Review Article

Gastrointestinal stromal tumor

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Abstract: Gastrointestinal stromal tumor has received a lot of attention over the last 10 years due to its unique biologic behavior, clinicopathological features, molecular mechanisms, and treatment implications. GIST is the most common mesenchymal neoplasm in the gastrointestinal tract and has emerged from a poorly understood and treatment resistant neoplasm to a well-defined tumor entity since the discovery of particular molecular abnormalities, *KIT* and *PDGFRA* gene mutations. The understanding of GIST biology at the molecular level promised the development of novel treatment modalities. Diagnosis of GIST depends on the integrity of histology, immunohistochemistry and molecular analysis. The risk assessment of the tumor behavior relies heavily on pathological evaluation and significantly impacts clinical management. In this review, historic review, epidemiology, pathogenesis and genetics, diagnosis, role of molecular analysis, prognostic factor and treatment strategies have been discussed.

Key Words: Gastrointestinal stromal tumor; GIST; KIT mutation; imatinib

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common (80%) mesenchymal tumor of the alimentary cannel (1-3). It accounts for less than 1% of all gastrointestinal tumors and about 5% all sarcomas (2-4). It represents a wide clinical spectrum of tumors with different clinical presentations, locations, histology and prognosis. GIST can occur throughout the entire gastrointestinal (GI) tract and may have extragastrointestinal involvement as well. The clinical relevance of this tumor was generated by the discovery of its molecular biology and, consequently, of a drug effective in treating the tumor. The following review will discuss the GISTs in all aspects including history, epidemiology, clinical presentation, diagnosis, prognosis and treatment and emphasize on those relevant to diagnosis.

Historic overview

Stromal tumors arising from the GI tract were initially classified as smooth muscle neoplasms including leiomyomas (5), leiomyoblastomas or sarcomas (6), following description by Stout and colleagues in 1940 (7). These descriptions were widely used until the 1970s when electron microscope found little evidence of the smooth muscle origin of these tumors (8,9). With the advent of immunohistochemistry during the 1980's it was soon appreciated that a large number of these tumors did not have immunophenotypic features of smooth muscle, and conversely, expressed antigens related to neural crest cells (10).

The term of "stromal tumors" was first described as a separate entity by Mazur and Clark (11) in 1983 and Schaldenbrand and Appleman in 1984 (12). However, this term was not widely accepted. In 1989, a distinctive subset of these stromal tumors revealing autonomic neural features was recognized and named "plexosarcoma" (13) and subsequently as gastrointestinal autonomic nerve tumor (GANT) (14). There was considerable confusion regarding the origin, differentiation and even clinical behavior of these tumors. In 1994, it was discovered that a significant proportion of GANTs were immunopositive for CD34 (15,16), which was the first relatively specific marker of GISTs during the mid-1990s. Based on the CD34 immunopositivity the possibility that GIST might be related to the interstitial cells of Cajal was raised by investigators (17). Interstitial cells of Cajal, also known as pacemaker cells for peristaltic contraction, are a group of cells found in the muscularis propria and around

the myenteric plexus along the GI tract and have the immunophenotypic and ultrastructural characteristics of both the neural and smooth muscle elements. Meantime, additional studies found that interstitial cells of Cajal express *KIT* and are developmentally dependent on stem cell factor which is regulated through the *KIT* kinase (17,18). However, the following critical issues were not resolved: the exact origin of GIST, the best way to diagnose GIST, and differentiation of benign from malignant GIST. As the developments in studies of GISTs, describing gain-of-function mutations and consequently, constitutive activation of *KIT* receptors in several human tumor cell lines was reported in the mid-1990s (19,20).

Finally in 1998, Hirota and colleagues (21) discovered a specific mutation in the intracellular domain of the *c-KIT* protooncogene in GISTs as well as a near-universal expression of *KIT* protein in GISTs by immunohistochemistry. In the same year, Kindblom and colleagues (22) corroborated findings from Hirota and colleagues by showing the immunoreactivity for *KIT* in 78 of 78 GISTs studied and GISTs shared striking ultrastructural and immunophenotypic similarities with interstitial cells of Cajal. Both studies supported the hypothesis that GIST may indeed derive from stem cells that differentiated toward interstitial Cajal phenotype and confirmed *KIT* as a diagnostic tool for GIST (23). The *KIT* mutation implied a gain-of function linked to the activation of the kinase even in the absence of the binding of the ligand. The identification of the *KIT* mutation was a major breakthrough in the biology of GIST and overall, in cancer biology.

The identification of the biologic driver, activating mutations in *KIT* provided a therapeutic target for the treatment of GIST. One patient with metastatic GIST refractory to multiple types of therapies was treated with STI-571 (Imatinib mesylate- Gleevec; Novartis, Basel, Switzerland), which is a small molecule tryosine kinase inhibitor (TKI) with potent activity against the transmembrane receptor *KIT*, *ABL* kinase and chimeric *BCR-ABL* fusion oncoprotein product of chronic myeloid leukemia. The treatment yielded an early, rapid, and sustained response (24) with supportive preclinical data (25,26). This case provided proof of principle that inhibition of *KIT* by drug therapy was associated with improvement in the disease and brought phenomenal growth in the understanding of GIST biology and therapeutics. Imatinib occupies the ATP binding pocket of *KIT*, thereby preventing substrate phosphorylation, downstream signaling, and thereby inhibiting cell proliferation and survival (23). The remarkable therapeutic efficacy of imatinib in patients with GIST along with accurate diagnoses using CD117 expression (a marker of *KIT* receptor tryosine kinase) resulted in subsequent approval of imatinib in this indication by the US Food and Drug Administration in February 2002 (27). In 2003, Heinrich and colleagues (28) and Hirota and colleagues (29) all found platelet-derived growth factor receptor alpha *(PDGFRA)* gene mutations as an alternative pathogenesis in GISTs without *KIT* gene mutation. In January 26, 2006, Sunitinib, a multitargeted TKI with activity against *KIT*, *PDGFR*, vascular endothelial growth factor (*VEGF*) receptor (*VEGFR*), and *FLT-1/KDR*, also received FDA approval for the management of patients who are refractory or intolerant to imatinib (30).

Overall, about 85% of GISTs are reported to have activating mutation in *KIT* or *PDGFRA* (28,31,32). CD117 (c-*Kit*) immunohistochemistry has proven to be a reliable and sensitive diagnostic tool (22,33,34). With the TKI therapies against *KIT* and *PDGFRA* (imatinib and sunitinib), inoperable or metastatic GISTs are now treatable, and a number of additional alternative drugs are in clinical trials.

Epidemiology

Although the exact incidence of GISTs in the world is hard to determine since the entity was not uniformly defined until the late 1990s, a few estimates and studies indicate the incidences of approximately 14.5 cases/million/year in Sweden (35), 14.2 in Northern Italy (36), 13.7 in Taiwan (37), 12.7 in Holland (38), 11 in Iceland (39) and 6.5 in Norway (40). In a recent report, about 5,000 new cases of GISTs were diagnosed annually (41) and a incidence of 6.8/million from 1992 to 2000 (38) in the United States. The overall incidence rates of GIST, therefore, ranges between 6.5 and 14.5 per million per year. In general, little information on the prevalence of GIST was available. It is believed that the prevalence of GIST is higher, as many patients live with the disease for many years or develop small GISTs only detected at autopsy or if a gastrectomy is performed for other causes (42). A study performed in Germany on consecutive autopsies revealed small (<10 mm) GISTs in 22.5% of individuals who were older than 50 years (43). Rubin and colleagues used the SEER (surveillance, epidemiology, and end results) cancer registry in US for patients with GIST from 1993-2002 to determine incidence, prevalence, and 3-year survival and found the overall incidence, prevalence, and 3-year-servival rate were 3.2/million, 16.2/million, and 73%, respectively (44).

GIST mainly affects middle aged to elderly adults, typically in their 60s (35,45) with no clear gender predilection (46) although some studies demonstrated a slight male predominance (39,47). GISTs are uncommonly seen in patients younger than 40, however, cases in children and young adults have been reported (46). The true

incidence of GIST in children is unknown. An incidence rate of 0.06/million/year was reported among young adults (20-29 years of age) (37). Other large series studies showed the percentage of patients with GIST below the age of 21 years ranged from 0.5% to 2.7% (45,46,48). Data from the UK National Registry revealed an annual incidence of 0.02 per million children below the age of 14 years, which appears to be the most accurate epidemiological data to date on pediatric GIST (49). Pediatric GISTs are considered a rare entity that can be quite different from its adult counterpart and seen predominantly in the second decade (46,50,51) with a predilection for female patients (46).

Sporadic GISTs are most common and familial GISTs with germline mutation of the *KIT* gene are rare, but have been well described (52-55). These patients usually have multiple GISTs and cutaneous hyperpigmentation (53). In addition, GIST rarely occurs in association with other syndromes such as neurofibromatosis type I (56-59) or Carney's triad, a nonfamilial condition with gastric GIST, paraganglioma, and pulmonary chondroma (60,61). The latter should be distinguished from Carney-Stratakis syndrome, an inherited tumor syndrome comprising gastric GIST and paragangliomas (62).

GIST co-existing with other tumors has been reported mainly as case report (63) and mostly with colorectal carcinomas or adenomas, followed by gastric carcinomas (64,65). p53, one of the most common involved genes in colorectal carcinogenesis, has also been found to have a prognostic significance in GISTs, and mutations in this tumor suppressor gene are more often observed in the high-risk GISTs (66). GIST colliding with other tumors, mostly gastric adenocarcinomas, is rarely seen in literature (67-69). Only one case of gastric GIST colliding with angiosarcoma was reported (70).

Pathogenesis and genetics

In 1995 Huizinga and colleagues reported a knockout mice model of *KIT* failed to express in interstitial cells of Cajal cells (17). This finding led to the hypothesis that *KIT* was essential for the development of interstitial cells of Cajal cells. In 1998, Hirota and colleagues published a groundbreaking discovery of *KIT* mutations in GISTs (21) and 95% GISTs are immunohistochemically positive for the receptor tyrosine kinase *KIT* (also known as CD117) (21,22). It is now established that *KIT* mutations, which cause the constitutive activation of the kinase, are found in 70-80% of GISTs. CD117 becomes a crucial diagnostic marker for GIST, and mutant *KIT* provides an important therapeutic target clinically in GIST treatment.

Initially, GISTs lacking any evidence of *KIT* mutation were classified as "wild type" (WT). In 2003, novel mutations in *PDGFRA* were found in WT GIST by Heinrich and colleagues (28). Currently *PDGFRA* mutations account for 5-10% of known mutations in GIST. About 9-15% of all GISTs do not exhibit mutations in either *KIT* or *PDGFRA* and are now termed "wild type" (WT) (71).

KIT is a member of the type III transmembrane receptor tyrosine kinase (RTK) family that includes *PDGFRA* and *PDGFRB*, as well as macrophage colony-stimulating-factor receptor (*CSF1R*) and Fl cytokine receptor (*FLT1*) (72). Normally, binding of the *KIT* ligand, stem cell factor (SCF) to *KIT* results in receptor dimerization and kinase activation (73). In contrast, the presence of *KIT* receptor-activating mutations will bypass the ligand binding requirement for activation and therefore become oncogenic, which has been implicated in the pathogenesis of several human tumors in addition to GIST and chronic myelogenous leukemia (CML), including seminomas (74), mastocytosis (19), acute myelogenous leukemia (75) and, more recently, in melanomas (76).

KIT oncogenetic activation is the dominant pathogenetic mechanism in GIST (77). Although familial GIST with germline mutations have been reported (52,55), the majority of *KIT* mutations in GIST are somatic. The most common mutations in *KIT* are found in the juxtamembrane domain that is encoded by the 5' end of exon 11 of the *KIT* receptor (*Figure 1*). Mutations in exon 11 change the normal juxtamembrane secondary structure and cause the active conformation of the normal kinase activation loop (78). The mutations vary from in-frame deletions of variable sizes, point mutations to deletions preceded by substitutions (79). The deletions are associated with a more aggressive behavior in comparison to other exon 11 mutations (80-83). Particularly, deletions involving codon 557 and/or codon 558 are associated with malignant behavior (84,85). A less common mutant spot is located at the 3' end of exon 11, which includes mainly internal tandem duplications mutations (ITDs) (86). These ITD-type mutations are considered to have a more indolent clinical course and a predilection in GISTs located in the stomach (86). The second most common *KIT* mutation, between 10% and 15% of GISTs, is a mutation in an extracellular domain encoded by exon 9 (87). GISTs with *KIT* exon 9 mutations are characterized by small bowel location and aggressive clinical behavior (86).

A minority of GISTs that lack *KIT* gene mutations have high levels of phosphorylation of *PDGFRA* resulted from an activation by mutations or small deletions (28). *PDGFRA* is a close homologue of *KIT* (28). Mutations in *PDGFRA* and *KIT* in GIST are mutually exclusive and about one-third of GISTs without *KIT* mutations harbor a mutation of *PDGFRA*, within exons 12, 14 or 18 (28,88,89). In GIST, mutant forms of *PDGFRA* have constitutive kinase activity

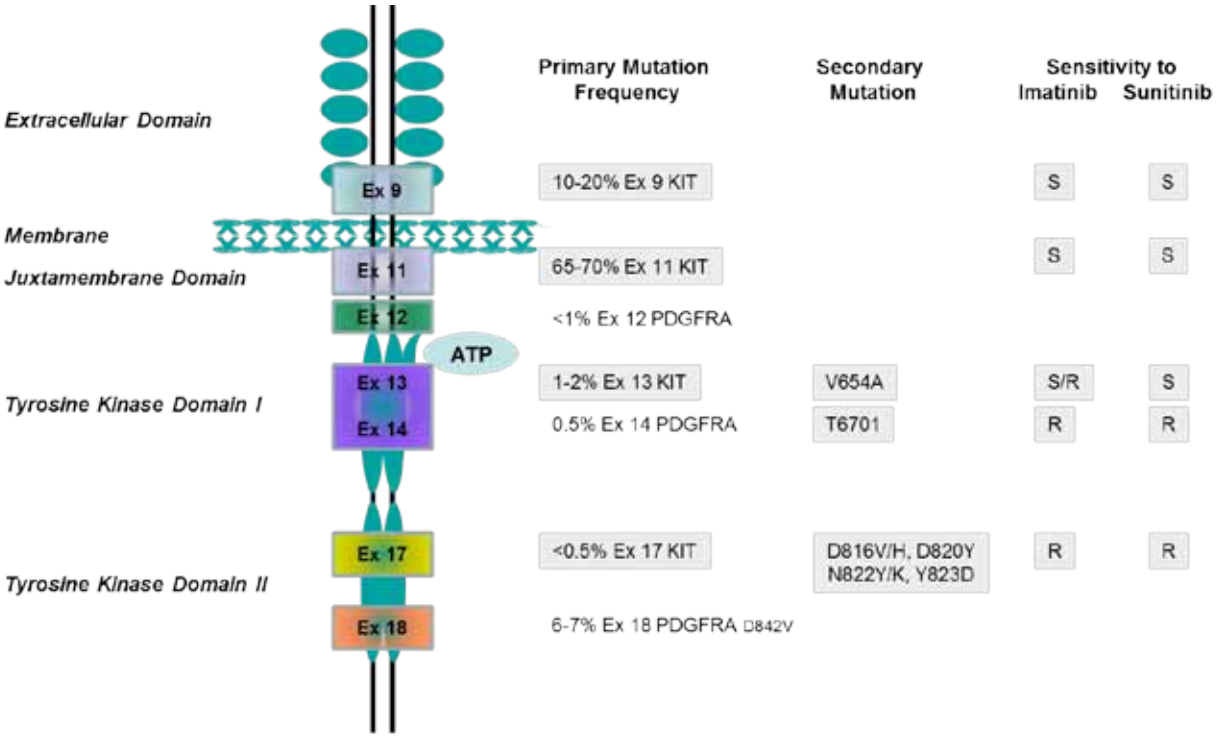

Figure 1 Schematic distribution of KIT or PDGFRA receptor mutations, frequency of mutations and TKI (Abbreviations: Ex, Exon; S, sensitive; R, resistant)

in the absence of their ligand-*PDGFRA* similar to those for *KIT* mutations, and the activated downstream pathways (28,29) are identical to those in *KIT*-mutant GISTs (28,90). In spite of the similarities in molecular aspect, most GISTs with mutated *PDGFRA* have distinct pathologic features, including gastric location, epithelioid morphology, variable/absent CD117 by immunohistochemistry and an indolent clinical course (88,91,92).

Recent studies indicate that a small portion of GIST wild-type for both *KIT* and *PDGFRA* genes may harbor mutations of the *BRAF* gene (93) and *KRAS* and *BRAF* mutations predict primary resistance to imatinib in GISTs (94).

Furthermore, GISTs demonstrate typical patterns of chromosomal gains and losses, including losses at 1p, 14q, 15q, and 22q. Tumor site appears to be associated with distinct chromosomal imbalances; for example, gastric GISTs show predominantly losses 14q, whereas intestinal GISTs more frequently exhibit losses of 15q (95).

Clinical presentation

Most GISTs remain 'silent' until reaching a large size. Symptoms vary according to location and size. Symptomatic GIST patients generally present with nonspecific symptoms including abdominal pain, fatigue, dyspepsia, nausea, anorexia, weight loss, fever and obstruction. Patients may present with chronic GI or overt bleeding due to mucosal ulceration or tumor rupture with life-threatening intraperitoneal hemorrhage. Some patients with large GISTs may have externally palpable masses (96,97). Aggressive GISTs have a defined pattern of metastasis to the liver and throughout the abdomen or both (45). Lymph node metastasis is not common. Spreading to the lung and bone in advanced cases has been reported (98). Metastasis often occurs 10-15 years after initial surgery (45).

More than 80% of GISTs are primarily located in GI tract and may occur throughout the GI tract with extra-GI tract GISTs reported in omentum, mesentery, retroperitoneum, gallbladder and urinary bladder (99-101). The majority of GISTs (60%) are seen in the stomach, usually in the fundus (35,39). The percentages of GISTs found in other portions of GI tract are reported as 30% in jejunum and ileum, 5% in duodenum, 4% in colorectum, and rarely in the esophagus and appendix (45,46,48,65). Reported tumor size in the stomach varies from a few millimeters to >40 cm with a mean size of 6 cm in the largest reported series (65). Apparently, the tumor size is one of the factors contributing to the clinical symptoms. A population-based study showed that the tumor size is 8.9 cm in patients with clinical symptoms, which is about 70% of GISTs studied, 2.7 cm in patients without clinical symptoms, 20%, and 3.4 cm in patients with GISTs detected at autopsy,

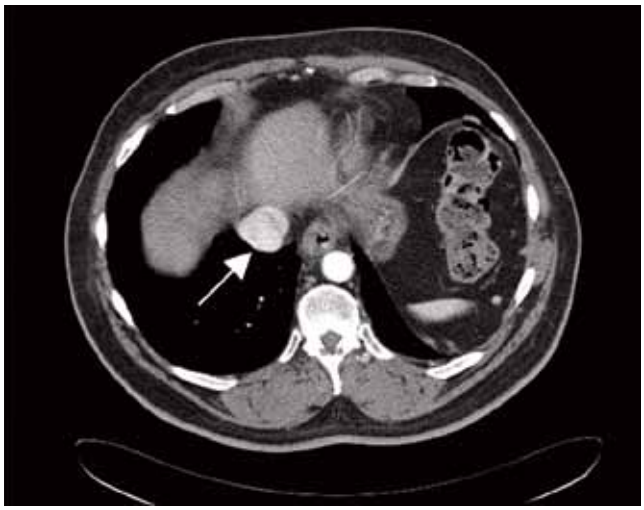

Figure 2 Computed tomography scan revealed a partially exophytic, dumbbell shaped solid mass (arrow) arising from the posterior aspect of the gastric fundus along the greater curvature, measuring approximately 6.7 cm × 4.5 cm

10% (35). Many smaller GISTs are detected incidentally during endoscopy, surgery, or computed tomography (CT) scans (35).

Diagnosis

The diagnostic evaluation of GISTs is based on imaging techniques (*Figure 2*), with a special role of endoscopic examination because it is usually accessible when tumors are in the stomach, esophagus and large intestine. In addition, endoscopic ultrasonography (EUS) also plays an important role in the diagnostic work-up of GISTs and is accurate and efficient in the diagnosis of GISTs (102). In general, externally bilging tumors are more common than intraluminal masses (103). Punch-out ulcer is the classical appearance of a submucosal tumor (104).

Macroscopy

Gastric GISTs are greyish-white sub-mucosal tumors with smooth contours and usually well-circumscribed and highly vascular tumors. They typically have a tan-white or fleshy pink cut surface often with hemorrhagic foci, central cystic degeneration, or necrosis (*Figure 3*). The overlying mucosa of large tumors is typically ulcerated (46).

Histopathology

Microscopically, GISTs have a broad morphological spectrum. Three main histological subtypes have been best widely accepted and they are spindle cell type (most common, 70%), epithelioid type (20-25%), and mixed spindle cell and epithelioid type (99,105,106) (*Figure 4*). In general, GISTs have a wide variation ranging from hypocellular to highly cellular with higher mitotic rates. Nuclear pleomorphism is relatively uncommon, and occurs more frequently in epithelioid type.

Spindle cell type of GIST is composed of cells in short fascicles and whorls. They have pale eosinophilic fibrillary cytoplasm, ovoid nuclei, and ill-defined cell borders. Gastric spindle cell GISTs often reveal extensive perinuclear vacuolization, a diagnostic feature formerly used for tumors of smooth muscle origin. The stroma sometimes demonstrates myxoid change or, rarely osseous metaplasia. Distinctive histological patterns among spindle cell GISTs including

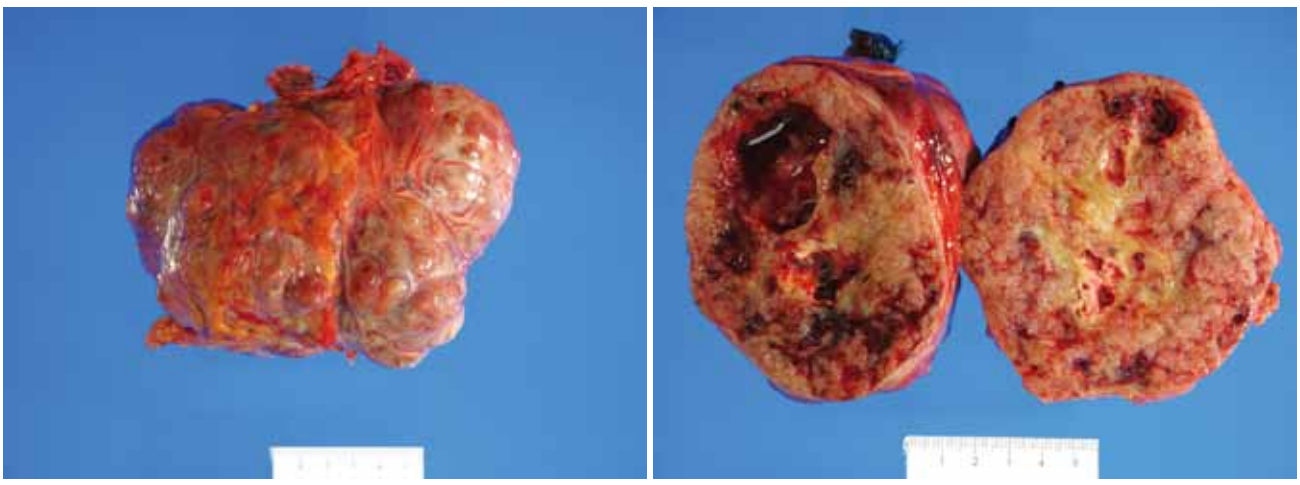

Figure 3 A gastric GIST with a nodulular surface and thin capusle. The cut surface reveals coarse granular and solid white tan suface with hemarrhage and cavities

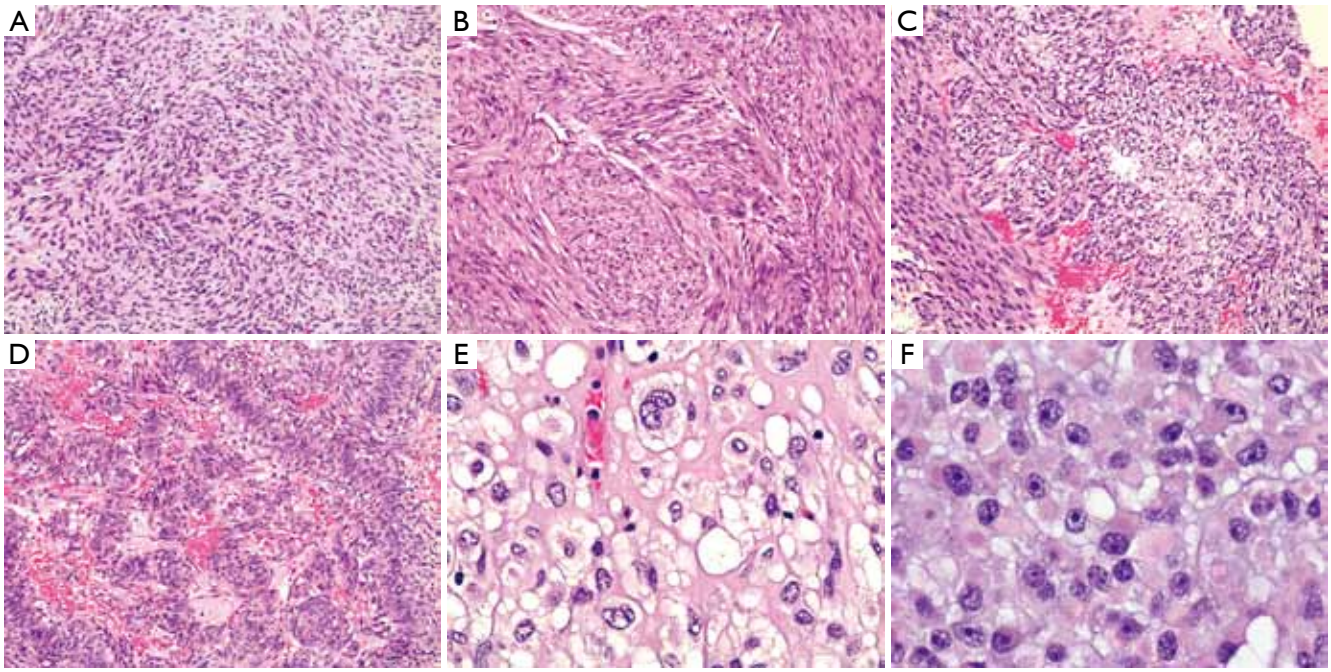

Figure 4 Common histologic al features of GISTs. A. Spindle cell GIST with short fascicles and whorls (×100); B. Spindle cell GIST with longer fascicles in bundles (×100); C. Spindle cell GIST with extensive perinuclear vacuolization (×100); D. Spindle cell GIST with prominent nuclear palisading (×100); E. Epithelioid cells GIST with pleomorphic nuclei and vacuolated cytoplasm (×400); F. Epithelioid cell GIST with rhabdoid features (×400)

sclerosing type and palisading-vacuolated type (65). The sclerosing spindle cell GISTs have slender spindle cells with no nuclear atypia and low mitotic activity and are usually paucicellular with extensive extracellular collagen. They are often small and contain calcifications. The palisading-vacuolated type is one of the most common gastric GISTs and usually cellular with plump and uniformed spindle cells. Nuclear palisading with perinuclear vacuolization is characteristic. There is usually limited atypia with mitotic activity rarely more than 10/50 high power fields (HPFs). However, some examples show diffuse hypercellular pattern, and others sarcomatoid features with significant nuclear atypia and mitotic activity (65,99,106).

Epithelioid cell GISTs are characterized by round cells arranged in nests or sheets and with eosinophilic to clear cytoplasm. They also have spectrums from sclerosing and paucicellular to sarcomatous and mitotically inactive to mitotically highly active. However, the epithelioid GISTs with atypia, even with pleomorphism are sometimes benign (65,99,106).

Immunohistochemically, the vast majority of GISTs (95%) are strongly and diffusely positive for KIT (CD117), which makes the KIT to be a very specific and sensitive marker in the differentiating GIST from other mesenchyma tumors in the GI tract (21,22,34,107). The stain appears as cytoplasmic, membrane-associated or sometimes as perinuclear dots (34). Although KIT positivity appears to have significant therapeutic implications, the intensity, extent and patters of KIT staining neither correlates with the type of *KIT* mutation nor have therapeutic significance (34). It is important to note that negative KIT does not exclude the patient from being treated with TKI (imatinib or sunitinib) since some wild-type GISTs for both *KIT* and *PDGFRA* genes respond to treatment with TKI (42). In addition, CD34 is another common marker for GISTs but it is not as sensitive or specific. It is positive in about 80% of gastric GISTs, 50% of small intestine GISTs, and in 95% of esophageal and colorectal GISTs (48,108) (*Figure 5*). Other markers which can be expressed by GISTs include h-caldesmon, SMA, S100, desmin, Vimentin, and cytokeratins 8 and 18 (100). Recently other CD markers for GISTs are reported including CD10 (109), CD133, and CD44 (110).

A small minority of GIST (<5%) are negative for KIT, or minimally, if any, positive for *KIT* by immunohistochemistry. These tumors appear to be either *KIT* wild-type or with mutant *PDGFRA*, have a predilection to stomach or omentum/peritoneum, and be usually epithelioid or mixed subtype (91,111). For the special interest in this subgroup of *KIT*-negative GISTs, several new antibodies for the diagnosis of GIST have been discovered based on the molecular studies. DOG1 (discovered on GIST1), known also as TMEM16A and ANO1, a transmembrane protein,

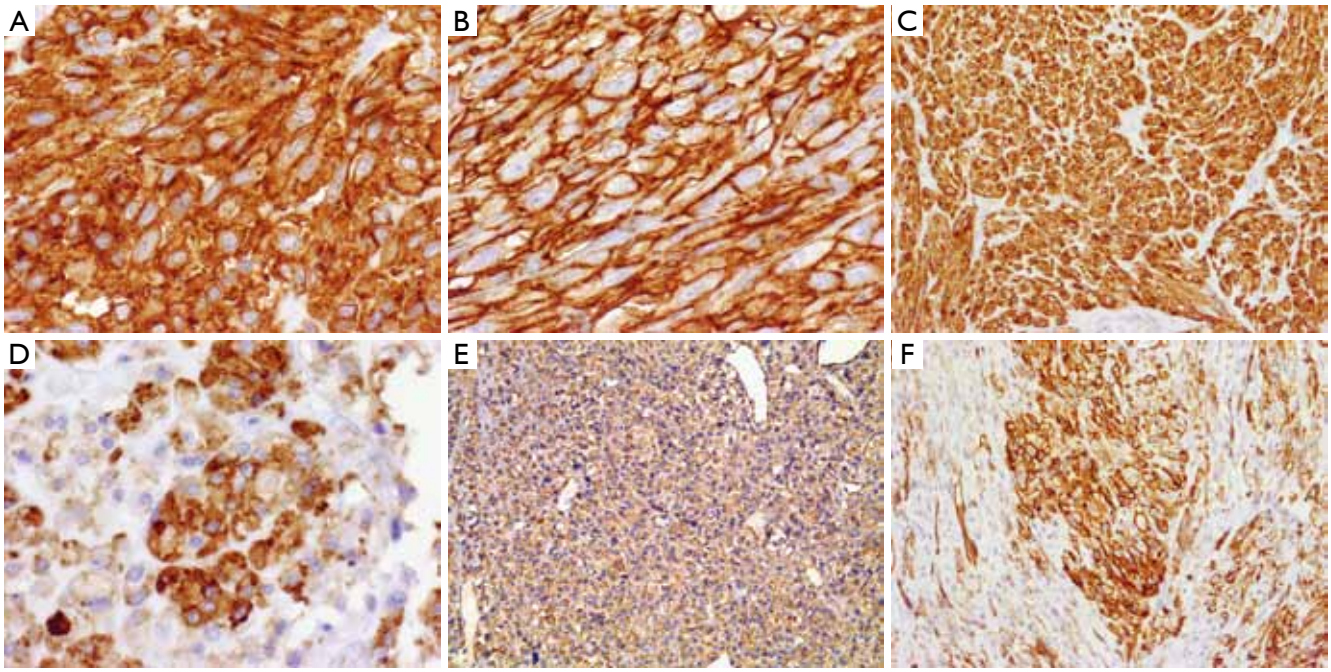

Figure 5 Immunohistochemical features of GIST. A. Spindle cell GIST with strong and diffuse cytoplasmic staining of CD117 (c-kit) (×400); B. Spindel cell GIST with strong and diffuse membrane staining of CD34 (×400); C. Epithelioid cell GIST with strong cytoplasmic staining of CD117 (×100); D. Epithelioid cell GIST with patchy and heterogeneous staining of CD34 (×400); E. Epithelioid cell GIST with punctate staining of h-Caldesmon (×100); F. Epithelioid cell GIST with patchy mambrane staining of h-Caldesmon (×400)

has been found specifically in GISTs and has emerged as a promising biomarker for GISTs (112,113). Recent studies have shown that antibodies against DOG1 have even higher sensitivity and specificity than KIT (CD117) and CD34 with 75% to 100% overall sensitivity (113-116). DOG1 is highly expressed in *KIT* mutant GISTs and also can detect up to one-third of *KIT*-negative GISTs, which mostly have *PDGFRA* mutation (113,116). In addition to GISTs, DOG1 is also positive in normal gastric epithelium, some carcinomas, germ cell tumors, melanomas, and some mesenchymal tumors (113,114), such as recently reported chondroblastoma (117). Like KIT, DOG1 is also expressed in interstitial cells of Cajal serving as an internal positive control. However, DOG1 does not stain mast cells which are usually positive for *KIT* (112,114).

Non-gastric gists and gists in specific populations

Non-gastric GISTs may vary in clinical presentation, histopathology, molecular profile, prognostic significance and management strategy compared with gastric GISTs. Small intestinal GISTs including the duodenal GISTs are more homogeneous histologically and have a significant tumor-related mortality if the tumor is >5 cm (48). They typically harbor *KIT* exon 11 mutations as seen in gastric GISTs and a small portion of small intestinal GISTs contain duplication of two codons in *KIT* exon 9 (86,118). Usually, small intestinal GISTs do not harbor *PDGFRA* mutations. The sigmoid colon is the most common segment involved by GISTs (39) in the colon. Histopathologic profile of colonic GISTs is similar to that of small intestinal GISTs.

Pediatric GISTs account for about 1-2% of GISTs. They are often misdiagnosed as having another acute or chronic abdominal condition and they are usually symptomatic and mostly located in the stomach with mainly epithelioid pattern (35,46,50,51). GIST occurs in children and young adults as a component of two distinct syndromes: Carney triad and Carney-Stratakis syndrome. Carney triad is composed of co-occurrence of GIST, pulmonary chondroma, and paraganglioma. Carney triad can be diagnosed when any of the two tumors are present in a patient. However, if only GIST and paraganglioma are present, it is considered to be Carney-Stratakis syndrome. GIST in patients with Carney triad tends to be multifocal and have high local recurrence rate and/or metastatic rate. However, the clinical course of GIST in Carney triad is usually indolent (61). Although pediatric GISTs express KIT protein, the majorities lack *KIT* or *PDGFRA* mutations (46,50,51). In 2002, a germline-inactivating mutation in the hereditary paraganglioma gene was found to be unique for Carbey-Stratakis (119,120). This germline mutation results in a cancer predisposition syndrome including GIST.

Patients with neurofibromatosis type 1 (NF1) have a high risk for GIST. Some autopsy studies have demonstrated as many as one of three NF1 patients to have GISTs (121). NF-associated GIST typically occur in duodenum or small intestine and often multifocal and small. They commonly have low risk parameters and are clinically indolent (57,121). In contrast to sporadic adults GISTs, NF1-associated GISTs lack *KIT* and *PDGFRA* mutations (57,121,122).

Familial GISTs were reported and account for a very small portion of GISTs (<0.1%). They have typically activated germline *KIT* or *PDGFRA* mutations with an autosomal dominant inheritance and high penetrance (52,55,123,124). They occur usually in middle age of life and typical multifocal or diffuse in the GI tract. Most of these GISTs have a benign course.

Differential diagnosis

Although GISTs are the most common mesenchymal tumor of the GI tract, a variety of other tumors should be included in the differential diagnosis. Accurate recognition of GIST is obviously important as the treatment differs according to the tumor type. The main differential diagnoses include smooth muscle tumors, schwannoma, desmoid fibromatosis, inflammatory myofibroblastic tumor, inflammatory fibroid polyp, solitary fibrous tumor, synovial sarcoma, follicular dendritic cell sarcoma, glomus tumor, and melanoma. Kirsch and colleagues have published extensive review of diagnostic challenges and practical approach to differential diagnosis of GISTs (125).

Anatomic location may be helpful in differential diagnosis. Intramural leiomyomas most commonly locate in the esophagus and are rare in the stomach and small intestine (126). Morphologically, leiomyomas have brightly eosinophilic cytoplasm with distinct cell borders whereas GISTs usually reveal syncytial cell morphology. Immunohistochemically, GISTs and leiomyomas share some markers, such as SMA and h-caldesmon, but spindle cell GISTs are rarely positive for desmin which is more specific for leiomyomas. Rare epithelioid GISTs that lack KIT expression do stain positive for desmin (116). Leiomyomas are negative for CD117.

Although gastric schwannomas are not commonly seen, they can be morphologically very similar to certain spindle cell GISTs. Distinct peripheral cuffing of lymphocytes and strong reactivity with S-100 and GFAP readily differentiate them from GIST in addition to the negativities of CD117 and CD34 (127).

Mesenteric fibrous lesions can be very challenging in terms of diagnosis of itself and confusion with GIST due to the location and gross appearance. Microscopically, intraabdominal desmoid fibromatosis usually display long sweeping fascicles of spindle cells embedded within a collagen matrix with an infiltrating patter at peripheral of the tumor. Immunohistochemical stain of beta-catenin is positive in about 75% of cases (128-130). Inflammatory myofibroblastic tumors are commonly seen in pediatric or young adult patients and recognized as a mesenteric mass. Microscopically, this tumor has cellular fascicular fibroblastic/myofibroblastic proliferation with a prominent mixed inflammatory components including significant number of plasma cells. About 50% of tumors express ALK-1 (131), which is essentially negative in GIST. Inflammatory fibroid polyp is a polypoid lesion of mucosa with collagenous or myxoid stroma admixed with fibroblasts. It can be CD34 positive but should be negative for CD117 and DOG1 (113,114,132). Interestingly, same *PDGFRA* mutations as seen in GISTs are also discovered in inflammatory fibroid polyps (133).

Histologically, epithelioid GISTs need to be distinguished from other epithelial or epithelioid tumors including carcinoma, melanoma, glomus tumor, germ cell tumor and clear cell sarcoma. Immunohistochemical studies play a major rule on the differential diagnosis and the evaluation of appropriate immunophenotypic markers in context with morphology in most cases allows an accurate classification (*Table 1*).

Role of molecular analysis

Mutational analysis of the *KIT* gene including exons 11, 9, 13, and 17, and *PDGFRA* gene including exons 12, 14, and 18 can be helpful in confirming the diagnosis of GISTs if immunohistochemical studies fail to support the diagnosis (particularly in CD117/DOG1-negative spindle cell suspect cases). Corless and colleagues (134) summarized the mutations of GISTs and classified GISTs based on the molecular findings (*Table 2*). Furthermore, mutational analysis probably has more clinical significance in therapeutic aspect as it has predictive value for sensitivity to molecular-targeted therapy (including dosage) and prognostic value. It is strongly recommended that it should be included in the diagnostic work-up of all GISTs (135). The correlation between *KIT* and *PDGFRA* mutational status and the response to tyrosine kinase inhibitors and their role in primary and secondary resistance has been widely investigated (31,136). Tumors harboring *KIT* exon 11 mutations have a better outcome under imatinib treatment than tumors harboring different mutation, whereas tumors with *PDGFRA* exon 18 mutations (D842V) have primary resistance to imatinib both *in vivo* and *in vitro* (27,71,137). Therefore, GIST mutational analysis is strongly recommended

Table 1 Immunophenotypic features of gastrointestinal mesenchymal tumors

Diagnosis	KIT	DOG1	Desmin	SMA	h-Cal	S100	CD34	HMB45	EMA	β-Cat	Clusterin	Keratin	Other
GIST	+++	+++	-	++ (40)*	++	-	+++	-	-	-	-	-	
Leiomyoma	-	-	+++	+++	+++	-	-	-	-	-	-	-	
Leiomyosarcoma	-	-	+ to ++	+++	++	-	+ (10)	-	-	-	-	-	
Schwannoma	-	-	-	-	-	+++	-	-	-	-	-	-	GFAP
Fibromatosis	-	-	-	++	-	±	-	-	-	++	-	-	
Synovial sarcoma	-	-	-	-	-	++ (30)	-	-	++	-	-	±	
PEComa	-	-	++	++	-	-	-	+++	-	-	-	-	Melan-A
FDCS	-	-	-	-	-	±	-	-	±	-	+++	-	CD21/23/35
Dermatofibroma	-	-	-	+++	-	-	+++	-	-	++	-	-	
IFP	-	-	-	±	-	-	++	-	-	-	-	-	
IMT	-	-	-	++	-	-	±	-	-	-	-	-	ALK-1
SFT	-	-	-	+	-	-	+++	-	-	-	-	-	

*Parenthetical numbers represent approximate percentage of cases that are positive. Abbreviations: SMA, smooth muscle actin; h-Cal, h-Caldesmon; -Cat, -Catenin; PEComa, Perivascular epithelioid cell tumour; FDCS, Follicular dendritic cell sarcoma; IFP, Inflammatory fibroid polyp; IMT, Inflammatory myofibroblastic tumor; SFT, Solitary fibrous tumor; -, negative stain; ±, sometimes positive and sometimes negative stain; +, <25% of cases positive; ++, 25-50% of cases positive; +++, >50% of cases positive

Table 2 Molecular classification of GISTs (134)*

Genetic type	Relative frequency	Anatomic distribution
KIT mutation (relative frequency 75-80%)		
Exon 8	Rare	Small intestine
Exon 9 insertion AY502-503	10%	Small intestine and colon
Exon 11 (deletion, single nucleotide substitution and insertions	67%	All sites
Exon 13 K642E	1%	All sites
Exon 17 D820Y, N822K and Y823D	1%	All sites
PDGFRA mutation (relative frequency 5-8%)		
Exon 12 (such as V561D)	1%	All sites
Exon 14 N659K	<1%	Stomach
Exon 18 D842V	5%	Stomach, mesentery and momentum
Exon 18 (such as deletion of amino acids IMHD 842-846	1%	All sites
KIT and PDGFRA wild-type (relative frequency 12-15%		
BRAF V600E	~7-15%	
SDHA, SDHB, SDHC and *SDHD* mutations	~2%	Stomach and small intestine
HRAS and *NRAS* mutation	<1%	
Sporadic pediatric GISTs	~1%	Stomach
GISTs as part of the Carney triad	~1%	Stomach
NF1-related	Rare	Small intestine

Adopted from Corless and colleagues [ref (134) Table 1]. Abbreviation: GIST, gastrointestinal stromal tumor; NF1, neurofibromatosis type I; PDGFRA, platelet-derived growth factor receptor- ; SDH, succinate dehydrogenase

in current NCCN (National Comprehensive Cancer Network) clinical practice guidelines (*Figure 6*) and in ESMO (European Society for Medical Oncology) clinical recommendations (138,139).

Prognostic factors, grade and stage

The risk of relapse of GISTs is estimated based on mitotic rate, tumor size, tumor site, surgical margins and the status of tumor rupture. Tumor size and mitotic count

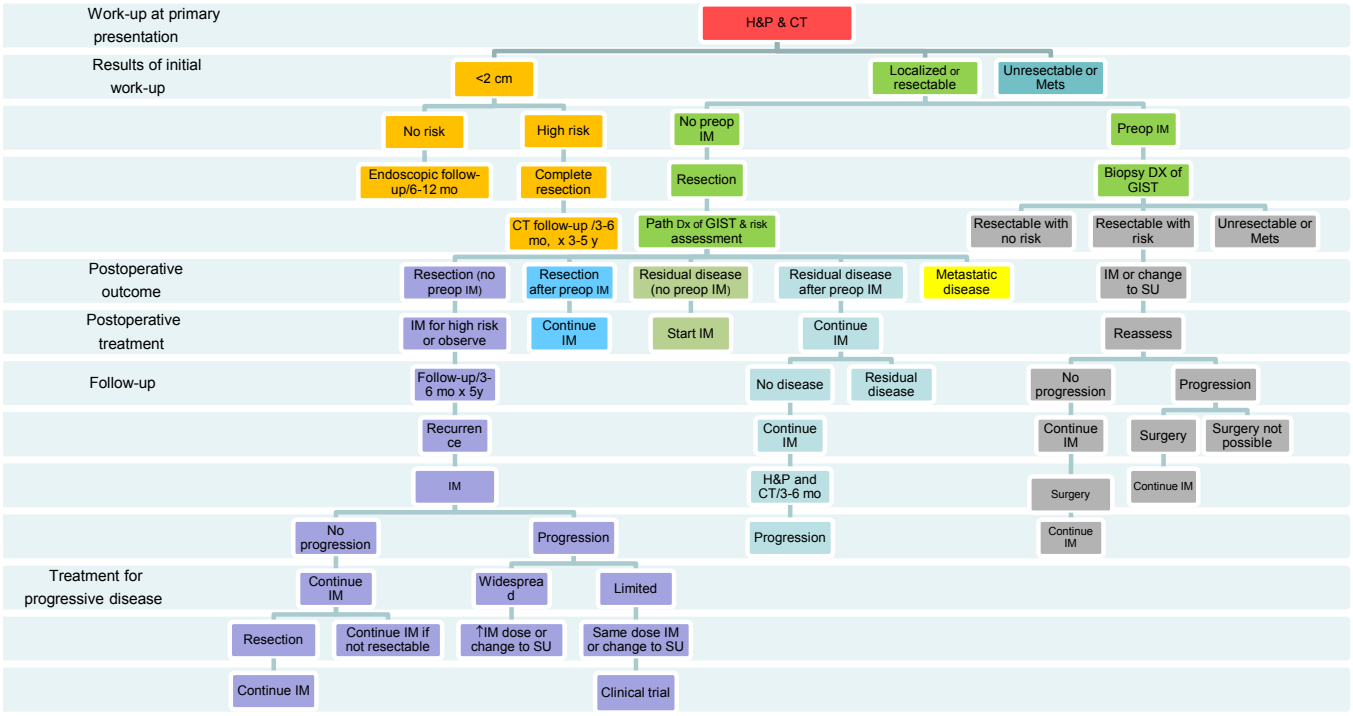

Figure 6 NCCN Guidelines Version 1.2012, Gastrointestinal Stromal Tumors (GIST) (Abbreviations: H&P, history & physical examination; Mets, metastatic disease; IM, imatinib; Preop, preoperative; DX, diagnosis; SU; sunitinib; mo, month; y, year)

Table 3 Risk assessment of GIST, 2002 by NIH

Risk category	Size (cm)	Mitotic count (50 HPF)
Very low risk	<2	<5
Low risk	2-5	5
Intermediate risk	5	6-10
	5-10	5
High risk	>5	>5
	>10	Any mitotic rate
	Any size	>10

Adopted from Fletcher and colleagues [ref (99) Table 2]. Abbreviations: HPF, high-power field

are considered to be the most useful and best studied prognostic factors by the 2002 Consensus risk classification (*Table 3*) (99). It is believed that indicating a risk level of GIST (low, intermediate, or high) is more appropriate than definitively labeling the tumor as benign or malignant. This risk classification was based on the cumulative experience of the authors in the committee. The most important cut-offs as indicators of aggressive clinical behavior were tumor size of 5 cm and 5 mitoses/50 HPF. This consensus guideline indicated that all GISTs may have malignant potential (99). Based on long-term follow-up of more than 1,600 GISTs (1,055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal), Miettinen and colleagues proposed risk classification incorporates primary tumor site in addition to the mitotic count and tumor size (*Table 4*) (140). It demonstrates the fact that gastric GISTs have a better prognosis than small intestine or rectal GISTs. The more recently updated consensus NCCN guidelines from 2007 (141) includes anatomic site as an additional parameter in risk assessment for GIST. Based on those guidelines, GISTs that are smaller than 2 cm are considered to be essentially benign. Recently, Gold and colleagues proposed a nomogram for estimating the risk of tumor progression (142), in which each GIST was assigned points on a scale based on tumor site, size, and mitotic index. The total points of a tumor should determine the 2- and 5-year recurrence free survival probabilities. From a clinical point of view, additional prognostic factors including non-radical resection and tumor rupture, whether spontaneous or at the time of surgical resection, are both associated with adverse outcome independent of any other prognostic factors (143). Furthermore, Takahashi and colleagues suggested the inclusion of a "clinically malignancy group" to include patients with peritoneal dissemination, metastasis, and invasion into adjacent organs or tumor rupture (144). In 2008, a proposal by Joensuu based on the NIH system included the presence of tumor rupture as a high risk factor irrespective of size and mitotic count (145). The Joensuu's revised NIH risk system is

Table 4 Risk assessment of GIST, 2006 by miettinen and lasota (ref 140)

Mitotic rate (50 HPF)	Tumor size (cm)	Stomach	Duodenum	Jejunum or ileum	Rectum
5	2	None	None	None	None
	>25	Very low	Low	Low	Low
	>510	Low	Moderate	Insufficient data	Insufficient data
	>10	Moderate	High	High	High
>5	2	None*	High*	Insufficient data	High
	>25	Moderate	High	High	High
	>510	High	High	Insufficient data	Insufficient data
	>10	High	High	High	High

Adopted from Miettinen and Lasota (ref 140). Abbreviation: HPF, high-power field; *Very small number of cases

Table 5 Risk Assessment of GIST, 2008 by Joensuu (ref 145)

Risk category	Tumor size (cm)	Mitotic rate	Duodenum
(50 HPF)	Primary tumor site	None	None
Very low risk	<2	5	Any
Low risk	2.1-5.0	5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	5	Gastric
High risk	Any	Any	Tumor rupture
	>10.0	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	5	Nongastric

Adopted from Joensuu [ref (145) Table 4]. Abbreviation: HPF, high-power field

shown in *Table 5*.

In the TNM staging (AJCC, 7th edition, 2010) (146), grading of GISTs is based on mitotic rate. Mitotic rate less than 5/50 HPFs is considered to be low (grade 1) and greater than 5/50 HPFs is considered to be high (grade 2). Please note that the staging criteria are different for gastric GISTs and small intestinal GISTs to emphasize the more aggressive clinical course of small intestinal GISTs even with similar tumor parameters (147). The seventh edition of the international union against cancer (UICC) published at the beginning of 2010 included for the first time a classification and staging system for GIST (148). This represents a significant step towards a more standardized surgical and oncological treatment for patients with GIST and, more importantly, may facilitate the establishment of a uniformed follow-up system based on tumor stage (*Table 6*) (149).

Treatment

Treatment of localized disease

Surgery

The only potentially curative treatment of GISTs, still, is complete surgical resection if it is a locally resectable or marginally resectable tumor (141,150). GISTs rarely metastasize to lymph node (142,151) and therefore regional lymph node dissection is generally not needed. In addition, organ-sparing resection (segmental resection) is also appropriate oncologically. However, about 40-90% of surgically treated patients experience disease recurrence (152). A recent study of 127 patients with localized GISTs who underwent complete resection demonstrated a 5-year recurrence-free survival (RFS) rate of 63% (153). This study concludes tumor size 10 cm, mitotic rate 5/50HPFs, and

Table 6 UICC TNM classification for GIST, 7th Edition, 2010

Mitotic rate (50HPFs)	Tumor size (cm)	T		N	M	UICC stage	
		Gastric	Non-gastric			Gastric GIST	Non-gastric GIST
5	2	T1	T1	N0	M0	IA	I
	2-5	T2	T2	N0	M0	IA	I
	5-10	T3	T3	N0	M0	IB	II
	>10	T4	T4	N0	M0	II	IIIA
>5	2	T1	T1	N0	M0	II	IIIA
	2-5	T2	T2	N0	M0	II	IIIB
	5-10	T3	T3	N0	M0	IIIA	IIIB
	>10	T4	T4	N0	M0	IIIB	IIIB
Any	Any	Any	Any	N1	M0	IV	IV
		Any	Any	Any	M1	IV	IV

Abbreviation: UICC, the international union against cancer; GIST, gastrointestinal stromal tumor; HPF, high-power field

tumor location in the small intestine were all independently associated with an increased risk of recurrence. In addition, intraperitoneal rupture or bleeding is also associated with a high risk of postoperative recurrence of nearly 100% (143,154,155).

Adjuvant therapy

Understanding the molecular changes of GISTs along with target treatments resulted in a considerable transformation in the management of GISTs. The remarkable efficacy of imatinib in treating metastatic GISTs has prompted interest in developing an adjuvant after complete resection of GISTs. Resent phase III randomized trial involved 778 patients with localized GISTs who underwent complete surgical resection followed by 1 year of imatinib (400 mg/day) and revealed that adjuvant imatinib significantly improved the 1-year RFS rate (98%) compared with the placebo (83%) (P<0.0001) (156). Based on the results of this trial, FDA approved imatinib as adjuvant therapy for GISTs (157). The most recent management guidelines in US (NCCN) (138) and Europe (ESMO) (139) recommended adjuvant imatinib for at least 1 year following complete surgical resection in patients with intermediate- to high-risk GIST. However, the optimal duration of adjuvant therapy has not been established yet.

Treatment of localized unresectable or metastatic gists

Although surgical intervention was applied to patients with metastases prior to the imatinib era, it was unlikely to completely resect the tumor and consequently with earlier recurrence than localized disease (45). Nunoby and colleagues (158) in Japan studied the outcome of surgical resection in 18 patients with liver metastases of GISTs and showed 83% complete resection of liver metastases with 64% 3-year postoperative overall survival (OS) rate and 34% 5-year postoperative OS rate. However, the recurrence rate in the remnant liver and in other organs reached 94% in this study. Surgical treatment alone for metastatic GISTs, therefore, is only palliative (158).

The application of imatinib for patients with advanced and non-resectable GISTs was first evaluated in the palliative setting in 2000 (24). A recent large clinical study of imatinib for unresectable or metastatic GISTs revealed up to 57 months of median OS rate (159), which is almost a threefold increase in OS from about 20 months (45) prior to the application of imatinib. Based on the clinical practice guidelines (NCCN & ESMO), treatment with imatinib (400 mg/day) now is the standard of care for patients with locally advanced, recurrent, or metastatic disease (138,139). Multiple phase III clinical trials have confirmed the effectiveness of imatinib with standard-dose (400 mg/day) or high-dose (800 mg/day) (159,160). Furthermore, the efficacy of imatinib certainly also depends on the mutant profile of GISTs. *KIT* exon 11 mutations show the greatest benefit from imatinib treatment (400 mg/day) (*Figure 1*) (135,161). *KIT* exon 11 codon 557/558 deletion/insertion mutations have a more aggressive clinical behavior (162). *KIT* exon 9 mutant GIST requires a higher imatinib dosage to reach a better response (135,163). In addition, sunitinib, another TKI, is beneficial for exon 9 mutated-GIST (30). Although wild-type patients are not likely to benefit from imatinib (161), some *in vivo* and *in vivo* studies on sunitinib (164), nilotinib, and dasatinib (165) are promising. Regarding *PDGFRA*-mutated GISTs, *PDGFRA* exon 18 mutations have better response to imatinib therapy but not with PDFGRA exon 18 *D842V*-mutation (71).

According to the NCCN guidelines, patients with progressive disease after imatinib treatment are allowed

to be re-assessed for surgery. Surgical resection has been achieved in those cases (166-168). However, the timing of the surgical intervention is very important and was recommended as the time at which patients reached maximum benefit from imatinib but before tumor progression occurs (139,169). In addition, neoadjuvant therapy with TKI should be considered to facilitate complete resection and allow for a less morbid operation, especially in duodenal GIST which can be sometimes hardly resected completely (170,171). With a short neoadjuvant imatinib therapy, tumor blood flow was decreased and apoptosis was increased within 3-7 days of starting therapy compared with pre-imatinib tumor tissue, although minimal size reduction was observed (171).

Assessment of treatment response

According to the NCCN guidelines, imaging study of contrast-enhanced CT scan is the technique of choice to detect recurrence or progression of GISTs (138,139,172). In rectal GIST, MRI should be used or additional PET or PET-CT/MRI may be useful for early detection of tumor response to neoadjuvant therapy (172). Choi and colleagues (173) proposed modified response evaluation criteria which is considered to predict response more accurately than previously proposed Response Evaluation Criteria in Solid Tumor (RECIST) (174) and has a better correlation with time to progression (175).

Resistant disease and alterative treatments

Although TKIs, especially imatinib, have resulted in disease-free survival for patients following surgical resection of their primary tumors and increased response rates and survival for patients with metastatic disease, some patients will eventually develop resistance to imatinib (176). Several potential mechanisms of resistance were proposed and include specific types of mutations (*KIT* exon 9, *KIT* wild-type or *PDGFRA* exon 18) (31,135), acquisition of secondary mutations within the *KIT* gene, *KIT* gene amplification, loss of the wild-type allele, or inadequate imatinib plasma levels (176-179). Sunitinib is the only second-line TKI approved for use after imatinib failure due to its inhibitory function on multi-kinases receptors (136). It has also been shown to be effective against secondary mutations *in vitro* and *in vivo* studies (136,161). However, as with imatinib, resistance has recently been documented in patients with prolonged exposure to sunitinib (180,181). In addition, it has been shown that sunitinib can cause serious, life-threatening adverse effects, including hypertension, cardiotoxicity, and hypothyroidism (30,182,183). According to the NCCN and ESMO guidelines, sunitinib is recommended as a second-line therapy in patients who experience disease progression after high-dose imatinib or who have life-threatening side effects. If further progression occurs with sunitinib, patients should be considered for clinical trials of new agents or new combinations or discontinuation of anti-cancer therapy.

The role of newer generation *KIT* and *PDGFRA* kinase inhibitors, e.g., nilotinib, remains to be determined in GIST patients with multiple resistants after imatinib and sunitinib therapies. Nilotinib has demonstrated activity against imatinib- and sunitinib resistant GISTs (184) and displays, by an ongoing pilot study (185), substantial clinical benefit and is safe in the first-line treatment of advanced GIST. Other agents, such as dasitinib (186), sorafenib (187), and masitinib (188), target multiple oncogenic receptor tyrosine kinases that have been implicated in the development and growth of GIST. These newer agents and a wide number of others (189) are currently under clinical trials for the management of advanced and resistant GISTs and likely to change the treatment of this disease soon.

Conclusions

GISTs have received much attention for many reasons. The rapid expansion of molecular and clinicopathological knowledge of GIST has given this disease a promising future. The molecular targets for therapeutic interventions are not only of importance for the treatment of GIST patients, but also in the development of novel drugs and new strategies in basic cancer therapy. Pathologists need to know their role as the diagnostic information they provided impacts on the choice of treatment as well as on estimation of its efficacy. Molecular testing of GISTs should be performed for treatment selection and assessment of disease progression. The cause of GIST is still unknown; therefore, little has been done preventively. However, with gradual understanding the molecular mechanisms of GIST, the etiology will be elucidated eventually.

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