SMGroup

Soft Tissue Tumors: Gastrointestinal Stromal Sarcomas

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INTRODUCTION AND EPIDEMIOLOGY

Gastrointestinal Stromal Tumors **(GISTs)** are the most common mesenchymal neoplasms of the gastrointestinal tract. The mean annual incidence of GISTs is 10-15 cases per million people [1-4]. GISTs represent a wide clinical spectrum of tumors with different dignity, which may arise throughout the entire gastrointestinal tract. They are located typically in the submucosa of the stomach and the small and large intestines. The most frequent localization is the stomach (55-60%), although GISTs occur throughout the gastrointestinal tract, including the jejunum and ileum (30%), duodenum (5%), and colorectum (5%) [5,6], and rarely in the esophagus, appendix, gallbladder, and extragastrointestinal organs such as the mesentery, omentum, and retroperitoneum [7].

GISTs originated from the interstitial cells of Cajal or their common stem cell. GISTs can be detected at any age, but occurs predominantly in adults older than 50 years, with a median age of 55-65 years [8]. GISTs occur slightly more frequently in men than women.

The most commonly encountered GIST is the sporadic form. Familial GISTs occur and result from a germline mutation in either the KIT or platelet-derived growth factor receptor alpha (PDGFRα) proto-oncogenes [9,10].

PATHOGENESIS

The central events in the pathogenesis of GIST are the exclusive mutations of the KIT and PDGFRA gene. In 1998, Hirota and colleagues published a ground breaking discovery of KIT mutations in GISTs [11] and 95% GISTs are immunohistochemically positive for the receptor tyrosine kinase KIT (also known as CD117) [12]. The KIT gene encodes a protein that serves as a receptor for the growth factor stem cell factor, and the intracellular domain contains a tyrosine kinase enzyme, which activates a cascade of activities ultimately causing mitosis. Mutations in the KIT gene lead to uncontrolled activation of the tyrosine kinase site and therefore enhanced cell proliferation [11]. The most common primary mutations (deletions, point mutations, and duplications) are being observed in exon 11 (juxtamembrane domain) of the KIT gene [13]. In gastric GIST, PDGFR-alpha mutations are found in up to 20% [14]. Mutations of the KIT kinase domains (i.e., exon 13, 14, and 17) are very rare, and GIST with such mutations shows variable sensitivity to imatinib.

CLINICAL PRESENTATION

Symptoms vary according to location and size. GISTs can cause a variety of symptoms ranging from vague abdominal pain to peritonitis as a result of tumor rupture and intra peritoneal bleeding. It can be presented with abdominal fullness, early satiety, weakness, and fatigue secondary to anemia from occult gastrointestinal bleeding. Bowel obstruction is rare. Small GISTs (<3cm) are often detected incidentally on CT scans, endoscopy, or at the time of laparotomy for other indications [15].

Median tumor size at presentation in symptomatic patients is 5cm. Asymptomatic GISTs, especially small lesions less than 1 cm, are frequently found in the specimens of total gastrectomy from gastric cancer and autopsies. On endoscopy, typical GISTs present as a bulge in the gastrointestinal tract, with smooth, intact, normal overlying mucosa.

Some patients with large GISTs may have externally palpable masses [16,17]. Lymph node metastasis is not common. Aggressive GISTs have a defined pattern of metastasis to the liver and throughout the abdomen or both [18]. Spreading to the lung and bone in advanced cases has been reported [19]. Metastasis often occurs 10-15 years after initial surgery [18].

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 [20-22].

DIAGNOSIS

The diagnosis of GIST requires a high index of suspicion because of the wide range of symptoms and rarity. The diagnosis of GISTs primarily based on the imaging techniques. Enhanced Computerized Tomography **(CT)** scan of the abdomen and pelvis is the main diagnostic technique of the disease. The characteristic findings on the CT scan are enhancing and exophytic mass in close association with the stomach or bowel wall. GISTs tend to displace rather than invade adjacent structures like other sarcomas. Larger GISTs (>10cm) can exhibit heterogeneity on CT that usually signifies hemorrhage or occasionally necrosis within the tumor (Figure 1).
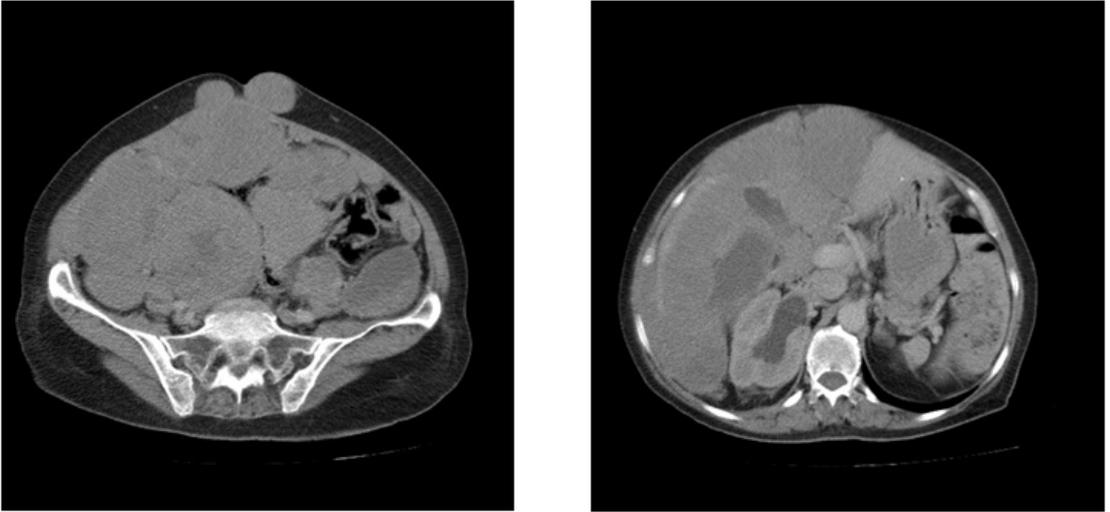

Figure 1: Computed tomography imaging of the GIST.

GISTs are often discovered incidentally during CT, endoscopy or gastrography. On endoscopy, typical GISTs present as a bulge in the gastrointestinal tract, with smooth, intact, normal overlying mucosa and cannot be completely differentiated from other mesenchymal tumors, including leiomyomas, leiomyosarcomas, glomus tumors, lipomas, liposarcomas, hemangiomas, neuromas, and granular cell tumors, vascular structures (aneurysms, varices), cysts, pseudocysts, neoplasms of adjacent organs, and even extramural structures [23,24].

The endoscopic biopsy generally yielded normal mucosa. Sometimes these biopsies can be valuable for pathological diagnosis if there is ulserative disease [25]. Because of difficulties in pathologic confirmation, other imaging tools can be used to help differentiate between a GIST and other benign diseases presenting as submucosal tumor. Endoscopic Ultrasound **(EUS)** is helpful for distinguishing the GISTs from lipomas or vascular lesions. EUS guided biopsy is not routinely recommended for lesions that are highly suspicious for GIST, but remains the preferred sampling method by experts [26,27]. Once adequate sampling is obtained by EUS, the diagnostic accuracy of immunohistochemically analysis can be as good as 80~91% [27]. However, EUS provides an inadequate tissue yield in up to 33.3% of the samples [28,29]. EUS guided core needle biopsy using

a 19 gauge Tru-cut needle has been proposed to overcome some of the limitations of Endoscopic Ultrasound with Fine Needle Aspiration **(EUS-FNA)**. Japanese guideline recommended EUS for GIST>2 cm [30]. Endoscopic guided fine needle aspiration has been shown to be nearly 80% sensitive in diagnosing GIST [31].

While PET is not used to diagnose GIST, it can be used to assess the response to tyrosine kinase therapy. PET can also be useful in patients with metastatic disease who are being considered for surgery or those on second line agents after failure of imatinib, in whom mixed responses may occur.

If endoscopy and EUS fail to obtain a biopsy sample, a percutaneous biopsy may be another option for pathologic diagnosis in cases when pathologic confirmation is mandatory. Percutaneous biopsy is reserved for patients with a plan to receive a tyrosine kinase inhibitor as the first line treatment because of the possibility to cause tumor seeding. It such as those patients with advanced localized disease or metastatic GISTs. Surgical excisional biopsy is generally suggested for the primary resectable GISTs [32,33]. Recent European Society for Medical Oncology **(ESMO)** guidelines stated that the risk of percutaneous biopsy is negligible if the procedure is properly performed [34].

PATHOLOGICAL FINDINGS

There are three histologic sub-types of GIST. The spindle cell form is the most common (70%) and consists of uniform, intersecting fasicles with eosinophilic cytoplasm. The epitheliod (20%) and the rare mixed type (10%) forms show more rounded cells with nuclear atypia [35].

Approximately 95% of GISTs stain positive for KIT **(CD117)** by Immunohistochemistry **(IHC)**. Epithelioid GISTs tend to have weaker KIT staining than the spindle cell type. Other commonly expressed markers include CD34 (70%), smooth muscle actin (30%) and desmin (<5%) [35]. Recently found markers, Discovered on GIST 1 **(DOG1)** and Protein Kinase C **(PKC)**-theta, are helpful for diagnosing KIT-positive as well as KIT-negative GISTs (36). DOG1, or anoctamin 1, is a calcium-activated chloride channel composed of 8 transmembrane domains. The overall sensitivity of DOG1 staining in GIST ranges from 75% to 100%, and the clone K9 DOG1 antibody was reported to be superior to the DOG1.1 antibody.

KIT mutations observed in patients with metastatic tumors are most frequently observed in exons 11 (67%), 9 (10%), 13 (1%), or 17 (1%), 51 while Platelet-Derived Growth Factor Receptor-A **(PDGFRA)** mutations (10%), which are less common than KIT mutations, occur mostly in exons 18 (6%), 12 (0.7%), or 14 (0.1%) [37]. Recently, ETV1 was shown to be a critical transcription factor in KIT oncogenesis and the development of GISTs [38]. Patients (~5-10%) who do not carry a mutation in either of the above described proto-oncogenes are classed as having Wild-Type **(WT)** GISTs.

The risk of relapse of GISTs is estimated based on mitoticrate, tumor size, tumor site, surgical margins and the status of tumor rupture. Tumor size and mitotic count are considered to be the most useful and best studied prognostic factors by the 2002 Consensus risk classification [20] (Table 1). 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 [20].

Table 1: Risk Assessment of GIST [35].

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

In the TNM staging [39], grading of GISTs is based on mitotic rate. Mitotic rateless than 5/50 HPFs is considered to be low (grade 1) and greater than 5/50 HPFs is considered to be high (grade 2).

TREATMENT

Resectabl Disease

Surgery remains the only chance for cure in patients with localized, primary GIST. The goal is to achieve negative microscopic margins with an intact tumor pseudocapsule. Wide margins have not been shown to improve outcomes [40]. Complete resection can usually be accomplished via wedge resection of the stomach or segmental resection of the bowel. Because GISTs spread hematogenously or by local invasion, lymph adenectomy is not routinely required unless adjacent nodes are obviously enlarged (Figure 2). En bloc resection is needed when adjacent organs appear to be involved. A study of 127 patients with localized GISTs who underwent complete resection demonstrated a 5-year Recurrence-Free Survival **(RFS)** rate of 63% [41]. This study concludes tumor size 10 cm, mitotic rate 5/50HPFs, and 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% [42,43].

Figure 2: En bloc resection of the GIST.

While there is little disagreement that all tumors larger than 2cm should be resected, the management of incidentally discovered small GISTs less than 2cm is controversial. In the absence of high-risk features on endoscopic ultrasound (echogenic foci, ulceration, irregular margins), some have advocated following these lesions with serial imaging and/or endoscopy. A retrospective analysis looking at the rate of growth of smaller GISTs using Endoscopic Ultrasound **(EUS)** found that ~13% with low risk features on endoscopy progressed to a point where they were resected [44].

The utility of EUS in the management of small GISTs remains unclear. The frequency of imaging is not well defined, and the need for potentially lifelong surveillance makes this option challenging for some patients and physicians. While endoscopic resection has been suggested by some, the risk of positive margins, perforation, and tumor spillage make this option generally less desirable.

Current National Comprehensive Cancer Network **(NCCN)** guidelines for the management of gastric GISTs without high-risk features on EUS include surveillance endoscopy with the permission of the patient [45]. NCCN guidelines suggest surgicalremoval of small GISTs less than 2 cm if they are accompanied with high risk EUS features such as an irregular border, cystic spaces, ulceration, echogenic foci, or heterogeneity. However, as previously mentioned, there is no consensus about the criteria to perform EUS for GIST <2 cm on endoscopy.

Watchful follow up for small GIST is supported by the observation of Lim et al., [46] reporting increasing size in only 8 out of 252 (3.2%) gastric submucosal tumors after a mean interval of 59.1±27.5 months (range, 12~86 months). Only 3 patients underwent surgical operations. Gill

et al.61 reported increasing size in 7 out of 51 (13.7%) submucosal tumors that were <3 cm during mean period of 29.7 months (range, 3~84 months), and three of those patients underwent surgery.

The primary goal is to remove the tumor with tumor free margins since 5-year overall survival in GIST patients with complete gross resection has been estimated at 42% compared to only 9% overall survival if the excision was incomplete [47].

Laparoscopic Approach

Although prospective trials are lacking, small series and retrospective analyses have shown low recurrence rates, shorter hospital stay and low morbidity with a laparoscopic approach [48,49]. It has been recommended for selected GISTs present in favorable anatomic locations like the anterior wall of the stomach, jejunum and ileum. The same surgical principles as open surgery are applicable in laparoscopic surgery for GIST. The specimen is removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites.

A consensus meeting in 2004 by ESMO recommended laparoscopic resection only for GISTs ≤2 cm however, GISTs can be handled without directly holding the mass with forceps, and they can be treated with techniques to prevent rupture and spillage, such as holding surrounding soft tissues or fibrous tissues, suturing at the nearby gastric wall for traction, the usage of endoscopic staplers, plastic bag, and other techniques [50]. Otani et al. [51] suggested 5 cm as an indication for laparoscopic wedge resection, and successful results have been reported with this technique [52].

Some series reported superiority of laparoscopic wedge resection for GIST over open surgery by showing fast oral intake, less pain, less inflammatory lab results, less blood loss, or shorter hospital stay lengths [53]. Long-term results in terms of recurrence and survival rates were also comparable to open surgery [54].

Irresectable Disease

The role of neoadjuvant imatinib in the setting of locally advanced disease has been investigated. The cyto reductive potential of imatinib in the pre-operative setting may enable surgeons to obtain R0 resections with less extensive resections and therefore lower morbidity. For example, pre-operative therapy for patients with rectal GISTs may increase rates of sphincter-preserving surgery. In addition, tumors located at the Gastro-Esophageal **(GE)** - junction may respond to imatinib such that esophageal resection is avoided. Both rectal and GE-junction GISTs have shown shrinkage with neoadjuvant imatinib [55].

In several studies, the effect of preoperative application of imatinib mesylate in patients with primary GIST of different sites was examined. While some authors report tumor shrinkage in all patients with a median size reduction of 34% and conclude that, in unresectable or locally advanced GIST, preoperative imatinib mesylate can be useful to improve resectability and

reduce surgical morbidity [56], others classify the response clinically into three groups: (1) early responders (up to 70% [57]), (2) those with stable disease, and (3) those with progressive disease while on targeted therapy [57].

When the tumor is very large and rupture, bleeding, or extensive combined resection is anticipated, neoadjuvant treatment with imatinib can be considered. The decision of the surgeon is important for deciding the neoadjuvant treatment with the National Comprehensive Cancer Network **(NCCN)** and ESMO guidelines [45,58].

When neoadjuvant imatinib is selected, pathologic confirmation is essential by endoscopy, EUS, or percutaneous access. Percutaneous access is typically the last option due to an unproven possibility of peritoneal dissemination of the tumor. Whenever possible, mutational analysis is suggested for identifying a baseline mutation and the presence of PDGFRA D842V mutation, which is known to be resistant to imatinib.

The duration of neoadjuvant treatment is not completely defined yet. Eisenberg et al. [59] recommend that the response of neoadjuvant imatinib mesylate in resectable GIST should be evaluated early and continuously, and surgical resection should be offered within 3-6 month to avoid tumor progression. According to the 2016 NCCN guidelines, neoadjuvant therapy is recommended for GIST that is resectable with risk of significant morbidity [45]. The duration for neoadjuvant treatment is currently discussed, and in therapy responders, a treatment of 4-6 months has been proposed.

Adjuvant Therapy

Without tyrosine kinase inhibitor treatment, the overall 5-year disease-specific survival rate has been reported as 35%after surgical resection [40]. The role of imatinib therapy in the adjuvant setting has been evaluated in several phase II and III clinical trials, namely ACOSOGZ9000 [60] and Z9001 [61] (conducted by the American College of Surgeons Oncology Group), SSGXVIII/AIO [62] (conducted by the Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie XVIII), RTOG S0132 [63] (conducted by the Radiation Therapy Oncology Group), and EORTC62024 (conducted by the European Organization for Research and Treatment of Cancer) [64]. Data from the phase III ACOSOG Z9001 trial [61] evaluating 1 year of adjuvant therapy with imatinib400 mg daily versus placebo in patients after microscopically radical (R0) resection of GISTs at least 3 cm india meter showed a significant reduction in the risk of recurrence from 17 to 2 % at 1 year. The current clinical practice guidelines [65] recommend surgical resection for limited disease and adjuvant imatinib therapy as an option for patients with a substantial risk of relapse Rupture and intraperitoneal hemorrhage have to be considered as metastatic GIST until proven otherwise.

NCCN guidelines 2016 suggest adjuvant imatinib after R0 resection in the patients with the significant risk of recurrence [45].

Recurrent and Metastatic Disease

In patients who develop recurrence, imatinib is the first line of therapy. Up to 80% of patients with metastatic GIST attain a partial or complete response with imatinib [66]. Since the toxicity of imatinib is dose dependent [67], current guidelines suggest initiating treatment at a dose of 400mg per day. Imatinib at 800mg per day should only be considered as a starting dose for patients with metastatic GIST and a confirmed mutation in exon 9. In patients on 400 mg per day, dose escalation to 800mg is considered if progression has been documented and toxicity is acceptable. NCCN guideline suggests imatinib therapy if there is unresectable, metastatic or recurrent disease.

Progression

Although 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 [68]. Sunitinib is the only second-line agent approved for use after imatinib failure due to its inhibitory function on multi-kinases receptors [69]. It has been shown that sunitinib can cause serious, life-threatening adverse effects, including hypertension, cardiotoxicity, and hypothyroidism [70,71]. According to the NCCN and guideline [45], 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.

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