Gastrointestinal Stromal Tumors of the Distal Gastrointestinal Tract

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Abstract

Keywords

- gastrointestinal stromal tumors
- mesenchymal tumors
- GIST management

Gastrointestinal stromal tumors (GISTs) are rare in occurrence, but comprise the most common mesenchymal tumors of the gastrointestinal tract and affect between 15 and 20 individuals per million per year. Due to recent advancements in molecular classification of these tumors, medical therapy has provided improved outcomes to a historically surgically managed disease. This review article briefly discusses the molecular characteristics, medical and surgical therapies, and future of GIST management.

Epidemiology

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal (GI) tract. They make up approximately 0.1 to 3.0% of all GI malignancies.^{1–4} These tumors originate from the interstitial cells of Cajal, the pacemaker cells of the smooth muscle within the GI tract. All GISTs are thought to have malignant potential; thus, they are generally not referred to as benign.⁵

While GISTs are rare overall, they are the most common mesenchymal tumor of the GI tract. The median age at diagnosis is 60 years, with a range between 40 and 80 years. GISTs affect men and women at an equal rate, and there is no known racial predominance.⁶ The overall incidence of GIST is difficult to ascertain but is estimated to be 10 to 20 cases per million per year worldwide. Data from the Surveillance, Epidemiology, and End Results database estimates the annual incidence in the United States at 15 to 20 cases per million. European studies have estimated the annual incidence at 11 to 15 cases per million.⁷

Tumor Characteristics

While hereditary cases of GIST occur, the vast majority of cases are sporadic, and can be associated with activation mutations of type III receptor tyrosine kinase (*KIT*), platelet-derived growth factor receptor α (*PDGFRA*), BRAF is B-raf proto-oncogene, serine/threonine kinase (BRAF), NRAS proto-oncogene, GTPase (NRAS), and newly identified succinate dehydrogenase (*SDH*) genes.

KIT Mutations

The *c-kit* proto-oncogene encodes a *KIT*, which was first identified by Hirota et al in 94% of CD-34+ mesenchymal tumors.⁸ Currently, we know that *KIT* alterations from deletions, point mutations, and insertions affect exons 11 and 9, and, rarely, exons 13 and 17 on chromosome 4. Cumulatively, *KIT* alterations are carried by approximately 70 to 80% of GISTs.⁹ Further research has identified that exon 11 carries the best and longest duration of response with imatinib and better survival in advanced disease. While exon 9 has a shorter duration of response to imatinib and overall poorer survival in advanced disease, it is most commonly observed in small bowel GISTs.

PDGFRA Mutations

PDGFRA is a related tyrosine kinase receptor that performs similar activation of signaling intermediates as *KIT*. It is seen in 35% of GISTs lacking *KIT* mutations.¹⁰ *PDGFRA* mutations are from deletions and point mutations in exons 18, 12, and 14 on chromosome 4. They are present in approximately 5 to 10% of the GIST population.⁹ These mutations carry a similar response rate and overall outcome to medical therapy as *KIT* mutations, with the exception of *PDGFRA* D842V, which has very limited response to standard kinase therapy, most commonly observed in gastric GIST.

SDH Mutations

Individuals without the earlier mutations were once considered wild-type (WT) GISTs; however, recent evidence suggests that they may have a *SDH* mutation. *SDH* is an

enzyme involved in the Krebs' cycle, which changes by mutation or altered gene methylation. The result is a loss of subunit *SDH-B* production, which leads to failed DNA methylation.¹¹ Four of 34 patients (12%) with WT GIST without a personal or family history of paraganglioma had germline mutations in subunit *SDH-B* or *SDH-C*. WT GISTs lacking somatic mutations or deletions in *SDH* subunits had either complete loss of or substantial reduction in *SDH-B* protein expression, whereas most *KIT* mutant GISTs have a strong *SDH-B* expression.¹² Testing for this mutation should be considered in any WT GIST,¹³ as this is considered the new classification for WT GISTs.

BRAF and NRAS Mutations

BRAF is a member of the *RAF* family of serine/threonine protein kinases. They are important effectors of the *RAS* activation in the *RAS-RAF-ERK* signaling pathway that connects extracellular signals to transcriptional regulation. *NRAS* is involved in this same pathway. In vitro experiments demonstrated in active *KRAS* and *BRAF* proteins that imatinib therapy was able to switch off *KIT* and its downstream signaling, but not extracellular signals driven by the mutated *KRAS* and *BRAF*.¹⁴ Specifically, the *BRAF V600E* mutation occurs in 7% of adult GIST patients lacking *KIT/PDGFRA* mutations. Although very rare, the *BRAF*-mutated GISTs show predilection for small bowel location and high risk of malignancy.¹⁵

Hereditary cases tend to present at a younger age, and are more likely to be multifocal in nature. Multiple syndromes are associated with GIST. Carney's triad is a syndrome that includes paraganglioma, pulmonary chondroma, and GIST. It is thought to be a variant of multiple endocrine neoplasia and has a strong female predilection. Esophageal leiomyomas, pheochromocytomas, and adrenocortical adenomas have also been described as part of the condition. Interestingly, these patients do not demonstrate mutations in *KIT* or *PDGFRA*.¹⁶ Carney-Stratakis' syndrome is an autosomal dominant dyad that consists of gastric GIST and paraganglioma. Patients with this syndrome also do not have *KIT* or *PDGFRA* mutations.¹⁶ Patients with either syndrome typically present at a young age, and most patients are diagnosed before the age of 30 years. Neurofibromatosis type 1 (NF1) is also associated with GISTs. Seven percent of patients with NF1 have GIST. Mutations in NF1 can also carry a *KIT* or *PDGFRA* mutation. Individuals will present with multifocal

small volume disease, often indolent in nature. Referral to genetic counseling is recommended, if a patient is not previously identified as a NF1 carrier.

Additional immunohistochemical tests for GISTs include CD117, CD34, DOG-1, and Ki-67. CD117, the *c-kit* oncogene product, is expressed in subsets of hematopoietic stem cells, mast cells, melanocytes, and interstitial cells of Cajal of the GI tract. CD117 was almost always (85%) expressed in both benign and malignant GISTs, and was observed both in the spindle cell and epithelioid subtypes of GISTs in all locations. In addition to reacting with the CD34-positive GISTs, CD117 was positive in some CD34-negative cases.¹⁷ CD34, expressed on mesenchymal cells, varies significantly in GISTs, based on their location. It was highest among the esophageal (100%) and rectal tumors (92%), whereas only 50% of the small intestinal GISTs were positive.¹⁸ DOG-1/TMEM16A is a novel marker for GIST, identified by using a conventional rabbit antipeptide antiserum and an in situ hybridization probe. *DOG1* antibodies showed high sensitivity and specificity for GIST, which yielded a positive staining in 370 of 425 (87%) scorable GISTs.¹⁹ It is positive in almost all tumors, and, in combination with the others, may facilitate classification of GISTs. Finally, human nuclear cell proliferation-associated antigen Ki-67, which is an important immunohistochemical marker of proliferation, may also be used as a prognostic factor for GISTs (►Table 1).²⁰

Presentation/Diagnosis

GISTs can occur anywhere in the GI tract. The most common site is the stomach (50–70%), followed by the small bowel (25–35%), colon/rectum (5–10%), mesentery/omentum (7%), and esophagus (< 5%). On rare occasions, GISTs have been reported in the appendix, gallbladder, and urinary bladder as well.⁶ GISTs originate within the bowel wall. They can erode inward toward the mucosa, or outward toward the serosa. Presenting symptoms are variable and depend on the location and behavior of the tumor. Symptoms include GI bleeding, hemo-peritoneum, obstruction, anemia, dysphagia, abdominal pain, and palpable abdominal masses.⁷ A population-based study in Sweden of 288 patients with GIST found that most GISTs were identified due to clinical symptoms (69%). In the same study, 21% were found incidentally at surgery for another disease process, and 10% were found at autopsy.²¹

Table 1 Associated locations and treatment response for known mutations of GIST tumors

Mutation	Rate of presence	Chromosome	Associations
<i>KIT</i>	85%	4	Exon 11: best response to imatinib Exon 9: shorter response to imatinib
<i>PDGFRA</i>	5–10%	4	Exon 18: limited response to imatinib Exon 12: responds to imatinib
<i>SDH</i>	10%	1	Loss of <i>SDH-B</i> : limited response to imatinib
<i>BRAF</i> , <i>NRAS</i>	Rare (1%)	1	Rare, small bowel tumors
<i>NF1</i>	Rare (<1%)	17	Multifocal small tumors

Abbreviation: GIST, gastrointestinal stromal tumor.

Scarpa et al performed a review of 46 studies, including 4,543 patients with GIST. They identified GI bleeding as the most common presenting symptom, with a pooled prevalence of 33%. Abdominal pain was the second most prevalent symptom, with a pooled prevalence of 19%. The pooled prevalence of palpable abdominal mass was 6.9%, and that of obstruction was only 3%.⁷ At the time of presentation, 15 to 50% of the patients had metastatic disease.^{22,23} The most common site of metastasis is the liver, followed by the peritoneum. Metastases to the lymph nodes, bone, and lung can occur but are rare.²² The likelihood of metastasis increases with GISTs > 5 cm, and > 5 mitoses per 50 high-power fields (HPFs).²⁴

Location of the GIST within the wall of the hollow viscera can make diagnosis challenging. Endoscopy should be performed for patients presenting with GI bleeding or anemia; however, endoscopy has a poor diagnostic yield (33%) as a screening tool for GIST, given its location within the bowel wall.⁷ When a GIST is visible on endoscopy, it appears as a submucosal lesion with or without mucosal ulceration. Mucosal biopsy does not often help with diagnosis, unless there is clear mucosal ulceration. Endoscopic ultrasound (EUS) and fine needle aspiration (FNA) have been shown to be more helpful in diagnosis, with a diagnostic yield of 69% for simple EUS, and a diagnostic yield of 84% when combined with FNA.⁷ Biopsy, however, is often not necessary preoperatively, and there is a risk of rupturing and disseminating a GIST with biopsy. Indications for preoperative biopsy include metastatic disease, an unresectable tumor, and suspicion of lymphoma.²⁵ If biopsy is performed, spindle cells, epithelioid cells, or a combination thereof will be identified.

Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are often used as initial imaging modalities to evaluate GISTs. Scarpa et al demonstrated a pooled diagnostic yield for CT of 73.6% and 91.7% for MRI, with no significant difference between the two.⁷ MRI may have an added use in evaluating tumor response to chemotherapy.²⁶ Positron emission tomography is generally not recommended for GIST; it has been shown to be highly sensitive, however, in detecting early response to therapy, and predictive of long-term response in metastatic GISTs with mutated *c-kit* receptor tyrosine kinase.²⁷

Surgical Therapy

Surgery continues to be the gold standard treatment for management of GISTs. A wedge resection, or segmental resection with 1 to 2 cm margins is the operative goal, although this is not well defined in the literature. It is important to avoid violating the tumor capsule, as it can lead to tumor seeding. The location of the GIST determines the operative intervention. For tumors of the small bowel and colon, segmental resections are recommended. Tumors of the upper rectum should be managed with an low anterior resection (LAR), while tumors involving the lower rectum can be treated with full-thickness transanal resection, although this may result in a higher recurrence rate, as reported in a series of 13 patients who underwent wide local excision with a follow-up over 30 years. The group with wide local excision had a higher local recur-

rence rate than that of the radical resection group (77 vs. 31%, $p = 0.006$), despite smaller tumors (4.5 vs. 7.2 cm, $p = 0.05$).²⁸ A discussion should therefore be held, regarding risk of recurrence and impact of quality of life following a more invasive procedure.

Operatively, one may attempt to perform segmental resections laparoscopically. Typically, smaller tumors, which may be removed via a plastic bag to prevent risk of port site tumor recurrence, are candidates for laparoscopic approach. For larger tumors, open procedures with a wound protector should be considered. Multiple retrospective reviews have focused on laparoscopic gastric resection; however, few have commented on small bowel resection. One institution performed a retrospective review of 42 patients with laparoscopic resection of the small bowel, and found minimal morbidity and no mortality.²⁹ Lymphadenectomy is not required, as there is a low risk of lymph node involvement, making a laparoscopic approach permissible in small tumors.

The over-arching goal of surgery to perform a R0 resection, although some retrospective series have identified no difference between R0 and R1 resections. Multiple retrospective series have been inconclusive. In one of the largest retrospective reviews, including 819 patients, 72 patients had R1 resections, which were associated with tumor size > 10 cm, rectal primaries, and tumor rupture. No significant difference in recurrence-free survival (RFS) was found between R1 and R0 resections, irrespective of adjuvant therapy, suggesting outcomes may be dependent on biology rather than surgery.³⁰ If an R0 resection is not feasible, an R1 resection may, therefore, still provide some advantage to the patient (—Fig. 1).

Medical Therapy (Neoadjuvant, Adjuvant, and Metastatic Disease Therapies)

The most well-known and supported medical therapy for GISTs is imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland). Imatinib mesylate (Gleevec) is a selective inhibitor of KIT and PDGFRA (as well as ABL/BCR-ABL, DDR, and CSF1R), and has become the first-line agent for GIST therapy. Imatinib was first identified and utilized in individuals with chronic myelogenous leukemia.³¹ In 2000, imatinib was identified as an effective treatment for metastatic GIST in initial case reports, and then its efficacy and dosing were later proven in phases II and III trials.^{32–35} Finally, in a meta-analysis of the two phase II trials, a lower dose (400 mg) of imatinib was identified as an effective treatment over increased doses.³⁶

Currently, imatinib is utilized in the adjuvant, neoadjuvant, and progressive or metastatic disease setting. Adjuvant therapy is recommended for 3 years, when the risk of recurrence is considered high. Risk of GIST recurrence is greatest in non-gastric tumor location and high mitotic rate;³⁷ however, DeMatteo et al were the first to report that larger size and non-R0 resection were positive predictors of recurrence in a study on 200 GIST patients. A later study, combining 10 series of patients to form a total of 2,560 patients, identified that large tumor size, high mitotic count, nongastric location, presence of

Fig. 1 (A, B) Management of gastrointestinal stromal tumor. EUS, endoscopic ultrasound.

rupture, and male sex were independent adverse prognostic factors, which best correlated to the National Institutes of Health consensus criteria.^{38,39} In addition, 6,430 patients over a median of 39 months demonstrated on a multivariate analysis mitotic count $>5/50$ HPF, tumor size >5 cm, and nongastric location were independent adverse prognostic factors.⁴⁰ Providers should consider using risk calculators to help predict prognosis and indications for adjuvant therapy.

Adjuvant therapy for these patients has been well demonstrated in multiple trials. All studies used 400 mg of imatinib daily, and recommended this dose for approximately 3 years.³⁸ These recommendations are based on three randomized studies: the American College of Surgeons Oncology Group trial Z9001,⁴¹ the European Organization for Research and Treatment of Cancer sponsored randomized trial 62024,⁴² and the Scandinavian Sarcoma Group (SSG).³⁸ In these studies, imatinib improved RFS, as compared with placebo or observation, and the SSG XVIII/AIO (AIO: German Sarcoma Group) study found 3 years of adjuvant imatinib to improve RFS and overall survival (OS), as compared with 1 year of imatinib in a patient population with KIT-positive high-risk GIST (–Table 2).

The use of tyrosine kinase inhibitors (TKIs) in the neoadjuvant setting may decrease the risk of morbidity, due to smaller extent of resection. A phase II trial (RTOG 0132) was designed to understand the use of preoperative imatinib in potential operable metastatic and recurrent disease. Primary lesions (group A) and metastatic/recurrent lesions (group B) had 2-year progression-free survival rates of 83 and 77%,

respectively, while OS was 93 and 91%, respectively.⁴³ An additional study reported on 19 patients with a primary rectal GIST. Neoadjuvant imatinib was used in 15 patients with primary rectal GIST, significantly reducing mean tumor size from 7.6 to 4.1 cm ($p < 0.001$). Nine of these patients underwent surgical resection. Imatinib therapy enabled sphincter-preserving surgery to be undertaken in seven patients who would otherwise have required abdominoperineal resection or pelvic exenteration for tumor clearance.⁴⁴ Neoadjuvant therapy may be used in the neoadjuvant setting safely and may reduce morbidity of resection.

In the setting of metastatic, progressive, or recurrent disease, the primary treatment continues to be imatinib; however, other options include sunitinib and regorafenib, which are both approved for the treatment of GISTs that advanced on prior TKIs (e.g., individuals with exon 9 mutations of *KIT*). Both demonstrate activity against *KIT*, *PDGFRA*, and vascular endothelial growth factors related to tyrosine kinase.

Although imatinib remains the recommended treatment for advanced disease, resistant tumors may benefit from metastasectomy. If individuals demonstrate stabilization of response to imatinib, there is evidence that lessening the tumor bulk may improve survival.⁴³ This is additionally supported by the improved OS in R0/R1 resections combined with therapy, compared with individuals with R2 resections.⁴⁵ If the patient has local progression due to resistance of TKIs, individuals may benefit from surgical resection (–Fig. 1).⁴⁶

Table 2 Medical therapy trials for advanced GIST

Study	N	Design	Year	Tumors	Median follow-up	Survival predictions	RFS
Zhan et al ⁴⁷ (2006) (abstract)	57	Phase II	2004–2005	CD117 + , >5 cm tumor, MR >5/50 HPF	Limited	–	2 patients relapsed at 350 and 680 d postresection
DeMatteo et al ⁴¹ (2009) (Z9001)	354 (359)	Phase III (400 mg imatinib vs. placebo)	2002–2007	KIT + GIST >3 cm	19.7 mo	–	1 y RFS 98 vs. 83% (placebo)
Joensuu et al ³⁸ (2012)	200	Phase III (12 vs. 36 mo of imatinib)	2004–2008	KIT + GIST	54 mo	No improvement survival in the KIT exon 9 or PDGFRA mutations	5 y RFS 65.6% (36 mo) vs. 47.9% (12 mo)
DeMatteo et al ⁴⁸ (2013) (Z9000)	106	Phase II (400 mg imatinib 12 mo)	2001–2003	Tumor >10 cm, rupture, multiple tumors, implants	7.7 y	Worse with tumor size, small intestine, exon 9 mutation, high MR, older age	5 y OS: 83%; 5 y RFS: 40%
Kang et al ⁴⁹ (2013)	47	Phase II (400 mg imatinib 24 mo)	2005–2007	KIT exon 11	56.7 mo	Worse with larger tumor size and high mitotic rate	5 y RFS 46%
Corless et al (2014) (ACOSOG Z9001)	645	RCT	2002–2007	KIT + GIST, >3 cm	74 mo	Worse with larger tumor size, small intestine location, and high mitotic rate	Superior in imatinib arm
Casali et al ⁴² (2015)	908	RCT, phase III (2 y imatinib vs. observation)	2004–2008	Tumor >5 cm, MR 0.10, R0	4.7 y	–	5 y RFS 69 vs. 63%

Abbreviations: GIST, gastrointestinal stromal tumor; HPF, high-power field; MR, magnetic resonance; OS, overall survival; RCT, randomized controlled trial; RFS, recurrence-free survival.

Follow-up

There are no definitive recommendations for follow-up following surgical resection or adjuvant treatment with imatinib. The National Comprehensive Cancer Network currently recommends history and physical examination with repeat CT imaging every 3 to 6 months for 5 years, then annually.¹³

Conclusion

GISTs rarely occur, but comprise the most common mesenchymal tumors of the GI tract. The field of GISTs is evolving, with new molecular classifications and emerging medical therapies. While surgery and medical therapy continue to offer improved RFS and OS, continued research is recommended to better understand progressive disease.

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