IDENTIFYING THE CURRENT STATE OF GIST

CLINICAL OVERVIEW

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the GI tract. Most of these tumors are gastric or small intestinal. Diagnosis relies on contrast-enhanced computed tomography (CT) and histology. Prognosis varies by location and is generally more favorable for patients with gastric tumors than for patients with GIST of the small intestine or other less common locations. Active mutations in KIT (CD117) and PDGFRα are involved with most of the cases of GIST and can be important diagnostic markers with prognostic value.1-3

KIT = stem cell factor receptor.
PDGFRα = platelet-derived growth factor receptor alpha.
US INCIDENCE AND PREVALENCE OF GIST

There are an estimated 4500 to 6000 new cases of GIST in the United States each year, although incidence is difficult to determine and may vary among studies. About 1500 of these cases are metastatic at presentation. The reported incidence has increased because of greater awareness, improved diagnosis, and perhaps an increase in the true incidence of the disease. Prevalence can also be difficult to determine; one study estimated that 129 per million people are living with GIST.2,4,5

PATIENT DEMOGRAPHICS

While most patients diagnosed with GIST are older than age 50, GIST may occur at any age. African Americans and men are more likely to develop GIST.4

CLINICAL PRESENTATION OF GIST

FREQUENCY OF THE DISEASE IN VARIOUS PRIMARY SITES1,2

- STOMACH: 60%
- DUODENUM: 5%
- JEJUNUM/ILEUM: 30%
- COLON/RECTUM/ANUS: <5%
- ESOPHAGUS, APPENDIX, OR OUTSIDE THE GI TRACT: <1%

*Estimate based on a population in Sweden.5

APPARENTLY

4500-6000
NEW CASES OF GIST PER YEAR

1500
CASES ARE METASTATIC
CLINICAL PRESENTATION OF GIST

SIGNS AND SYMPTOMS

GISTs smaller than 2 cm do not generally produce symptoms and are detected incidentally. Larger tumors can exhibit more symptoms, such as early satiety, abdominal discomfort from pain or swelling, intraperitoneal hemorrhage, GI bleeding, or anemia-related fatigue. Some patients present with acute, severe abdominal pain, which may be a sign of a medical emergency.

MEDIAN TUMOR SIZE AT PRESENTATION

GISTs may occur anywhere along the GI tract. The majority present as a single, well-circumscribed nodule. GIST lesions range in size from a few millimeters to more than 35 cm. Median size at presentation is approximately 5 cm. A recent population-based study suggested that the median size of GISTs is generally larger when patients are diagnosed based on disease symptoms.

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>TUMOR SIZE (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental findings</td>
<td>2.7</td>
</tr>
<tr>
<td>Autopsy</td>
<td>3.4</td>
</tr>
<tr>
<td>Symptoms</td>
<td>8.9</td>
</tr>
</tbody>
</table>

LOCATION OF METASTASES

GISTs most commonly metastasize to the liver and/or disseminate within the abdominal cavity. Metastases beyond the abdominal cavity are observed in late-stage disease only. Lymph node metastases are uncommon.

DIAGNOSIS OF GIST

Imaging studies, such as CT, magnetic resonance imaging (MRI) or positron emission tomography (PET), are used for diagnosis, initial staging, restaging, monitoring response to therapy, and follow-up surveillance of recurrence.

Contrast-enhanced CT is the imaging modality of choice to characterize an abdominal mass, assess the extent of the mass, and determine if the mass has metastasized. PET scans can facilitate differentiation of an active tumor from necrotic or inactive tissue, malignant from benign tissue, and recurrence from benign changes.

HISTOLOGY

Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Immunohistochemical staining for KIT, in addition to anatomic localization of the lesion, is essential for confirming the diagnosis. Tissue samples may be obtained via biopsy or primary tumor resection.

Endoscopic ultrasound–guided biopsy may be considered when appropriate. A core needle biopsy may be preferred over fine-needle aspiration biopsy because this offers the opportunity to obtain information on mitotic rate. Supportive techniques, such as molecular genetic testing for KIT or PDGFRα mutations, are also useful.

STAGING

Staging can be determined using the American Joint Committee on Cancer Staging System for Soft Tissue Sarcoma (7th ed, 2010) as adapted in the table below.

<table>
<thead>
<tr>
<th>ANATOMIC STAGE/PROGNOSTIC GROUP</th>
<th>PRIMARY TUMOR SIZE</th>
<th>REGIONAL LYMPH NODE METASTASIS</th>
<th>DISTANT METASTASES</th>
<th>HISTOLOGIC GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA (≤5 cm)</td>
<td>None</td>
<td>None</td>
<td>1 or cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>IB (&gt;5 cm)</td>
<td>None</td>
<td>None</td>
<td>1 or cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>IIA (≤5 cm)</td>
<td>None</td>
<td>None</td>
<td>2 or 3</td>
<td></td>
</tr>
<tr>
<td>IIB (&gt;5 cm)</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>III (&gt;5 cm)</td>
<td>None</td>
<td>None</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Present</td>
<td>None</td>
<td>Any grade or cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Present/none/cannot be assessed</td>
<td>Present</td>
<td>Any grade or cannot be assessed</td>
<td></td>
</tr>
</tbody>
</table>
Prognosis is generally more favorable for patients with gastric GISTs than for those with GISTs of the small intestine.\(^1\)

**RISK STRATIFICATION\(^1,2\)**

The most important and widely used prognostic features of a primary tumor are tumor size, location, and mitotic index. Gastric GISTs ≤2 cm with a mitotic index of ≤5 per 50 high-power fields (HPF) are considered benign; however, lesions >2 cm with the same mitotic index have a risk of recurrence. GISTs of the small intestine are usually associated with the greatest risk of recurrence or progression and are more aggressive than gastric GISTs of the same size.

While tumor size and mitotic rate are useful in predicting the malignant potential of GISTs, the likelihood of progressive disease varies among individuals.

**RISK STRATIFICATION OF PRIMARY GIST BY MITOTIC INDEX, SIZE, AND SITE\(^2\)**

<table>
<thead>
<tr>
<th>Mitotic rate</th>
<th>Size</th>
<th>Stomach</th>
<th>Jejunum/ileum</th>
<th>Duodenum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 per 50 HPF</td>
<td>≤ 2 cm</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
<td>None (0%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 2, ≤ 5 cm</td>
<td>Very low (1.9%)</td>
<td>Low (4.3%)</td>
<td>Low (8.3%)</td>
<td>Low (8.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5, ≤ 10 cm</td>
<td>Low (3.6%)</td>
<td>Moderate (24%)</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>Moderate (10%)</td>
<td>High (52%)</td>
<td>High (34%)</td>
<td>High (57%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 HPF</td>
<td>≤ 2 cm</td>
<td>None*</td>
<td>High*</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td>&gt; 2, ≤ 5 cm</td>
<td>Moderate (16%)</td>
<td>High (73%)</td>
<td>High (50%)</td>
<td>High (52%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 5, ≤ 10 cm</td>
<td>High (55%)</td>
<td>High (85%)</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>High (86%)</td>
<td>High (90%)</td>
<td>High (86%)</td>
<td>High (71%)</td>
</tr>
</tbody>
</table>

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.

*Defined as metastasis or tumor-related death.

*Denotes small number of cases.

Adapted from Demetri GD, von Mehren M, Antonescu CR, et al.

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**SURVIVAL RATES\(^2\)**

Recurrence-free survival (RFS), based on tumor size, mitotic index, and anatomic site, may be estimated using a nomogram.

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**DETERMINING THE SPECIFIC MUTATIONAL STATUS OF PATIENTS WITH GIST MAY HAVE VALUE IN ESTIMATING SURVIVAL.\(^2\)**

Patient example: a 2.5-cm tumor (15 points) with a mitotic index of ≥5/50 HPF (80 points) located in the colon (7 points) has a total point value of 102. A value of 102 on the “Total Points” line corresponds to a 2-year RFS of approximately 62% and a 5-year RFS of approximately 38%.
MUTATIONS IN GIST

Exon mutations can result in structurally and functionally abnormal receptors that can lead to continual (“constitutive”) activation and tumor development.6,7

RECEPTOR MUTATIONS ARE KNOWN TO CAUSE TUMOR CELL PROLIFERATION8,9
- When functioning normally, KIT regulates cell proliferation and survival
- PDGFRα mutations have similar biological consequences to KIT mutations and drive the progression of GIST

INCIDENCE OF SPECIFIC PRIMARY MUTATIONS IDENTIFIED IN GIST1
- Approximately 80% have a mutation in the gene encoding the KIT receptor
- 5% to 10% have a mutation in the gene encoding the PDGFRα receptor
- About 10% to 15% do not have any detectable mutation (wild type); however, the absence of such a mutation does not exclude the diagnosis of GIST

RELATIVE FREQUENCY OF PRIMARY MUTATIONS IN GIST10-15

KIT: 78% to 88%
- Exon 9: 10% to 18%
- Exon 11: 66% to 67%
- Exon 13: 1% to 2%
- Exon 17: 1% to 2%
- Exon 18: 2% to 6%

PDGFRα: 5% to 7%
- Exon 12: 1% to 2%

Juxtamembrane domain

MUTATIONS VARY BY LOCATION

KIT exon 11 mutations occur in various sites throughout the GI tract. KIT exon 9 mutations occur mostly in the small intestine, while KIT exon 17 mutations occur more frequently in the small intestine than in the stomach.2

PDGFRα mutations are more common in the stomach and omentum, a fatty layer in the abdomen.2

IDENTIFYING THE SPECIFIC MUTATION MAY HAVE PROGNOSTIC VALUE1,2
GISTs with KIT exon 9 mutations may be more clinically aggressive than tumors with KIT exon 11 mutations. Based on data from a large phase 3 study, the presence of KIT exon 9 mutations is strongly associated with mutational prognostic factors for the risk of progression or death in patients with GIST, even in patients currently receiving therapy. In particular, the presence of KIT exon 9 mutations in tumors outside the stomach appears to be associated with an unfavorable clinical course. In randomized clinical trials, the presence of KIT exon 11 mutations was associated with better rates of response, progression-free survival, and overall survival compared with KIT exon 9 mutations or wild type.

Patients with no detectable KIT or PDGFRα mutations are also at increased risk of progression and death. Studies have shown that patients with KIT mutation–negative GIST have similar time to tumor progression but inferior overall survival compared with patients with KIT mutation–positive GIST.

In comparing KIT with PDGFRα mutations, GISTs with PDGFRα mutations may be less aggressive than those with KIT mutations.
The following laboratories in the United States conduct GIST mutational testing:

**ARUP LABORATORIES**  
500 Chipeta Way  
Salt Lake City, UT 84108-1221  
Tel: 800-522-2787  
Fax: 800-522-2706  
E-mail: clientservices@arulab.com  
Web site: www.arulab.com  

**CITY OF HOPE™ MOLECULAR DIAGNOSTIC LABORATORY (MDL)**  
1500 E. Duarte Rd.  
Duarte, CA 91010  
Tel: 888-826-4362  
Fax: 626-301-8142  
E-mail: mdl@coh.org  
Web site: www.cityofhope.org/mdl

**FOX CHASE CANCER CENTER**  
Clinical Molecular Genetics Laboratory  
West Building, Room W232  
333 Cottman Avenue  
Philadelphia, PA 19111-2497  
Contact: Betsy Bove, PhD  
Tel: 215-728-4785  
E-mail: betsy.bove@fccc.edu  
Web site: www.fccc.edu/research/facilities/clinical/cmgl/index.html

**MAYO CLINIC LABORATORIES**  
(For Mayo Clinic account members; if you are not currently a member and would like to join, please call the number below)  
3050 Superior Drive NW  
Rochester, MN 55901  
Tel: 800-533-1710  
E-mail: mml@mayo.edu  
Web site: www.mayomedicallaboratories.com/test-catalog/Overview/89669

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E-mail: info.pathology@UCDenver.edu  
Web site: http://www.ucdenver.edu/academics/colleges/medicalschool/departments/Pathology/aboutus/Pages/contactus.aspx

**UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER**  
(for MD Anderson/KIT mutation patients only)  
Molecular Diagnostic Laboratory  
8515 Fannin Street  
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Contact: Raja Luthra, PhD (technical director) or Cindy Lewing (laboratory manager)  
Tel: 713-794-4780; 713-792-2730  
Fax: 713-794-4773  
E-mail: clewing@mdanderson.org  
Web site: www.mdanderson.org

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3181 SW Sam Jackson Park Road  
Portland, OR 97239  
Contact: Erin Popelka  
Tel: 503-494-6834  
Fax: 503-494-2025  
E-mail: popelka@ohsu.edu  
Web site: www.heinrich-corless.net/services

**SAMPLE COLLECTION**  
Stained or unstained slides or formalin-fixed, paraffin-embedded blocks containing histologically confirmed GIST tissue are generally accepted. Larger amounts of sample tissue are preferred. It’s important to discuss specific requirements with the local pathologist or to contact the lab conducting the mutational testing directly to verify the appropriate specimen-collection techniques.
Pfizer Oncology is committed to raising awareness of GIST.

For more information, visit www.pfizeroncology.com.

References: