anorectal tumors, most of which were initially thought to be leiomyomas, and found that they were in fact all GISTs and positive for CD117.¹² Recent work has uncovered the molecular pathways in these tumors and has led to the discovery that a targeted molecular chemotherapy, imatinib mesylate, can effectively treat GISTs.

The goal of this review is to describe the pathogenesis, diagnosis, and management of colorectal GISTs.

PATHOGENESIS

GISTs appear to arise from a mutation in the c-kit tyrosine kinase of the ICCs that results in the tyrosine kinase being in a continuously activated state.^{6,8,11} ICCs regulate peristalsis within the GI tract. They have been shown to express the cell surface markers CD34, a hematopoietic progenitor cell antigen, and CD117, or c-kit, a transmembrane tyrosine kinase. GISTs share these markers, and thus it is thought that ICCs and GISTs arise from the same progenitor cell line or that GISTs may arise from a subset of ICCs.^{8,9} Normal function of the c-kit tyrosine kinase involves stimulation by stem cell factor, resulting in cell proliferation and growth¹³ (Fig. 1).¹⁴ Mutations of this gene that cause its constitutive activation result in tumor growth.¹¹ C-kit's tyrosine kinase activity is essential for the development of GISTs,¹⁵ and CD117 has become the standard marker for diagnosing the tumor by immunophenotyping.¹¹

Figure 1 Schematic of c-kit tyrosine kinase. (Adapted from figure from Novartis Glivec website.¹⁴)

The most common mutations of the c-kit gene occur on exon 11, which translates to the transmembrane domain of the molecule.^{2,11,12,16} Other mutations have been demonstrated on exons 9 and 13, which result in modifications of the extracellular and kinase domains, respectively.^{11,16} Exon 17 has also been described to contain an activating mutation.¹⁷ Whereas one study¹⁶ appeared to show a similar prognosis for tumors with exon 9 or exon 11 mutations, others have indicated that tumors with mutations on exon 11 are more aggressive.¹¹ A small percentage of GISTs appear to be c-kit negative on immunostaining and usually have a mutation on a different tyrosine kinase, the platelet-derived growth factor receptor- α (PDGFRA). There is no consensus on how many GISTs are c-kit negative, but the vast majority contain activated c-kit. This is why GISTs appear to be susceptible to molecular therapy that targets this molecule.¹⁷

EPIDEMIOLOGY

GISTs from the entire GI tract have a described incidence of 6.8¹⁸ to 14.5 cases per million.⁷ The average age of presentation is about 60 years with ranges extending from 16 to 94.^{12,18-22} The male-to-female ratio has been reported as from 1:1 up to a 2:1 male predominance.^{18,20,21,23,24} In a population-based study utilizing SEER data from Tran et al, a majority of cases were localized in the stomach (51%), with the small bowel being the next most common location (36%). Colorectal GISTs constituted 12% of the total, and esophageal lesions made up the remaining 1%.¹⁸ Although not described in this study, a small percentage of GISTs also occur in the omentum, mesentery, and retroperitoneum.² This distribution pattern is similar to that in most other published studies. Racial breakdown of the patients showed 71% to be white, 14% black, and the remaining 15% not specified.¹⁸

Up to 30% of GISTs are considered malignant.^{2,25} Median survival for patients presenting with GISTs was 3 years, with an estimated 1-year survival of 80% and 5-year survival of up to 45%.^{18,26} Survival may not be affected by anatomic location,¹⁸ but some studies have suggested that people with esophageal or gastric GISTs have better survival.²⁷ One study evaluating 69 lesions had a high proportion of small, gastric lesions and an overall 5-year survival of 84.3%, suggesting a better prognosis for patients with stomach lesions.²⁸

DIAGNOSIS

There are several case reports of colorectal GISTs, and most arose with bleeding or obstruction.²⁹⁻³³ Published series have described GI bleeding, constipation, rectal or pelvic pain or both, obstruction, and mass on examination as being the most common initial

Figure 2 Computed tomography of a rectal gastrointestinal stromal tumor. White arrows are directed at the lesion. (Courtesy of C.O. Menias, M.D., Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO.)

symptoms.^{20,24,34–37} Other signs and symptoms on presentation can include anemia, weight loss,²⁴ or even urinary symptoms such as hesitancy and decreased stream strength, which was seen with a rectal mass abutting the prostate.³⁸ Up to 21% of tumors are found incidentally on radiologic examinations done for other reasons.⁷ The most common imaging modalities used to diagnose colorectal GISTs are computed tomography (CT), magnetic resonance imaging (MRI), and endoscopy or endoscopic ultrasonography (EUS).

CT scans with intravenous contrast are excellent for diagnosing, staging, and surgical planning. Most lesions are extraluminal or intramural. Smaller tumors, under 6 cm, are usually homogeneous, whereas larger tumors tend to have a heterogeneous appearance with central areas of necrosis. Colonic lesions can grow circumferentially, which may result in proximal bowel dilatation. Anorectal lesions appear well defined and usually do not have any lymphadenopathy.²⁶ CT has the ability to evaluate for size, shape, local invasion, and distant metastatic disease (Fig. 2).

MRI can be used in a similar manner to examine the entire abdominal cavity. Three studies evaluating rectal GISTs showed a low-intermediate signal intensity on T1-weighted images and a heterogeneous or homogeneous high signal intensity on T2-weighted images.^{35,38,39} MRI gave a benefit similar to that of CT in evaluating size, border, and metastatic disease. EUS gives information different from that of either CT or MRI, such as demonstrating a tumor's origin from the

muscularis propria.⁴⁰ Endoscopy can be used when tumors are small and polypoid²⁴ and it allows tumors to be removed by biopsy alone if they are small enough. For large masses, preoperative biopsy is not a part of the treatment algorithm as it is associated with a high risk of bleeding and could seed the biopsy tract with tumor.⁴¹

The histologic descriptions of GISTs demonstrate three common morphologies: spindle cell, epithelioid, or a combination of the two^{1,24,42} (Fig. 3). The report from the GIST Workshop suggests that the spindle cell variant constitutes about 70% of tumors from the entire GI tract, the epithelioid variant is apparent in only 20%, and the remaining tumors have a mixed appearance.⁴² A study by Tworek et al, evaluating 22 anorectal GISTs, found that anorectal lesions were most likely to be of the spindle cell variant.³⁶ This differed from the same group's evaluation of colonic GISTs, where the morphology appeared more epithelioid and more heterogeneous in nature.⁴³

As described earlier, the definitive diagnosis of GIST now relies on the tumor's positive expression of the c-kit tyrosine kinase molecule, also known as CD117. Much work has gone into the immunophenotyping of GISTs and separating them from other mesenchymal tumors of smooth muscle and neural origin. Normal colonic smooth muscle is positive for desmin and actin but negative for CD34 and CD117. An early marker used to diagnose GISTs was CD34, the hematopoietic progenitor cell antigen. CD34 expression appears to vary in GISTs depending on anatomic location.

Figure 3 (A) Spindle cell variant. (B) Epithelioid variant. (Courtesy of H. Wang, M.D., Department of Pathology, Washington University School of Medicine, St. Louis, MO.)

One study showed CD34 expression to be 46% in gastric GISTs and up to 100% in tumors from the rectum.⁴⁴ Another group described 91% expression in a series of more than 100 GISTs, but the subset of small intestine tumors was limited to only 38% expression.¹⁹ CD34 expression has been as low as 38% up to 94% in varying studies.^{12,19,45} The original work on CD117 expression, from Sarlomo-Rikala et al, showed CD117 to be positive in at least 85% of GISTs, with limited expression in other mesenchymal tumors such as leiomyomas and gastric schwannomas, making it more useful than CD34.⁴⁶ As later studies revealed the role of c-kit in the pathogenesis of GISTs, the CD117 expression was seen to be almost 100%, with few exceptions.¹⁷ Nestin is another marker and has been reported in one study to be expressed in 90 to 100% of GISTs.⁴⁵

The differential diagnosis for GISTs varies with the method of evaluation. Although CD117 is expressed in almost all GISTs, there are several other tumors that are also CD117 positive, including metastatic melanoma and Ewing's sarcoma^{2,44,46} (Table 1). Other markers, such as desmin, s-100, and β -catenin, can be used to differentiate GISTs from solitary fibrous tumors, schwannomas, and desmoid-type fibromatoses, respectively, by their higher expression in these tumors.⁴⁷ A common benign lesion that is CD34 positive but c-kit negative is the inflammatory fibroid polyp.^{24,44,48} Histologically similar tumors include smooth muscle tumors, inflammatory fibroid polyps, fibromatoses, schwannomas, inflammatory myofibroblastic tumors, and solitary fibrous tumors.^{25,45,49} Radiologic studies

Table 1 C-Kit-Positive Tumors

Gastrointestinal stromal tumor (GIST)
Mast cell neoplasias
Malignant melanoma
Seminoma/dysgerminoma and intratubular germ cell neoplasia (IGCN)
Endometrial cancer
Follicular and papillary thyroid cancer
Merkel cell carcinoma
Adenoid cystic carcinoma of salivary gland
Malignant glioma
Angiomyolipoma
Acute myeloid leukemia
Small cell lung cancer
Malignant fibrous histiocytoma
Clear cell sarcoma
Ewing's sarcoma

Adapted from Orosz et al.²⁴

give an alternative differential for intramural intestinal tumors including carcinoma, lymphoma, melanoma, carcinoid, and other mesenchymal tumors. Lymphadenopathy is often seen with some of these other tumors, notably lymphoma and carcinoma, but is not seen with GISTs.³⁵ Other small submucosal tumors seen on endoscopy include leiomyomas,²⁰ which have low cellularity and are negative for CD34 and CD117, and benign inflammatory fibroid polyps, which have a spindle cell appearance.²⁴

PROGNOSTIC INDICATORS

Many authors have tried to separate GISTs into malignant and benign subgroups. Appelman initially listed mitotic rate, size, local invasion, and cellularity as the best indicators of malignant tumors.⁴ One study of 41 patients with gastric-only tumors from 1982 concluded that high histologic grade, size greater than 5 cm, and local invasion were associated with a worse outcome. Higher grade tumors are associated with worse survival regardless of tumor size and invasion. One study comparing high-grade and low-grade tumors in the setting of complete resection, high grade being defined as more than 10 mitoses per 50 high-power fields (HPF) and low grade as less than 10, showed that low-grade tumors were associated with a 5-year overall survival of 72%, versus only 18% in the high-grade subset.²¹ Another study demonstrated an 8-year disease-free survival of 80% for low-grade tumors, whereas patients with high-grade tumors had a mean disease-free interval of only 18 months.⁵⁰

Currently, the most commonly cited characteristics indicative of a worse prognosis are tumor size and mitotic index or activity, described as the number of mitoses per 50 HPF.^{12,42,51,52} The minimum size for

tumors to be considered at risk for malignancy varies from as low as 5 cm² to as high as 10 to 11 cm.^{19,22,26,28} McGrath et al cited 78% 5-year overall survival in patients with tumors smaller than 10 cm versus only 38% in patients with tumors larger than 10 cm.³⁷ The number of mitoses per HPF also varies. When evaluating anorectal GISTs, Haque and Dean stated that more than 1 mitosis per 50 HPF indicated a high mitotic rate and high risk,⁵² but a more recent study by Tworek et al lists 6 mitoses or more per 50 HPF as a better indicator of malignancy.⁴³ One series of colonic mesenchymal tumors showed that a mitotic index greater than 5 per 50 HPF was consistent with fatal disease.²⁰ The GIST Workshop created a consensus recommendation of risk assessment based on tumor size and number of mitoses, which suggests that size greater than 5 cm with more than 5 mitoses per 50 HPF, size greater than 10 cm with any mitotic rate, or any size with more than 10 mitoses per 50 HPF indicates a high risk for malignancy (Table 2).¹¹

It is unclear whether the anatomic site of initial tumor presentation has a significant impact on prognosis, although some work appears to indicate that patients with gastric GISTs have a decreased risk of dying compared with patients with nongastric GISTs.^{7,27} A separate study appeared to show that higher grade tumors appeared more often in the intestine and rectum than in the esophagus and stomach.²⁸ It is not clear that colorectal GISTs have a worse prognosis, although they may arise later than tumors of the upper GI tract. The large population study by Tran et al did not see any difference in prognosis based on anatomic location.¹⁸ A small review of 20 colonic GISTs evaluated outcomes on the basis of location within the colon. It suggested that ascending colonic lesions may metastasize more frequently than other colonic lesions, but this was not statistically significant.⁴³ There is currently no consensus on whether or not anatomic origin is important to prognosis.

Other prognostic indicators include radiologic examination findings, tumor location, surgical results, and type of mutation. Heterogeneous enhancement and central necrosis on CT have been shown to be a significant predictor of high-grade lesions or metastatic disease, or both.^{23,28} Other findings that correlated with a higher grade include larger size (> 11 cm), irregular surface, local invasion, and metastatic disease.²⁸ EUS can be helpful to distinguish benign from malignant tumors. Chak et al described findings of size greater than 4 cm, irregular extraluminal border, echogenic foci, and cystic spaces within the tumor, all of which are linked with malignancy.⁵³

Unresectability of the primary tumor was associated with a poor outcome prior to the use of imatinib mesylate. In a prospective evaluation of 200 GISTs by DeMatteo et al, there was a median survival of 66 months for patients with complete resection,

Table 2 Risk Assessment in Gastrointestinal Stromal Tumors

	Size	Mitotic Count
Very low risk	< 2 cm	< 5/50 HPF
Low risk	2–5 cm	< 5/50 HPF
Intermediate risk	< 5 cm	6–10/50 HPF
	5–10 cm	< 5/50 HPF
High risk	> 5 cm	> 5/50 HPF
	> 10 cm	Any mitotic rate
	Any size	> 10/50 HPF

From the NIH GIST Workshop.¹¹

whereas those without complete resection had a median survival of only 22 months.²² In another study, patients with GI tract-only disease had a 5-year overall survival of 58% versus 20% in those with local invasion.³⁷ Location of tumor in the muscularis propria has correlated with a higher percentage of malignant tumors.^{36,43,52} Tumors that contain exon 11 mutations appear to be associated with higher mitotic rates, more recurrent disease, and higher mortality than with those without exon 11 mutations.⁵⁴ In the 2001 study by Miettinen et al, in which about 59% of 144 tumor samples had exon 11 mutations, the mean survival of patients with exon 11 mutations was 54 months versus 114 months for patients without those mutations.¹² Although these results are not incorporated in the current risk assessment model, they can complement the tumor size and mitoses data in determining malignant potential. Unfortunately, all of these methods are indicators at best, as these tumors are extremely unpredictable and can still metastasize even when appearing benign.⁴²

TREATMENT

Surgery has long been the mainstay of curative treatment of GISTs regardless of their location and extent. There have been a few case reports of colonic GISTs treated with surgical resection^{30,31} but no large-scale prospective studies evaluating colorectal disease alone. Most studies have looked at GISTs from the entire GI tract and have reported that complete surgical excision of known tumor is optimal.¹ There is no known benefit of achieving specific margins on resected specimens.¹¹

Even with early surgical treatment, there is a high risk of hepatic and local recurrence.^{21,24,55} Recurrence rates are usually around 50%,²⁶ with one study showing 42% of patients with recurrent disease at a median of 2 years³⁷ and another reporting 40% recurrence at 2 years from surgery.²² Recurrence rates as high as 76% from gastric primaries and 64% from small bowel primaries have been reported, although no mention of colorectal-specific disease was made.¹ In Miettinen's series of 144 colorectal GISTs, tumors smaller than

2 cm with less than 5 mitoses per 50 HPF had a 5% recurrence rate. This rate increased to 25% when tumor size increased to the 2 to 5 cm range and an 8% incidence of tumor-related death was seen.¹² Up to 66% of all patients with recurrence have liver metastases, making it the most frequent site for recurrence.^{21,22} Peritoneal and local metastases are the next most common. Other locations of recurrence include lungs, pleura, retroperitoneum, bone, and soft tissue.²³ DeMatteo et al saw that lymph node spread occurred in only 6% of patients.²² Whereas GISTs predominantly spread to the liver, leiomyosarcomas spread primarily to the lungs.⁵⁶ This difference could aid in the diagnosis of a difficult to categorize tumor.

There have been a few published cases of colorectal GISTs arising with recurrent disease long after primary resection, one 8 years and another 12 years after resection.^{57,58} Tworek's review of anorectal GISTs suggests that they may have a long potential time for recurrence, more than 4 years after initial resection.³⁶ As a result, a long follow-up of more than 5 years for patients with colorectal GISTs appears to be indicated.

In view of such a high rate of recurrence, many clinicians have tried different chemotherapies, with no success. Doxorubicin and ifosfamide are two treatments that have been used without effect.²² Others have evaluated drug-resistant protein production in GISTs and seen that P-glycoprotein and multidrug-resistant protein (MRP) are more highly expressed in GISTs than in leiomyosarcomas. This may correlate with leiomyosarcomas being more sensitive to chemotherapy and having a better prognosis.⁵⁶ All of this work predated the discovery that imatinib mesylate, a selective inhibitor of certain tyrosine kinases, has an effect on GISTs. Imatinib was initially found to help patients with chronic myeloid leukemia, as it inhibits the activity of the tyrosine kinase BCR-ABL. It was also found to block GIST growth in cell culture through c-kit inactivation while not blocking sarcoma cell line growth.¹⁵ The phase I study showed a dose of 400 mg twice a day to be well

tolerated, with most patients achieving stable disease or partial responses.⁵⁹ A later study showed that a median duration of response was not yet seen at 24 months and that 82% of patients had stable disease or partial responses.⁶⁰ Almost 14% of patients appeared to have early resistance, which is comparable that in to other published data that demonstrated a 12% resistance rate.⁶¹ Patients with PDGFRA mutations may be resistant to imatinib,²⁴ although the tyrosine kinase inhibitor is thought to block this kinase's actions also.¹⁷ Many of these studies led the Food and Drug Administration to approve imatinib mesylate for use with metastatic or unresectable GISTs, or both, in February 2001.⁶²

Responses to imatinib can be seen on imaging, with CT demonstrating decreases in tumor size, density, and contrast enhancement.⁶³ MRI can also reveal a decrease in size and show a decrease in tumor density.⁶⁴ Positron emission tomography (PET) and PET/CT have been shown to be more accurate than CT alone in assessing a tumor's response to imatinib because of PET's ability to assess metabolic activity.⁶⁵ Complete responders to treatment are rare, but in some patients unresectable disease can become resectable. Scaife et al evaluated 126 patients with unresectable disease treated with imatinib. Seventeen patients were able to undergo later surgical resection.⁶⁶ Another case report described a patient with a rectal GIST who refused an abdominoperineal resection but after imatinib treatment was able to receive a sphincter-sparing operation.³² These reports indicate that imatinib treatment can increase the number of patients able to undergo surgical resection for curative intent and reinforce the fact that even in the light of a new, targeted chemotherapy, surgical resection is still an essential part of treatment of this disease.⁶⁶ A treatment algorithm was described from Memorial Sloan-Kettering Cancer Center. It suggests the use of adjuvant therapy with imatinib mesylate after complete resection in high-risk patients and proposes the use of operative therapy after a complete response to neoadjuvant imatinib mesylate (Fig. 4).¹⁷

Figure 4 Treatment algorithm combining surgery and imatinib. (From van der Zwan and DeMatteo.¹⁷ Adapted with permission from John Wiley and Sons.)

FUTURE DIRECTIONS

With GISTs clearly being defined by their CD117 expression, more research is seeking ways to differentiate tumor behavior at the time of diagnosis. A study evaluating gene expression in GISTs has shown significant overexpression of certain gene pairs in tumors that later developed recurrence versus those that did not.⁶⁷ This suggests that tumors with malignant potential could have a measurable expression pattern, or “fingerprint,” that is different from that of benign lesions and that this can be evaluated at the time of initial resection. Also, there is discussion of expanding the role of imatinib in the treatment of patients with resectable GISTs. Although current recommendations are for patients with metastatic or unresectable disease to receive adjuvant imatinib mesylate, there is debate about whether patients with resected but high-risk GISTs should also receive imatinib treatment.¹¹ There are many ongoing studies seeking to evaluate these questions; therefore, patients with GISTs should be considered for several current oncology trials.^{55,68}

CONCLUSIONS

GISTs appear to be a well-defined group of neoplasms resulting from mutations in the c-kit gene and arising from the nonepithelial cells of the GI tract, specifically the interstitial cells of Cajal. They require multimodality therapy as well as long-term follow-up to provide the best chance for cure.

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