Gastrointestinal stromal tumors: current translational research and management modalities

R.-X. HUANG, P. XIANG, C. HUANG

Digestive Endoscopy Center, Affiliated Huadong Hospital, Fudan University, Shanghai, P.R. China

Epidemiology

GISTs may arise almost anywhere along the gastrointestinal tract, but the most common site of occurrence is the stomach (50-70%), followed by the small intestine (25-35%), the colon and rectum (5%-10%), and the esophagus (<5%). Metastatic disease may be found intraparenchymally within the liver and along the peritoneal, serosal, and omental surfaces of the abdominal cavity. Metastases in the lung, bone, and other soft tissue sites are rare and are generally only seen in late stages of the disease. In terms of diagnosis, these lesions most commonly occur in patients with a median age of 60, with equal distribution between men and women. Several population-based studies suggested that the clinically relevant incidence of GISTs is 6.5 to 14.5 per million, with a median age at diagnosis of 63-66 years.

Pathogenesis

In 1998, Sarlomo Rikala M et al. established the KIT protein (CD117) in GIST cells using immunohistochemical methods. The cellular KIT protein is a transmembrane cytokine receptor with an intracellular region that functions as a tyrosine kinase. Subsequently, researchers found that the KIT protein is coded through the c-kit proto-oncogene, which is well documented in humans. Human c-kit is located on the long arm of chromosome 4, consisting of 21 exons. KIT proto-oncogene plays a role in the development of GISTs.
Gastrointestinal stromal tumors: current translational research and management modalities

Figure 1. KIT structure and localization of common KIT mutations.

alpha (PDGFRα), which is also located on the long arm of chromosome 4 close to c-kit. This encodes a related receptor, TK PDGFRα, and was observed in approximately 30% of c-kit-negative GISTs. Grover et al6 indicated that primary PDGFRα mutations were found in exons 12 and 18. These mutations changed the activation loop and, when activated, PDGFRα triggers the same signaling pathways as KIT, giving rise to GISTs. Another gene DOG1 (Discovered On GIST1) has been found to be overexpressed in most GISTs. DOG1, a monoclonal antibody against a chloride channel protein expressed by GISTs, is immunoreactive in 95% of GISTs, irrespective of their mutation status, i.e., in unusual GIST subgroups that lack c-kit or PDGFRα mutations19,20. Overall, DOG1 exhibits high sensitivity and specificity and is considered an easier stain for histopathological interpretation than CD117. Hence, it has become a very promising new marker for GISTs.21-23 In the latest publication of Hwang et al24, the authors demonstrated that DOG1 is a more sensitive and robust marker than KIT on GIST cell blocks, and is a useful marker in the diagnosis of GISTs in cytological specimens.

Assessment of Malignant Potential

The clinical behavior of GISTs can vary widely, making it difficult to discern aggressive lesions from nonaggressive tumors based on clinical and histological features. Approximately 10-30% of GISTs are regarded as clinically malignant; therefore, all GISTs have malignant potential and no
GIST can truly be considered benign\textsuperscript{25,26}. In 2008, in an attempt to predict and assess the malignant potential of GISTs, Joensuu\textsuperscript{27} proposed a method for risk stratification of patients diagnosed with GISTs, and this method was favored by many (Table I). Although researchers have attempted to improve the accuracy of assessment of the malignant potential of GISTs, a reliable set of histopathological criteria based on nonsurgical specimens does not currently exist.

Clinical Presentation
Population-based studies have reported that approximately 70\% of GISTs are clinically symptomatic, 20\% are incidentally discovered during surgery, and 10\% are identified at autopsy\textsuperscript{28,29}. However, these estimates are probably attributable to case-finding bias as many more small asymptomatic GISTs go unrecognized. Of those with symptoms, the majority (53\%) presented with gastrointestinal bleeding. Overt gastrointestinal bleeding was noted in 34\% of patients, whereas anemia with suspected occult gastrointestinal bleeding was noted in 19\% of patients\textsuperscript{30}. Other presenting symptoms were abdominal pain (32\%) and the presence of a palpable mass (13\%). Rare symptoms that were specific for the site of involvement included dysphagia for esophageal GISTs and obstruction or perforation for colonic GISTs. A significant number of GISTs are asymptomatic and are incidentally discovered on imaging, during endoscopic examination for other reasons, after surgical resection or at autopsy. Although the incidence of asymptomatic subepithelial masses identified during endoscopy is unclear, such lesions are increasingly being recognized with heightened awareness and improved endoscopic imaging.

Clinical Diagnostics
Clinical diagnoses of GISTs are generally based on imaging and endoscopic examination techniques.

Imaging
Contrast-enhanced computed tomography (CT) might be useful in detecting tumors that are 2 cm or larger, particularly for extraluminal tumors or tumors with calcifications, necrosis, or substantial vascularization\textsuperscript{31}. In addition, CT scanning plays an important role in the detection and monitoring of post-treatment metastasis regression\textsuperscript{32}. Positron Emission Tomography (PET) scans are generally only used to evaluate lesions showing ambiguity on CT scanning (for example, to confirm a GIST via high $^{18}$F-fluorodeoxyglucose (FDG) uptake)\textsuperscript{6}. Kamiyama et al\textsuperscript{33} found a significant correlation between the FDG uptake and both the Ki67 index and the mitotic index in GISTs, indicating that FDG uptake is a predictor of the malignant potential of a GIST.

Light Endoscopy
During general light endoscopy, most subepithelial lesions present as a bulge in the gastrointestinal tract, with smooth, intact, normal overlying mucosa. Light endoscopy can assess the subepithelial lesions for estimated size, mucosal appearance, and pulsation\textsuperscript{34}. Probing of the lesion with closed biopsy forceps is often performed and can provide additional information regarding mobility and consistency. However, the accurate diagnosis of GISTs with light endoscopy alone is poor. In the study of Hwang et al\textsuperscript{35}, the diagnostic specificity for light endoscopy was only 64\%.

Table I. Malignancy Risk Stratification of Patients Diagnosed with GISTs.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor diameter (cm)</th>
<th>Mitotic index (per 50 HPFs)</th>
<th>Primary tumor site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt; 2.0</td>
<td>≤ 5</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1–5.0</td>
<td>≤ 5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.1–5.0</td>
<td>&gt; 5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>&lt; 5.0</td>
<td>6–10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>5.1–10.0</td>
<td>≤ 5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>&gt; 10.0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt; 10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0</td>
<td>&gt; 5</td>
<td>Non-gastric</td>
</tr>
<tr>
<td></td>
<td>2.1–5.0</td>
<td>&gt; 5</td>
<td>Non-gastric</td>
</tr>
<tr>
<td></td>
<td>5.1–10.0</td>
<td>≤ 5</td>
<td>Non-gastric</td>
</tr>
</tbody>
</table>
**EUS**

Endoscopic ultrasonography (EUS) can provide valuable information about submucosal lesions with regard to tumor size, wall layer of origin or extramural origin, echogenicity, vascularity, and appearance of the tumor margins. GISTs arise from the fourth sonographic layer, which correlates with the muscularis propria. GISTs are typically hypoechoic, homogeneous lesions with a smooth, rounded appearance. Hunt et al. used the criteria of submucosal tumors larger than 4 cm and those with ulcerations or cystic spaces for the diagnosis of GISTs with EUS, concluding the sensitivity was 64.7% and specificity was 91.7%. Brand et al. reported a sensitivity and specificity of 95% and 72%, respectively for an EUS-based diagnosis of GISTs, by using the simple criterion of any hypoechoic lesion not originating from the submucosa. Conversely, other researchers have demonstrated that the diagnostic accuracy of EUS alone was subject to inter-observer variability and has reported it to be as low as 48%, with the conclusion that the diagnostic accuracy heavily depended upon the experience of the endoscopist.

**EUS-FNA**

As tissue acquisition and immunohistochemical analysis is required to confirm the diagnosis of GISTs, EUS-guided fine-needle biopsy has emerged as a preferred method for sampling lesions. EUS-guided fine-needle aspiration (EUS-FNA) is the most commonly practiced method for obtaining tissue from subepithelial lesions. Immunohistochemical staining for KIT receptor (CD117) has been routinely performed for lesions arising from the fourth wall layer. Many studies have demonstrated the superiority of EUS-FNA for diagnosing GISTs with high sensitivity (up to 95%) and satisfactory diagnostic accuracy (up to 60%). However, other studies have suggested a much lower rate of sensitivity (58%) and specificity (8%) with EUS-FNA of GISTs. EUS-FNA does have its limitations. Inadequate tissue acquisition may occur in up to 33.3% of samples, which may result in the inability to determine malignant potential. Mitotic count cannot be routinely calculated with cytology specimens and a reliable set of histopathological criteria for malignancy does not yet exist. Although there is still controversy surrounding the best management strategy for diagnosing GISTs, most experts still recommend performing EUS-FNA for suspected lesions.

**EUS-CNB**

EUS-guided core needle biopsy (EUS-CNB) has been proposed as an alternative to EUS-FNA. This uses a 19-gauge core needle to obtain a core of tissue rather than a cluster of cells. Therefore, EUS-CNB has the potential advantage of obtaining more tissue for performing immunohistochemical staining as well as the ability to calculate the mitotic rate. Several studies reported that EUS-CNB had a higher diagnostic accuracy than EUS-FNA. However, other studies did not demonstrate a difference in the diagnostic yield between EUS-FNA and EUS-CNB. Moreover, EUS-CNB has also been associated with higher rates of complications, such as bleeding, and technical difficulties, as the spring-loaded cutting sheath of the core needle is limited by the angulation of the echoendoscope, meaning its use is limited to lesions in the esophagus, stomach, and rectum.

**Laparoscopic or Open Biopsy**

In lesions that are not amenable to endoscopic biopsy, a laparoscopic or open biopsy may be necessary. However, transperitoneal biopsy is associated with the risk of hemorrhage, perforation and peritoneal seeding. Thus, laparoscopic or open biopsy is not generally recommended.

**Treatment of Primary Localized GISTs**

Along with obtaining more knowledge about GISTs and improving the operative instruments and techniques, various methods have been adopted to improve the treatment of primary localized GISTs. Although recognized guidance and regulation of the treatment of GISTs are still absent, substantial developments have been made in this respect during recent years.

**Endoscopic Surveillance**

The American Gastroenterological Association recommends removal of all GISTs with a diameter ≥ 3 cm, as well as tumors with a < 3-cm diameter with concerning endosonographic features (for example, an irregular border, presence of cystic spaces, echogenic foci, or heterogeneity). The European Society for Medical Oncology recommends removal of all GISTs > 2 cm in diameter. However, the management of incidentally discovered small GISTs of less than 2-cm diameter remains controversial. Nowadays, most experts advocate EUS surveillance for incidentally discovered small (< 2-cm diameter)
asymptomatic GISTs. Guidelines for the period of EUS surveillance have not yet been established. Traditional Open Surgery

Traditional open surgery is the first-line treatment and the only treatment approach that might lead to full remission in patients with a primary localized GIST larger than 2 cm in diameter. Unlike carcinomas, GISTs exhibit distinct features, in particular, an absence of metastases within locoregional lymph nodes. Therefore, operations requiring extended lymph node dissection, typically designed for carcinomas such as gastrectomy with extended lymph node dissection; Whipple’s procedure; and total mesorectum excision, are inappropriate for treating GISTs originating from the stomach, duodenum, and rectum, respectively. Instead, limited wedge or segmental resections are the correct operative choices.

Laparoscopic Surgery

Laparoscopic wedge resection, which is less invasive than traditional open surgery, has demonstrated promising results with regard to efficacy, safety profile, and length of hospitalization. To date, most of the available data on laparoscopic resection are limited to gastric GISTs, while outcomes following laparoscopic resection of GISTs at other sites are still unknown. NCCN Guidelines suggest that laparoscopic wedge resection may be used for tumors ≤ 5 cm in diameter. However, with the improvement of surgical techniques, Jeong et al. indicated that laparoscopic surgery for gastric GISTs is also safe and feasible even in large (> 5-cm diameter) tumors.

Endoscopic Resection

As endoscopic devices and techniques have been developed, some researchers have considered endoscopic resection of GISTs. Multiple small case series have demonstrated adequate endoscopic resection of small GISTs using various techniques, including endoscopic submucosal dissection (ESD), band ligation, and endoscopic enucleation. Liu et al. reported that endoscopic muscularis dissection of GISTs localized in the esophagus and stomach appears to be a feasible and minimally invasive treatment. Although there is a higher risk of perforation than with ESD, perforations have become manageable endoscopically. Zhou et al. reported successful endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originating from the muscularis propria. However, it is still doubtful whether full-thickness suturing for gastrostomy closure with a conventional loop clip is safe enough, as the clip can only hold the mucosal surface. Thus, development of a full-thickness suturing device for a flexible endoscope is essential. Jeong et al. specified that although endoscopic resection showed good results with no recurrence, until the suitability for oncological principles and the long-term safety of this approach were clarified, this approach should be limited to select cases with a high operative risk or a need for preservation of organ function.

Laparoscopic and Endoscopic Cooperative Surgery

As judging the location of GISTs is often difficult under laparoscopic examination alone and suture techniques are still immature for endoscopic resections at present, laparoscopic and endoscopic cooperative surgery (LECS) may be an alternative choice. Mori et al. and Tsujimoto et al. both demonstrated the feasibility and satisfactory surgical outcome for gastric GISTs after LECS.

Targeted Therapy

The discovery of the orally available imatinib mesylate (Gleevec, Novartis, Basel, Switzerland) is a key breakthrough that has revolutionized the management of GISTs. Imatinib mesylate inhibits the TK domains of various receptors, including wild-type and mutant forms of KIT (CD117) and some mutant forms of PDGFRα, except for the mutation in exon 18 D842V. Duflaud et al. indicated that preoperative treatment with imatinib might reduce the primary tumor to a size small enough to be removed surgically. Eisenberg et al. also evaluated the safety and feasibility of imatinib as a neoadjuvant agent and found that the neoadjuvant imatinib is a well-tolerated and feasible treatment option. Other studies have investigated the effects of adjuvant therapy with imatinib following resection of primary localized GISTs and, according to these studies, adjuvant therapy of imatinib extends the recurrence-free period. Although the optimal duration of adjuvant therapy remains uncertain, it does appear that 3 years is better than 1. Patients with advanced GISTs who progress on or are intolerant of the first-line imatinib therapy usually start the second-line sunitinib malate (Sutent, Pfizer Inc., New York, USA) therapy. Tumors with sec-
Gastrointestinal stromal tumors: current translational research and management modalities

orynary mutations (new mutations acquired after imatinib exposure, resulting in imatinib intolerance) involving KIT exons 13 or 14 are especially sensitive to sunitinib. Sunitinib targets KIT, PDGFRα, PDGFRβ, several vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), the ret proto-oncogene receptor, and Fms-like tyrosine kinase-3 receptor (Flt3)6,26. To deal with GISTs resistant to both imatinib and sunitinib, more clinical trials involving novel drugs such as nilotinib, sorafenib, and crenolanib, targeting the inhibition of other signaling pathways, are currently underway6,70-72.

Treatment of Locally Advanced, Metastatic, Recurrent GISTs

Imatinib is approved by the Food and Drugs Administration (FDA) as the first-line therapy for patients with advanced GISTs, in order to improve progression-free survival rates and overall survival rates. Once imatinib therapy is instituted for metastatic or recurrent GISTs, most researchers suggest treatment should be continued. In studies, patients with responsive or stable disease who discontinued imatinib therapy after 1, 3, and 5 years had a much higher rate of disease progression than did those who continued with therapy73,74. Reichardt et al75 indicated that standard therapy for locally advanced or metastatic GISTs was imatinib at a dose of 400 mg/day, while patients with mutations in KIT at exon 9 should be treated with 800 mg imatinib/day, since they profited from a significantly longer progression-free survival. However, it is also important to note that there were very few true complete remissions from medical therapy alone. Thus, along with the effective targeted therapy, cytoreductive surgery has been pursued in patients with metastatic or recurrent GISTs6,26.

The figure below shows the summarized strategy for GIST therapy (Figure 2).

Prediction of Recurrence of GISTs

Due to the malignant potential of GISTs it is important to be able to predict the possibility of recurrence after surgical or endoscopic resection of the primary localized GIST. Several researchers have evaluated the recurrence predicting factors of GISTs. Kim et al76 demonstrated that after resections of gastric GISTs of diameters ≤ 5 cm, high mitotic index (>10 per 50 High Power Fields) and abnormally high levels of p53 expression were predictive factors of recurrence. Interestingly the authors indicated that a positive microscopic resection margin was not associated

Figure 2. Strategy of GISTs therapy.
with recurrence. A multicentric, prospective analysis in a much larger population should be carried out in the near future to confirm the predictors of recurrence for GISTs.

**Conclusions**

Over the past decade, increased knowledge of the pathogenesis of GISTs has led to improved understanding of these lesions and the ability to readily identify and differentiate GISTs from other submucosal tumors. EUS-FNA is considered as the preferable and feasible option for confirming the diagnosis of GISTs. EUS-CNB is also a promising method for their diagnosis. Although surgical resection is the first-line treatment, and the only method that might lead to full remission in patients with primary GIST, various new techniques for endoscopic resections are emerging. Many researchers demonstrated satisfactory results with endoscopic resections, but more studies should take place to confirm the prognosis of endoscopic therapy. Last but not the least, targetted therapy represented by imatinib and sunitinib has clearly improved the survival rates in patients with primary, metastatic, or recurrent GISTs. As various novel techniques are persistently improving the management of GISTs it is expected that both individual risk assessment and therapy for each lesion may be provided to each patient someday.

**Acknowledgements**

The work is supported in part by grants 81101844 and 8120108027 (to C. Huang) from the National Natural Science Foundation of China and grant 2012040 and 13PJD024 (to C. Huang) from Shanghai Municipal Human Resources and Social Security Bureau.

**Conflict of Interest**

The Authors declare that there are no conflicts of interest.

**References**


14) **Fletcher J.** Role of KIT and platelet-derived growth factor receptors as oncoproteins. Semin Oncol 2004; 31: 4-11.
Gastrointestinal stromal tumors: current translational research and management modalities


