The Most Common Sarcomas Arising From the GI Tract

Girish Mishra, MD, MS, FACP
Associate Professor of Internal Medicine
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Introduction
Gastrointestinal stromal tumors (GISTs) are the most common sarcomas arising from the gastrointestinal (GI) tract, with an incidence of 6.8 to 20 cases per 1 million individuals.1,2 According to the American Cancer Society, there are approximately 4,500 to 6,000 new cases in the United States per year.3

Generally, GISTs, which are potentially malignant, emanate from the GI wall and are thought to originate from the interstitial cells of Cajal (ICC), the “pacemaker cells” that regulate GI motility.4 More than 75% of patients with GIST present after age 50 (approximately age 60); men and women are equally affected.5,6 According to a study of 53 patients, approximately 70% of GISTs produce clinical symptoms, with the remainder found incidentally at endoscopy or on computed tomography (CT).7 Overt GI bleeding due to an ulcerated mass is the most common symptom and is observed in approximately 65% of patients; occult bleeding with ensuing anemia may be found in nearly 20% of individuals. Other presenting symptoms may include abdominal pain or fullness (32%) and the presence of a palpable mass (13%).8

GISTs can develop anywhere along the GI tract, from the esophagus to the rectum. GISTs are most commonly seen in the stomach (60%).9 Overall, GISTs represent the most common primary small bowel tumor (32%).10 Approximately 10% to 30% of GISTs are clinically malignant; however, GISTs have malignant potential.11 Clinically malignant behavior includes omental, mesenteric, or peritoneal seeding; invasion of adjacent organs; or frank metastasis. The most common metastatic sites include the abdominal cavity, liver, lung, and bone.12 GISTs exhibit variable and unpredictable behavior; a large GIST may remain stable for years, whereas a small, incidentally discovered GIST may follow a more malignant course. Germane to this feature, GISTs should not be classified as benign or malignant, but rather evaluated for clinical risk for disease progression based on tumor size, which dictates whether it can be safely resected; location, which affects surgical approach and the risk for tumor recurrence; and mitotic rate, which indicates cell proliferation (higher rates often result in a worse prognosis).13,14

Pathology
GISTs are histologically composed of fairly uniform spindle cells (70%), but in some cases may be dominated by epithelioid cells (20%) or consist of a mixture of these 2 morphologies15 (Figure 1A). Close to 90% of GISTs exhibit mutations, usually involving the KIT gene, but may have a defect in the platelet-derived growth factor receptor (PDGFRα) gene (approximately 7%).8 c-KIT is a proto-oncogene that is a transmembrane receptor kinase. This gene is responsible for activating stem cell factor, which results in cell proliferation. c-KIT signaling pathways regulate apoptosis and chemotaxis. CD117 antigen is part of the c-KIT receptor as identified on immunohistochemistry16 (Figure 1B). GISTs also may stain positive for the cell surface glycoprotein CD34 (60%-70%); positive staining for S100 protein and desmin are less commonly observed.17,18

Diagnosis
Routine evaluation in patients with abdominal symptoms often leads to a CT scan. CT scan is ideal for defining the endoluminal and exophytic extent of tumor, as well as discerning features associated with aggressiveness such as calcifications, ulcerations, necrosis, cystic areas, fistula formation, metastases, ascites, and other signs of infiltrative disease.19 However, CT is unable to delineate the site of origin nor can it discriminate between other submucosal lesions frequently encountered in the GI tract. GISTs are metabolically active, and thus take up the positron emission tomography (PET) imaging agent [18F]fluorodeoxyglucose, a radiolabeled synthetic analog of glucose. Yet, the value of a PET scan has been confined to determining distant metastasis.20

The mainstay of diagnosis relies on detection of GISTs by endoscopy and subsequent endoscopic ultrasound (greatest impact in nonulcerated lesions). The hallmark of GISTs and other subepithelial lesions is a bulge in the GI tract with a smooth overlying mucosa21,22 (Figure 2). Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) employing various needle sizes has been employed with varying success23,24 (Figure 3). In a recent study of 112 GISTs, Hoda and colleagues showed that in nearly 62% of cases, EUS-FNA achieved a firm diagnosis based on spindle cell histology and immunohistochemical staining for CD117; whereas in 22% of patients, the sample showed spindle cells, but there was insufficient material for immunohistochemistry.25 In a retrospective analysis, Sepe et al showed that the sensitivity of preoperative EUS-FNA was 78% in 37 surgically resected specimens with c-KIT–positive GISTs.26

Surgery
The majority of GIST experts recommend surgical removal of GISTs greater than 2 cm—except when resection carries a significant risk for morbidity—because of the uncertainty surrounding the assessment of malignant potential. Surgical excision of metastatic GISTs is becoming more common. In 2010, the National Comprehensive Cancer Network (NCCN) released an update of their clinical practice guidelines for the optimal management of patients with GIST. The NCCN panelists agreed that the

Figure 1. Diagnostic cell staining for GIST.
(A) Cytology smear from EUS-FNA showing “cigar-shaped” spindle cells. (B) Cell block material obtained from EUS-FNA showing diffuse brown staining for c-KIT immunohistochemistry.

Figure 2. Endoscopic imaging of a GIST tumor.
Endoscopic imaging of an approximately 2-cm GIST in the body of the stomach showing the classic smooth, submucosal bulge with normal overlying mucosa.

GIST, gastrointestinal stromal tumor
Photo reproduced with permission from Girish Mishra, MD, MS, FACP.

Notes
standard treatment for localized, resectable GIST is surgery. The NCCN recommends a CT-guided core biopsy if preoperative radiotherapy or chemotherapy is given. The primary goal of surgery is complete tumor removal with clear margins (R0 resection). Because GISTs tend not to infiltrate but grow out of the primary organ, either a wedge or segmental resection of the stomach is considered adequate for the panel. However, as wedge resections are technically difficult for esophageal, duodenal, and rectal primaries, a wide resection in these areas is recommended. Omental or mesenteric GISTs necessitate a complete en bloc resection of visible disease. Adherent, adjacent organs should be resected en bloc with the tumor in order to avoid capsule rupture and intra-abdominal spillage. Lymphadenectomy is unnecessary given the low risk for nodal spread in GISTs.

Laparoscopic wedge resection has become an attractive alternative to traditional technique with similar outcomes. Novotny and colleagues reported a 92% disease-free survival at 36 months in a consecutive series of 50 patients undergoing laparoscopic or laparoscopic-resection of GISTs. The NCCN suggests that laparoscopic wedge resection can be considered for tumors in favorable anatomic locations (eg, anterior wall of the stomach, jejunum, and ileum). A study of 35 GIST patients showed that when this technique is used on tumors 2 cm to 5 cm in size, it led to shorter postoperative stays and positive 5-year disease-free survival. Following resection, the NCCN recommends surveillance with abdominal and pelvic CT scans every 3 to 6 months. In the setting of locally advanced or metastatic GISTs, patients should be referred to an oncologist following surgery to discuss further management.

Recurrent Risk and Overall Survival

The risk for GIST recurrence and/or metastasis is significant, with 1 in 2 patients experiencing recurrence within 5 years following surgery. As GISTs are heterogeneous in presentation, morphology, and behavior, their aggressiveness is largely unpredictable. Prognostic features most useful in judging malignant potential can be found within Figure 4. Small bowel GISTs larger than 5 cm behave aggressively with respect to metastasis and tumor-related deaths, despite having a low mitotic rate.

Key Considerations

The need for a multidisciplinary approach—including gastroenterology, pathology, medical, and surgical oncology—to the management of GISTs is absolutely critical for optimizing patient outcome. Radiologists also play a crucial role in interpreting images at initial diagnosis and in assessing treatment outcomes. Imaging with either EUS or CT scan cannot predict the malignant potential of GISTs. Histologic grading is also devoid of prognostic potential. As such, GISTs have malignant potential and should be monitored carefully with the assistance of the medical oncologist.

Figure 3. EUS for the diagnosis of GIST.

(A) EUS image of a well-defined, hypoechoic, 1.9 × 2.3-cm mass in the submucosa. Note the small, anechoic central areas indicative of hypervascularity. (B) EUS-FNA image of GIST.

EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; GIST, gastrointestinal stromal tumor.

Figure 4. Key prognostic and assessment considerations for GIST.

Adapted from references 10, 11, and 21.

A

B

Prognostic factors for GIST patients

- Tumor location
- Tumor size
- Mitotic rate
- Mucosal/intestinal invasion
- Tumor necrosis or rupture
- Number of metastases/risk for recurrence
- Mutations of exon 9 or 11
- Cellularity
- Patient age
- Patient medical history, including comorbidities

Points of assessment for patients with GIST

- GISTs may arise anywhere along the GI tract.
- GISTs have malignant potential.
- Approximately 95% of GISTs are KIT-positive.
- The presence of the KIT protein is a key tumor marker for GIST.
- Classify risk for tumor pursuing aggressive course.
- Decide whether tumor is resectable with low risk for morbidity.
- A multidisciplinary approach with expertise in sarcomas is recommended.
- EUS should be considered for GISTs and other submucosal lesions.

References