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MINIREVIEWS

Current update on molecular cytogenetics, diagnosis and management of gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and are thought to arise from precursors of the interstitial cells of Cajal. GISTs can arise anywhere in the GI tract, but most commonly originate from the stomach and small intestine. The majority of GISTs occur as a result of activating mutations in two receptor protein tyrosine kinases: KIT and/or platelet-derived growth factor receptor-α. Mutational analyses allow for predicting patient prognosis and treatment response. Clinical presentations can vary from no symptoms, typical in the case of small incidentally found tumors, to GI bleeding, abdominal discomfort, and ulcer-related symptoms when the tumor is enlarged. Imaging plays a critical role in the diagnosis and management of these tumors with multiphasic computed tomography serving as the imaging modality of choice. Magnetic resonance imaging and positron emission tomography-computed tomography can serve as imaging adjuncts in lesion characterization, especially with liver metastases, and subsequent staging and assessment for treatment response or recurrence. Surgical resection is the preferred management for small GISTs, while tyrosine kinase inhibitors − imatinib mesylate and sunitinib malate − serve as crucial molecular-targeted therapies for locally advanced and metastatic GISTs. This review article highlights the clinical presentation, pathology and molecular cytogenetics, imaging features, and current management of GISTs.

Key Words: Gastrointestinal stromal tumors; Cytogenetics; Diagnostic imaging; Computed tomography; Magnetic resonance imaging; Imatinib mesylate

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Core Tip: Gastrointestinal stromal tumors (GISTs) often occur as a result of activating mutations in two receptor protein tyrosine kinases: KIT and/or platelet-derived growth factor receptor-α, allowing for effective molecular targeted therapies for these patients. Mutational analyses help predict patient prognosis and treatment response. Imaging plays a critical role in the diagnosis and management of GISTs. Multiphasic computed tomography serves as the imaging modality of choice in their diagnosis and follow-up. It is crucial to understand and identify the key imaging features of GISTs and their expected appearance with treatment response and disease recurrence.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and are thought to arise from the precursors of the interstitial cells of Cajal. GISTs can arise anywhere in the GI tract, most commonly from the stomach and small intestine[1,2]. The majority of GISTs occur as a result of activating mutations in two receptor protein tyrosine kinases: KIT and/or platelet-derived growth factor receptor-α (PDGFRA)[1]. Clinical presentations can vary from no symptoms, typical in the case of small incidentally found tumors, to GI bleeding, abdominal discomfort, and ulcer-related symptoms when the tumor is enlarged. Imaging plays a critical role in the diagnosis and management of these tumors with multiphasic computed tomography (CT) serving as the imaging modality of choice. Magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) can serve as imaging adjuncts in lesion characterization, especially with liver metastases, and subsequent staging and assessment for treatment response or recurrence. Surgical resection is the preferred management for small GISTs, while tyrosine kinase inhibitors − imatinib mesylate and sunitinib malate − serve as crucial targeted therapies for locally advanced and metastatic GISTs[1].

This review article highlights the clinical presentation, pathology and molecular cytogenetics, imaging features, and current management of GISTs.

EPIDEMIOLOGY

The annual incidence of GISTs is estimated to be at least 3000 per year in the United States[1]. GISTs are often diagnosed in older adults ages 50-70 years with a median age at diagnosis ranging from 59 to 66 years[3-5]. GISTs can occur in all geographic and ethnic groups, and men and women are equally affected[6]. There are no known risk factors for developing GIST. A small subset of patients may present with the non-inherited Carney's triad, which is comprised of GIST, often with loss of function of succinate dehydrogenase (SDH), paragangliomas, and pulmonary chondromas[1]. While most GISTs occur sporadically, rare hereditary GISTs have been reported[5]. Familial GISTs are related to inherited germline mutations in either KIT or PDGFRA and also manifest with cutaneous hyperpigmentation, irritable bowel syndrome, dysphagia, and diverticular disease[1]. In Caryney-Stratakis syndrome, patients present with GIST and paragangliomas related to loss of function mutations within SDH genes. Small intestinal GISTs can also be associated with neurofibromatosis type 1, an autosomal dominant disorder in which patients more often present with café au lait spots, gliomas, and neurofibromas[1,5]. A very small group of GISTs (1%-2%) occur in the pediatric population.

CLINICAL FEATURES

Clinical presentations vary depending on the size and location of tumors. GISTs can arise anywhere along the GI tract. They most often arise from the stomach (60%), followed by the jejunum and ileum (30%), duodenum (5%), colorectum (4%), and esophagus or appendix (< 1%)[2]. Rarely, GISTs can develop outside the GI tract in the mesentery, omentum, or retroperitoneum. The majority of GISTs are benign (70%-80%). Patients are often asymptomatic, especially when the tumor size is small (less than 2 cm)[1]. When the tumor is enlarged, symptoms may include abdominal pain, bleeding, abdominal distension, early satiety, fatigue, and palpable mass[7]. Unfortunately, these nonspecific symptoms may result in delayed diagnosis and management of the disease. Infrequently, patients with advanced GISTs may present with severe hypoglycemia and hypothyroidism[8,9]. Laboratory work-up may reveal anemia, which may be related to bleeding or intratumoral hemorrhage. Metastases are uncommon (10%-20% of cases); however, when they do occur, they can occur *via* local or hematogenous spread. The most common metastatic sites include the liver, omentum, and peritoneal cavity[1,2]. Lymph node and extra-abdominal metastases are extremely rare[5]. In severe cases, patients may present with acute abdomen, melena, or hematemesis secondary to frank hemorrhage due to tumor invasion or rupture. Such emergent clinical presentation is more often seen in small intestine GISTs compared to gastric GISTs[5].

Pediatric GISTs occur in approximately 1%-2% of cases and are predominantly seen in girls presenting with multiple nodules in the stomach. These patients typically present with anemia, weakness, and syncope due to GI bleeding[1]. In addition to liver and peritoneal metastases, lymph node metastases uniquely occur in this group of patients.

PATHOLOGY AND MOLECULAR CYTOGENETICS

In gross pathology, GISTs can widely vary in size, ranging from 1-2 cm to more than 20 cm in diameter. The median size at presentation is approximately 5 cm[1]. They are well-circumscribed gray-white to red-brown masses in the bowel wall that can be submucosal, intramural, or subserosal in location[10]. They are generally unencapsulated but may have pseudocapsules. GISTs typically arise from the muscularis propria and exhibit an exophytic growth pattern. Intraluminal or mixed growth patterns may also be seen. There are three main histologic subtypes: (1) Spindle cell (60%-70%); (2) Epithelioid (30%-40%); and (3) Combination of both spindle cell and epithelioid in various proportions[10]. On microscopy, spindle cell subtypes demonstrate highly cellular, fascicular, whorled, storiform, or palisading architecture, while epithelioid tumors appear more fascicular or nested[10]. The mitotic rates can vary widely from virtually absent to high. Other findings may include areas of hemorrhage or necrosis.

The majority of GISTs (80%-90%) occur as a result of activating mutations in two receptor protein tyrosine kinases: KIT and/or PDGFRA. In 1998, Hirota *et al*[11] published the revolutionary finding that the majority of GISTs (94%) expressed activating mutations in KIT (CD117), now a key diagnostic immunohistochemical marker for GIST that distinguishes it from leiomyomas, leiomyosarcomas, or other mesenchymal tumors. KIT belongs to the type II transmembrane receptor tyrosine kinase family that includes PDGFRA and PDGFRB. The c-kit proto-oncogene encodes KIT; in combination with the stem cell factor extracellular ligand, this c-kit product normally plays an essential role in cellular survival, proliferation, and differentiation [10]. Activating mutations in KIT result in altered cell growth. In addition, Hirota *et al* [11] demonstrated that the interstitial cells of Cajal, which are the pacemaker cells involved in regulating the peristalsis located primarily in the muscularis propria, were the only cells that were double-positive for KIT and CD34 in the GI wall. Therefore, GISTs, which share morphological, structural, and immunohistochemical features with interstitial cells of Cajal, are thought to arise from them or their stem cell precursors [10-12]. Germline or sporadic gain of function mutations in c-kit result in both benign and malignant GIST tumorigenesis[10]. Aside from KIT mutation, PDFGFRA mutation can be an alternative cytogenetic change that can also result in similar downstream effects of tumor progression[13]. Hence, imatinib mesylate, a selective adenosine triphosphate-competitive inhibitor of KIT, PDGFRA and PDGFRB, serves as a groundbreaking therapy for GISTs[14]. Furthermore, DOG1, a calcium-dependent, receptor-activated chloride channel protein, has been found to be expressed in GISTs regardless

of mutation type; this marker can aid in the diagnosis of KIT-negative tumors, such as those with PDGFRA mutations that are KIT-negative[15].

Other markers for GISTs include CD34 antigen (70%), smooth muscle actin (30%-40%), desmin (< 5%), and S100 protein (approximately 5%)[16]. The expression of these markers varies depending on the location of the tumor. CD34 is often found in esophageal, gastric, and rectal tumors, while smooth muscle actin is seen in small intestine tumors. Prognostic predictors vary considerably in the literature. It has been suggested that mitotic activity and tumor size are potential prognostic predictors: A mitotic index of at least 5 per 50 high power fields (HPF) and a size greater than 5 cm are suggestive of malignant behavior, while a mitotic index of 5 or less per 50 HPF and a size less than 2 cm are suggestive of benign GIST[1,6,17]. Ki-67 can also be used to predict malignant potential[18]. Tumor location is another prognostic factor; intestinal GISTs demonstrate worse outcomes compared to gastric GISTs with regard to tumor size and mitotic rates[19]. GISTs that carry KIT exon 11 point mutations and insertions have a favorable prognosis, while those with KIT exon 9 mutations or KIT exon 11 deletions have a worse prognosis[19,20]. A small number of patients with GISTs may harbor concomitant *BRAF* gene mutations, which may portend poorer prognosis due to their primary resistance to imatinib mesylate therapy[21]; in such cases, patients may benefit from selective *BRAF* inhibitors. Further genotyping is advised for patients with KIT-negative GIST for management planning.

In the pediatric population, GISTs typically do not have KIT or PDGFRA mutations, and generally demonstrate the epithelioid subtype and express CD117[22]. Compared to adults, these pediatric GISTs uniquely overexpress fibroblast growth factor 4 (FGF4), brain and acute leukemia, cytoplasmic, insulin-like growth factor I receptor, NEL-like 1, cytokine receptor-like factor 1, pleomorphic adenoma gene 1, and FGF3)[23]. With KIT activation, these GISTs are similar to adult GISTs that carry KIT mutations. Although there is limited literature on the clinical benefits of tyrosine kinase inhibitors, sunitinib malate is suspected to be superior to imatinib mesylate in these pediatric cases[23].

IMAGING FEATURES

Fluoroscopic examination

Fluoroscopic examination is not routinely used for identifying GISTs. However, patients who undergo double-contrast barium studies may demonstrate a submucosal or well-circumscribed mass with smooth mucosal surface and obtuse angles at the margins[24]. With necrosis or ulceration, they may demonstrate irregular contours. Evaluation of extraluminal structures is limited with this approach. Further evaluation of the lesion and presence of metastatic disease with cross-sectional imaging is ultimately required.

Ultrasonography

Ultrasonography is not routinely used for imaging GISTs, especially since the tumor origin cannot be well-identified. When small, GIST may be homogeneously hypoechoic. When large, GIST may present as a heterogenous mass, which may reflect internal necrosis or hemorrhage; these findings suggest high malignant potential[25]. Hepatic metastases can be identified, although their sonographic appearance is nonspecific.

CT

CT serves as the imaging modality of choice in the diagnosis and follow-up of GISTs. Multiphasic protocol with noncontrast, arterial, and portal venous phases should be obtained. The noncontrast images help identify hemorrhage and provide a baseline for evaluating tumor enhancement. Adequate gastric distension is essential to help distinguish intramural mass; therefore, negative oral contrast agents can aid in the visualization of the enhancing mucosa[26]. The imaging appearance of GISTs depends on their size and aggressiveness. Classic CT features of GISTs include large, hypervascular, enhancing masses that may demonstrate heterogeneity due to hemorrhage, cystic degeneration, or necrosis[27]. These tumors typically displace adjacent structures and vessels, although they may exhibit direct invasion of adjacent structures resulting in ulceration and fistulization in the GI tract in advanced stages. When small, GISTs appear homogeneous and may be incidentally found on CT or endoscopy. Metastases are present in approximately 50% of patients, and metastases often involve the liver and mesentery; they demonstrate similar imaging features as primary GISTs

[24,27]. Lymph node metastases are extremely rare[27]. Features of high-grade GISTs include liver metastasis, GI wall infiltration, irregular surface, ill-defined margins, inhomogeneous enhancement, and peritoneal spread[28].

Regardless of tumor size, a change from a heterogeneously hyperattenuating mass to a homogeneously hypoattenuating mass with decreased enhancing tumor nodules and intratumoral vessels suggest response to imatinib mesylate[24,27]. The attenuation of treated lesions reaches approximately 20-25 Hounsfield units, which is close to simple density[29]. Although the tumors may enlarge during treatment as a result of intratumoral hemorrhage or myxoid degeneration, this does not suggest disease progression in the setting of decreased tumor enhancement[27]. The Response Evaluation Criteria in Solid Tumors has been found to be insensitive in evaluating treatment response as it does not account for tumor density, intratumoral vessels, or tumor metabolism[30]. Therefore, Choi *et al*[31] proposed a modified CT response evaluation criteria to account for such features on CT as tumor response to tyrosine kinase inhibitor therapy cannot be determined based on size alone (Table 1). Disease recurrence is signified by the development of enhancing tumor nodules within the treated hypoattenuating tumor[27]. A summary of key imaging features is highlighted in Table 2.

MRI

MRI serves as an imaging adjunct, especially for young patients for whom repeated ionizing radiation exposure should be minimized, for evaluating liver metastases, and for evaluating rectal tumors. MRI has been found to be superior in characterizing treated liver metastases compared to CT, especially with identifying foci of hypervascularity[32]. Conversely, MRI is less helpful in identifying mesenteric lesions due to the lack of oral contrast and respiratory gating[32]. Generally, the recommended MRI sequences include T1-weighted in and out of phase axial, T2-weighted coronal turbo spin echo, T2-weighted fat-saturated axial respiratory triggered turbo spin echo, and T1-weighted fat-saturated 3D volumetric acquisition in noncontrast, early arterial, portal venous, and hepatic venous phases[32].

MRI features of GISTs vary depending on the amount of hemorrhage, necrosis and cystic degeneration. Solid tumor components demonstrate low T1 signal, intermediate-to-high T2 signal, and enhancement with contrast[24]. The presence of intratumoral cystic change with low apparent diffusion coefficient (ADC) values are predictors of high malignant potential[33]. A negative correlation between mean ADC values and malignancy risk of GISTs has been demonstrated[33]. Upon treatment response, GIST metastases demonstrate increased T2 signal with increased cystic degeneration of solid tumoral components and increased ADC values[34]. With disease recurrence, new peripheral thickening and enhancement of cystic metastases can be seen[24].

PET-CT

18F-fluorodeoxyglucose (18F-FDG) PET-CT can aid in staging, detecting early response to treatment, and detecting early recurrence of GIST[34]. PET-CT can be helpful in distinguishing tumors from benign tissue given the expected increased glucose metabolism of viable tumor cells. PET-CT is more sensitive than CT in detecting treatment response due to detecting decreased 18F-FDG uptake, which is typically observed before a change in tumor size[35]. Such changes can be detected 24 h to 1 mo after therapy initiation[36]. For patients on imatinib mesylate, increased 18F-FDG uptake may signify treatment resistance or lack of medication compliance.

MANAGEMENT AND SURVEILLANCE

Surgical resection is the mainstay of treatment, especially for small-to-medium sized GISTs without metastasis. Obtaining preoperative biopsy is controversial due to the risk of tumoral hemorrhage and seeding; therefore, postoperative pathology is required for diagnosis[1]. During resection, the tumor should be handled carefully to avoid bleeding, rupture, and peritoneal seeding. Ideally, the tumor resection should include an intact pseudocapsule and negative microscopic margins. Follow-up imaging intervals depend on the GIST's risk group categorization: A very low-risk GIST is likely cured by surgery and does not require follow-up; a low-risk GIST may need annual CT or MRI follow-up for 5 years; an intermediate-risk GIST needs annual CT or MRI follow-up for 5 years with the first scan completed 6-8 mo after surgery; and a high-risk GIST should be followed every 6 mo for the first 5 years, then annually for the next 5 years[35].

Table 1 Modified computed tomography response evaluation criteria for gastrointestinal stromal tumors

Response	Definition
Complete response	Disappearance of all lesions; No new lesions
Partial response	A decrease in size[1] of ≥ 10% or decrease in tumor density (HU) ≥ 15% on CT; No new lesions; No obvious progression of nonmeasurable disease
Stable disease	Dose not meet criteria for complete response, partial response, or progressive disease; No symptomatic deterioration attributed to tumor progression
Progressive disease	An increase in tumor size of ≥ 10% and does not meet criteria of partial response by tumor density (HU) on CT; New lesions; New intratumoral nodules or increase in size of existing intratumoral nodules

[1]The sum of longest diameters of target lesions as defined in RECIST. CT: Computed tomography.

Table 2 Imaging features of gastrointestinal stromal tumors

	CT	MRI
Primary and metastatic GISTs	Small: Homogeneous mass; Large: Hypervascular, enhancing masses with heterogeneity due to hemorrhage, cystic degeneration, or necrosis	Depend on the amount of hemorrhage, necrosis and cystic degeneration; solid tumor components with low T1 signal, intermediate-to-high T2 signal, and enhancement; low mean ADC values may predict high malignancy potential
Treatment response	Homogeneously hypoattenuating mass with decreased enhancing tumor nodules and intratumoral vessels	Increased T2 signal, increased cystic degeneration of solid tumoral components, increased ADC values
Disease recurrence	Development of enhancing tumor nodules within the treated hypoattenuating tumor	New peripheral thickening and enhancement of cystic tumor

CT: Computed tomography; MRI: Magnetic resonance imaging; GISTs: Gastrointestinal stromal tumors; ADC: Apparent diffusion coefficient.

Prior to 2000, cytotoxic chemotherapy had not been found to be clinically effective in the management of GISTs[1]. However, following the Food and Drug Administration approval of imatinib mesylate for treating metastatic and locally advanced KIT-positive GISTs in 2002, the management of GISTs has rapidly expanded. As previously stated, imatinib mesylate is a potent tyrosine kinase inhibitor that acts on enzymes including KIT, leukemia-specific BCR-ABL chimera, and PDGFRA. Imatinib mesylate can be utilized preoperatively to downsize the tumor and/or as adjuvant therapy to prevent recurrence. Preoperative imatinib mesylate can be utilized for large and poorly positioned GISTs that may be marginally resectable; imatinib mesylate has been shown to induce tumor cell apoptosis and decrease tumor glucose metabolism on PET-CT[37]. Postoperatively, 1-year of adjuvant imatinib mesylate has been shown to prolong overall survival, although the optimal duration of postoperative treatment is unclear[38]. For unresectable or metastatic GISTs, a phase II trial of imatinib mesylate therapy demonstrated 68% objective response rate regardless of imatinib dosage, and the median time to at least partial response was 2.7 mo[39]. The median survival of patients with metastatic GISTs improved significantly from 19 mo as reported by DeMatteo *et al*[40] in the pre-imatinib era to 73 mo with imatinib mesylate as reported by Menge *et al*[5]. If there is imaging evidence of disease progression despite using standard-dose imatinib mesylate, dose escalation of imatinib mesylate or utilization of sunitinib malate, a second line tyrosine kinase inhibitor, may be considered[1]. Sunitinib malate acts as a less specific tyrosine kinase inhibitor on KIT, PDGFR, vascular endothelial growth factor receptors, Fms-related tyrosine kinase 3, colony-stimulating factor-1R, and RET; as a result, sunitinib malate demonstrates activity against angiogenesis in addition to tumor activity related to receptor tyrosine kinase inhibition[1]. For imatinib and sunitinib-resistant GISTs, investigational therapeutic options include second generation tyrosine kinase inhibitors, such as sorafenib, dasatinib, and nilotinib[1]. Follow-up CT should be obtained within 3 mo of initiating imatinib mesylate with surveillance scans completed every 3 to 6 mo for unresectable or metastatic GISTs; the follow-up interval can be less frequent for low-risk GISTs[1].

With the advancement of these molecular-targeted therapies, multiple associated adverse effects have been demonstrated, and some of these may be identified on follow-up imaging. Fluid retention is commonly seen with imatinib mesylate and can manifest with pleural effusions, pericardial effusion, ascites, or extensive

subcutaneous edema[27]. Imatinib mesylate can be associated with intratumoral hemorrhage, especially in patients with large bulky tumors[1,27]. Tyrosine kinase inhibitors are associated with pancreatic findings. For instance, imatinib mesylate is associated with asymptomatic pancreatic swelling; a ≥ 22% increase in pancreatic volume has been shown to be a poor prognostic indicator[41]. Conversely, sunitinib malate is associated with pancreatic atrophy, and this finding is associated with poor prognosis[42]. Moreover, there are several case reports of pancreatitis associated with sunitinib malate and sorafenib therapy[43]. It is important to identify these adverse effects on imaging, which would allow for dose reduction, dose interruption, or drug discontinuation in the appropriate setting.

CONCLUSION

GISTs are the most common mesenchymal tumors of the GI tract and often arise from the stomach or small intestine. The majority of GISTs occur as a result of activating mutations in two receptor protein tyrosine kinases, KIT and/or PDGFRA, leading to tumorigenesis. Mutational analyses allow for predicting patient prognosis and treatment response. Clinical presentations can vary from no symptoms to GI bleeding, abdominal discomfort, and ulcer-related symptoms. While most GISTs are benign, some cases can be aggressive with metastases. Imaging plays a key role in the diagnosis and follow-up of these tumors. It is crucial to understand and identify the key imaging features of GISTs and their expected appearance upon treatment response and disease recurrence. Surgical resection is the preferred management, especially for small tumors, while tyrosine kinase inhibitors, including imatinib mesylate and sunitinib malate, can serve as a neoadjuvant and/or adjuvant therapies.

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