

## **GASTROINTESTINAL STROMAL TUMORS (GIST)**

### **Background**

- GISTs are mesenchymal tumors that are most often located in the stomach and proximal small intestine
- May occur in any portion of the alimentary tract that contains smooth muscle within its wall
- Constitute only 1% of primary GI tumors
- However, autopsy studies have shown small asymptomatic GISTs are present in the GI tract in >50% of individuals >50 years old
- Annual incidence is 4,500-6,000 in the U.S.
- Typically occurs in older patients, peak occurrence in 5th and 6th decades

### **Molecular Characteristics**

- GISTs were originally considered to originate from smooth muscle; however they rarely showed features of complete muscle differentiation; as do leiomyomas
- GISTs nearly universally express CD117 antigen; this is not seen in leiomyomas or other spindle-cell tumors of GI tract
- CD117 molecule is part of the c-kit receptor, a membrane tyrosine kinase that is a product of the c-kit or KIT protooncogene
- Majority of GISTs are c-kit +
- Current view is that most mesenchymal tumors arising in GI tract are GIST. These are identified by c-kit immunoreactivity, or presence of activating mutations in KIT or PDGFRA (a related TK receptor, platelet derived growth factor receptor alpha)
- In contrast, smooth muscle tumors (leiomyomas) and schwannomas of GI tract lack KIT mutations, and are c-kit negative
- “Gain of function” mutations in KIT are observed in both sporadic and hereditary cases
- These “gain of function” mutations lead to the constitutive activation of the c-kit tyrosine kinase receptor independent of the receptor ligand. This leads to uncontrolled cell proliferation and inhibition of normal apoptotic cell death.
- In addition to CD117; GISTs are positive for CD34 approx 60-70% of the time
- Immunohistochemical staining for CD34 and CD117 is essential for positive ID and diagnosis of GIST
- On the other hand; leiomyomas stain positive for desmin and SMA (smooth muscle actin), & schwannomas are + for S100; and both are negative for CD117 and CD34

**Immunohistochemical Schema for the Differential Diagnosis of Spindle Cell Tumors of the Gastrointestinal Tract<sup>†</sup>**

Type	CD117	CD34	SMA*	S100 Protein	Desmin
<b>GISTs</b>	<b>+</b> (>95 percent)	<b>+</b> (60-70 percent)	<b>+/-</b> (30-40 percent)	<b>-</b> (5 percent +)	<b>Very rare</b>
<b>Leiomyoma</b>	-	<b>+</b> (10-15 percent)	<b>+</b>	-	<b>+</b>
<b>Leiomyosarcoma</b>	-	-	<b>+</b>	-	<b>+</b>
<b>Inflammatory</b>	-	<b>+</b>	<b>+/-</b>	-	-
<b>Schwannoma</b>	-	-	-	<b>+</b>	-

\* Alpha smooth muscle actin  
<sup>†</sup> Modified from Fletcher, CD, et al. Int J Surg Pathol 2002; 10:81 and Miettinen, M, et al. Mod Pathol 2000; 10:1134.

### Clinical Presentation

- 10-30% of patients with GISTs may be asymptomatic, with the tumor being incidentally discovered
- Symptoms at time of presentation depend on location and size of tumor
- Location of GISTs
  - Stomach (60-70%)
  - Small intestine (20-30%)
  - Esophagus, rectum, colon, mesentery, omentum, and retroperitoneum (<10%)
- GISTs of stomach and small intestine usually present with GI bleeding (20-50%), abdominal pain (40-50%), or a palpable mass (25-40%)
- Esophageal GISTs commonly present with dysphagia and weight loss
- GISTs of the colon commonly present with GI bleeding, abdominal pain, palpable mass, or change in bowel habits
- Primary GISTs of the omentum, mesentery, and retroperitoneum present as solitary intra-abdominal masses instead of multiple, scattered nodular lesions seen in metastatic spread of primary GISTs.

### Histopathology

- Three main categories:
  - Spindle cell type: 70-80%
  - Epithelioid type: 20%
  - Mixed type: <10%
- Data suggests that histologic type may help to predict prognosis. In a study of 48 patients, the five-year recurrence free survival rate was significantly higher among patients with spindle cell as compared to epithelioid or mixed histology (49 vs. 23% respectively)
  - Singer, S et al. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in GISTs. J Clin Oncol 2002; 20: 3839.

## Malignancy

- Up to 30% of GISTs may be malignant
- Malignant behavior is defined by omental, mesenteric, or peritoneal seeding; invasion of adjacent organs; tumor recurrence after surgical resection; or metastases to extra-intestinal organs or the abdominal wall.
- Most common extra-intestinal metastases:
  - Liver (50%)
  - Lung (10%)
  - Bone (<10%)
- GISTs do not exhibit lymphatic spread
- Mitotic activity and tumor size have been identified as the most useful morphological features in predicting malignant behavior
- In general, a tumor size greater than 5 cm is associated with high risk of metastasis or recurrence
- A mitotic count of > 5 mitoses per 50 high-power fields is associated with malignancy
- Additionally, site of origin is a factor. Gastric GISTs have a lower rate of metastases than small bowel GISTs
- CT or endoscopic ultrasound characteristics of malignancy include tumor > 5 cm, lobulated, enhance heterogeneously rather than homogeneously, mesenteric fat infiltration, ulceration, and exophytic growth pattern.

**Proposed Approach for Defining Risk of Aggressive Behavior in Gastrointestinal Stromal Tumors†**

	Size*	Mitotic count●
<b>Very low risk</b>	<2 cm	<5 per 50 HPF
<b>Low risk</b>	2-5 cm	<5 per 50 HPF
<b>Intermediate risk</b>	<5 cm 5-10 cm	6-10 per 50 HPF < 5 per 50 HPF
<b>High risk</b>	>5 cm >10 cm Any size	>5 per 50 HPF Any mitotic rate >10 per 50 HPF

HPF: high powered fields.  
 \* Size represents the single largest dimension. Admittedly this may vary somewhat before and after fixation and between observers. There is a general but poorly defined sense that perhaps the size threshold for aggressive behaviour should be 1-2 cm less in the small bowel than elsewhere.  
 ● Ideally mitotic count should be standardized according to surface area examined (based on size of high power fields), but there are no agreed definitions in this regard. Despite inevitable subjectivity in recognition of mitoses and variability in the area of high power fields, such mitotic counts still prove useful.  
 † Reproduced with permission from: Fletcher, CD, Berman, JJ, Corless, C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Int J Surg Pathol 2002; 10 :81. Copyright ©2002 Westminster Publications.

## Diagnostic workup

- GIST is often seen by CT or ultrasound that was performed because of abdominal pain, mass, or other symptoms
- CT findings of GIST: a solid mass that enhances brightly with IV contrast; may see exophytic growth

- Endoscopy: GISTs usually appear as a submucosal lesion or a bulge in the lumen with normal overlying mucosa. Occasionally, there is an area of umbilication or mucosal ulceration.
- Endoscopic ultrasound is a vital component in the evaluation, diagnosis, and management of GISTs
- On EUS, GISTs typically appear as hypoechoic mass lesions arising from the muscularis propria. Majority are ovoid or elliptical in shape.
- EUS-guided FNA biopsy has emerged as an important method for the diagnosis of GISTs.
- Using this procedure, CD117 expression can be determined which is necessary for making the diagnosis of GIST
- The FNA specimen may also undergo immunohistochemical staining for Ki-67, a labeling index that indicates mitotic activity and cell proliferation.
- The use of Ki-67 staining, in combination with EUS findings and EUS-FNA cytological results, was found to have a sensitivity and specificity of 100% for malignant GISTs.

## Treatment

- Surgical resection is the primary treatment for GISTs
- Surgery is indicated for all GISTs that cause symptoms and those tumors suspected of being malignant or potentially malignant.
- Goal is to resect all gross disease; additionally, lymphadenectomy is not performed because LN mets are very rare.
- For those patients undergoing surgery, survival is primarily related to tumor size and completeness of resection. Patients with incompletely resected disease have significantly worse outcome.
- Laparoscopic resection of GISTs have been reported primarily for those found in the stomach
- No current guidelines for the management of small GISTs that are asymptomatic and have low-risk features for malignancy on histopath and EUS
- Interval follow-up with EUS is recommended
- There is approx. a 50% recurrence rate at 5 years following complete resection.
- There does not seem to be a survival benefit in re-operating recurrent disease
- Imatinib (Gleevec) selectively inhibits certain tyrosine kinases, including c-kit, leading to decreased cell proliferation and apoptosis.
- In one study in 2000, 147 patients with unresectable or metastatic GISTs received Imatinib. Results showed that 53.7% of patients had a partial response to treatment, which meant a 50-96% reduction in bulk of tumor; 27.9% had stable disease, and 13.6% had disease progression
  - Demetri, et al. Efficacy and safety of imatinib mesylate in advanced GIST. N Engl J Med 2002; 347: 472-80.
- In May 2002, imatinib mesylate was approved by the FDA for the treatment of unresectable, metastatic GIST
- “Imatinib 400 mg/day with or without surgery is the recommended first-line treatment for recurrent or metastatic GIST; a higher dose may be considered in patients who progress, develop secondary resistance or present with specific genotypic characteristics. Adjuvant

or neoadjuvant imatinib is not advised for resectable nonmetastatic GISTs. Neoadjuvant imatinib may be considered when surgery would result in significant morbidity or loss of organ function. Follow-up computed tomography imaging is recommended every three to six months for at least five years. Patients with metastatic disease should be continued on imatinib due to the high risk of recurrence on discontinuation of therapy. Treatment should be continued until there is progression or intolerable adverse effects... The present recommendations were developed at a surgical subcommittee meeting and a subsequent full Advisory Committee meeting held in Toronto, Ontario, in April 2005, under the sponsorship of Novartis Pharmaceuticals Canada Inc.”

- Blackstein, M.E., et al. Gastrointestinal stromal tumours: Consensus statement on diagnosis and treatment. *Can J Gastroenterol*. 2006 Mar;20(3):157-63.

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