Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST)

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
- Biopsy
- Resection

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CAP GIST Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: GIST 3.0.2.1

Summary of Changes
The following changes have been made since the February 2011 release.

Resection

Pathologic Staging (pTNM)
Regional Lymph Nodes (pN)
“Not applicable” was added, as follows:

Regional Lymph Nodes (pN)
___ Not applicable
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
**Surgical Pathology Cancer Case Summary**

Protocol web posting date: June 2012

**GASTROINTESTINAL STROMAL TUMOR (GIST): Biopsy**

Select a single response unless otherwise indicated.

**Procedure**
- ___ Core needle biopsy
- ___ Endoscopic biopsy
- ___ Other (specify): ____________________________
- ___ Not specified

**Specimen Size**
- + Greatest dimension: ___ cm
- + Additional dimensions: ___ x ___ cm
- + ___ Cannot be determined (see “Comment”)

**Tumor Site**
Specify: ____________________________ (Note A)
- ___ Not specified

**Tumor Size**
- + Greatest dimension: ___ cm
- + Additional dimensions: ___ x ___ cm
- + ___ Cannot be determined (see “Comment”)

**GIST Subtype**
- ___ Spindle cell
- ___ Epithelioid
- ___ Mixed
- ___ Other (specify): ____________________________

**Mitotic Rate**
Specify: ___ /50 high-power fields (HPF)

*Note: The required total count of mitoses is per 5 mm² on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm². Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm². If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm².*

**Necrosis**
- + ___ Not identified
- + ___ Present
  - + Extent: ___%
- + ___ Cannot be determined

**Histologic Grade (Note B)**
- ___ GX: Grade cannot be assessed
- ___ G1: Low grade; mitotic rate <5/50 HPF
- ___ G2: High grade; mitotic rate >5/50 HPF

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Risk Assessment (Note C)
___ None
___ Very low risk
___ Low risk
___ Intermediate risk
___ High risk
___ Overtly metastatic
___ Cannot be determined

Distant Metastasis (Note D)
___ Cannot be assessed
___ Distant metastasis
   Specify site(s), if known: ______________________________

+ Additional Pathologic Findings
+ Specify: ______________________________

Ancillary Studies (select all that apply) (Note E)

Immunohistochemical Studies
___ KIT (CD117)
   ___ Positive
   ___ Negative
___ Others (specify): ______________________________
___ Not performed

Molecular Genetic Studies (eg, KIT or PDGFRA mutational analysis)
___ Submitted for analysis; results pending
___ Performed, see separate report: _________________________
___ Performed
   Specify method(s) and results: ______________________________
___ Not performed

Prebiopsy Treatment (select all that apply)
___ No therapy
___ Systemic therapy performed
   Specify type: ______________________________
___ Therapy performed, type not specified
___ Unknown

+ Treatment Effect (Note F)
+ Specify percentage of viable tumor: ___%

+ Comment(s)
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

GASTROINTESTINAL STROMAL TUMOR (GIST): Resection

Select a single response unless otherwise indicated.

Procedure
___ Excisional biopsy
___ Resection
   Specify type (eg, partial gastrectomy): ________________
___ Metastasectomy
___ Other (specify): ____________________________
___ Not specified

Tumor Site
Specify (if known): ____________________________
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see “Comment”)

Tumor Focality
___ Unifocal
___ Multifocal
   Specify number of tumors: ___
   Specify size of tumors: _______________________

GIST Subtype
___ Spindle cell
___ Epithelioid
___ Mixed
___ Other (specify): __________________________

Mitotic Rate
Specify: ___ /50 HPF
Note: The required total count of mitoses is per 5 mm² on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm². Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm². If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm².

+ Necrosis
+ ___ Not identified
+ ___ Present
   + Extent: ___%
+ ___ Cannot be determined

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Histologic Grade (Note B)
___ GX: Grade cannot be assessed
___ G1: Low grade; mitotic rate ≤5/50 HPF
___ G2: High grade; mitotic rate >5/50 HPF

Risk Assessment (Note C)
___ None
___ Very low risk
___ Low risk
___ Intermediate risk
___ High risk
___ Overtly malignant/metastatic
___ Cannot be determined

Margins
___ Cannot be assessed
___ Negative for GIST
  Distance of tumor from closest margin: ___ mm or ___ cm
___ Margin(s) positive for GIST
  Specify margin(s): ________________________

Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence for primary tumor
___ pT1: Tumor 2 cm or less
___ pT2: Tumor more than 2 cm but not more than 5 cm
___ pT3: Tumor more than 5 cm but not more than 10 cm
___ pT4: Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (pN) (Note D)
___ Not applicable
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

Distant Metastasis (pM) (Note D)
___ Not applicable
___ pM1: Distant metastasis
  + Specify site(s), if known: ________________________

+ Additional Pathologic Findings
+ Specify: ___________________________
Ancillary Studies (select all that apply) (Note E)

**Immunohistochemical Studies**
- [ ] KIT (CD117)
  - [ ] Positive
  - [ ] Negative
- [ ] Others (specify): ____________________________
- [ ] Not performed

**Molecular Genetic Studies (eg, KIT or PDGFRA mutational analysis)**
- [ ] Submitted for analysis; results pending
- [ ] Performed, see separate report: ____________________
- [ ] Performed
  - Specify method(s) and results: ____________________________
- [ ] Not performed

**Preresection Treatment (select all that apply)**
- [ ] No therapy
- [ ] Previous biopsy or surgery
  - Specify: ____________________________
- [ ] Systemic therapy performed
  - Specify type: ____________________________
- [ ] Therapy performed, type not specified
- [ ] Unknown

*+ Treatment Effect (Note F)*
+ Specify percentage of viable tumor: ___%

*+ Comment(s)*

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Explanatory Notes

A. Location
Gastrointestinal stromal tumors may occur anywhere along the entire length of the tubal gut, as well as in extravisceral locations, which include the omentum, mesentery, pelvis, and retroperitoneum. Typically, they arise from the wall of the gut and extend inward toward the mucosa, outward toward the serosa, or in both directions. Lesions that involve the wall of the gastrointestinal (GI) tract frequently cause ulceration of the overlying mucosa. Infrequently, lesions invade through the muscularis mucosae to involve the mucosae. Mucosal invasion is an adverse prognostic factor in numerous studies. Because the anatomic location along the GI tract affects prognosis, with location in the stomach having a more favorable prognosis, it is very important to specify anatomic location as precisely as possible.

B. Histologic Grade
Histologic grading, an important component of soft tissue sarcoma staging, is not well suited to GISTs, because most of these tumors have low or relatively low mitotic rates below the thresholds used for grading of soft tissue tumors, and because GISTs often manifest aggressive features with mitotic rates below the thresholds used for soft tissue tumor grading (the lowest tier of mitotic rates for soft tissue sarcomas being 10 mitoses per 10 HPF). In GIST staging, the grade is determined entirely by mitotic activity.

GX: Grade cannot be assessed
G1: Low grade; mitotic rate <5/50 HPF
G2: High grade; mitotic rate >5/50 HPF

Note: The required total count of mitoses is per 5 mm$^2$ on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm$^2$. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm$^2$. If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm$^2$.

C. Risk Assessment
Because GISTs can recur many years after initial excision, we now regard most GISTs as having at least some potential for distant metastasis. This concept was originally the result of a National Cancer Institute-sponsored consensus conference that was held in 2002. More specific data generated by large follow-up studies refined the biologic potential assessment. Criteria obtained from those data were adopted in a National Cancer Care Network (NCCN) Task Force report on GIST. We have adopted the criteria for risk stratification, as indicated in the Table. The scheme includes anatomic site as a factor, because small bowel GISTs carry a higher risk of progression than gastric GISTs of similar size and mitotic activity. For anatomic sites not listed in this table, such as esophagus, mesentery, and peritoneum, or in the case of “insufficient data,” it is best to use risk criteria for jejunum/ileum.
### Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Diseasea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastric</td>
</tr>
<tr>
<td>Mitotic Rate</td>
<td></td>
</tr>
<tr>
<td>≤5 per 50 high-power fields (HPF)</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>&gt;2 - ≤5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
<td>&gt;5 - ≤10 cm</td>
<td>Low (3.6%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td>&gt;5 per 50 HPF</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None**</td>
</tr>
<tr>
<td>&gt;2 - ≤5 cm</td>
<td>Moderate (16%)</td>
</tr>
<tr>
<td>&gt;5 - ≤10 cm</td>
<td>High (55%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

a Defined as metastasis or tumor-related death.

** Denotes small number of cases.

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs from the pre-imatinib era.4-6,8

Note: The required total count of mitoses is per 5 mm² on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm². Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm². If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm².

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### D. Metastasis

Gastrointestinal stromal tumors generally metastasize to a very limited subset of anatomic sites.1 They rarely metastasize to lymph nodes, which is important to note because lymphadenectomy is unnecessary except in rare circumstances when an enlarged or otherwise suspicious lymph node is encountered. Gastrointestinal stromal tumors metastasize predominantly to the liver or to the peritoneal surfaces, where there can be disseminated intra-abdominal disease presenting as innumerable metastatic nodules. Very rarely, GISTs metastasize to the lungs. This situation is associated with rectal location or very advanced disease.5 Metastasis to bone has also been documented, but it is very rare.

### E. Ancillary Studies

Immunohistochemistry

Because of the advent of small-molecule kinase inhibitor therapy in the treatment of GIST (see the following), it has become imperative to distinguish GIST from its histologic mimics, mainly leiomyoma, leiomyosarcoma, schwannoma, and desmoid fibromatosis.10,11 Immunohistochemistry is instrumental in the workup of GIST. Approximately 95% of GISTs are immunoreactive for KIT (CD117).12 Most KIT-negative GISTs are gastric or extra-visceral GISTs that are positive for the platelet-derived growth factor receptor A (PDGFRα) mutation.13 KIT immunoreactivity is usually strong and diffuse but can be more focal in unusual cases (Figure 1, A and B). It is not unusual for GISTs to exhibit dot-like perinuclear staining (Figure 1, C), while less commonly, some cases exhibit membranous staining (Figure 1, D). These patterns do not clearly correlate with mutation type or response to therapy. Approximately 70% of GISTs are positive for
CD34, 30% to 40% are positive for smooth muscle actin, 5% are positive for S100 (usually focal), 5% are positive for desmin (usually focal), and 1% to 2% are positive for keratin (weak/focal).\(^1\)

**Figure 1.** Patterns of KIT staining in gastrointestinal stromal tumor (GIST). A, Diffuse and strong immunoreactivity in a typical GIST. B, Focal and weak pattern in an epithelioid gastric GIST with a PDGFRA mutation. C, Dot-like perinuclear staining. D, Membranous pattern. (Original magnification X400.)

**Molecular Analysis**
Approximately 85% of GISTs possess activating mutations in the KIT gene, whereas another 10% have activating mutations in the PDGFRA gene.\(^{14-17}\) These mutations result in virtually full-length KIT proteins that exhibit ligand-independent activation. KIT and PDGFRA each contain 21 exons. However, mutations cluster within “hotspots”: exons 9, 11, 13, and 17 in KIT, and exons 12, 14, and 18 in PDGFRA (Figure 2). About 5% to 10% of GISTs appear to be negative for both KIT and PDGFRA mutations. The most recent NCCN Task Force on GIST strongly encourages that KIT and PDGFRA mutational analysis be performed if imatinib therapy is begun for unresectable or metastatic disease and that mutational analysis be considered for patients with primary disease, particularly those with high-risk tumors. KIT and PDGFRA mutation status can be determined easily from paraffin-embedded tissue. Secondary or acquired mutations can be associated with development of tumor resistance in the setting of long-term imatinib mesylate treatment. These are usually point mutations that occur most commonly in KIT exons 13, 14 and 17.\(^{18}\) The clinical utility of these mutations is an evolving concept, but it is important not to confuse them with the primary or initial mutation in GIST.
Figure 2. Locations and frequency of activating KIT and PDGFRA mutations in GIST. Adapted with permission from Heinrich et al. Copyright 2003 by the American Society of Clinical Oncology. All rights reserved.

KIT and PDGFRA are excellent targets for small-molecule tyrosine kinase inhibitors, and two compounds of this class, imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland) and sunitinib malate (Sutent, Pfizer Pharmaceuticals, New York, New York), have shown efficacy in clinical trials and have been approved by the US Food and Drug Administration for the treatment of GIST. Because different treatments may have more efficacy in genetic subsets of GIST, the molecular era of GIST analysis has arrived, and oncologists may want to know the mutation status of each GIST, because this may impact which drug each patient should receive. Secondary resistance mutations may also affect drug selection as their significance is further defined.

F. Treatment Effect
Gastrointestinal stromal tumors respond well to the newer targeted systemic therapies, imatinib mesylate and sunitinib malate. The types of treatment effects that have been seen are hypocellularity, myxoid stroma, fibrosis, and necrosis. Nests of viable tumor cells are virtually always seen. Because all of these histologic features can be seen in untreated GISTs, it is not possible to know whether they are due to treatment or not. As a practical compromise, we think it is best to report the percentage of viable tumor after treatment.

G. TNM and Stage Groupings
The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) GIST staging system is recommended.

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.
The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

**T Category Considerations**

In the case of ruptured tumors, estimates of tumor size can be obtained from radiologic data, if available.

**N Category Considerations**

Nodal metastasis is extremely rare in GIST, and there is no routine indication for lymph node biopsy or lymph node dissection. In the absence of information on regional lymph node status, N0/pN0 is appropriate; NX should not be used.

**M Category Considerations**

Most GISTs metastasize to intra-abdominal soft tissues, liver, or both. Intra-abdominal metastasis refers to tumor involvement in the abdominal cavity away from the primary mass. Such metastasis is usually to the serosal surfaces of the abdomen, pelvis, and retroperitoneum. Multiple primary tumors can be seen in the setting of neurofibromatosis type 1 or familial GIST syndrome and should not be considered intra-abdominal metastasis. Rare cases of multiple independent GISTs at different GI locations have been reported. In the absence of a primary gastrointestinal GIST, solitary omental, mesenteric, pelvic, or retroperitoneal GISTs should be considered primary tumors because extra-gastrointestinal GISTs have been described. Liver metastasis implies the presence of metastatic tumor inside the liver parenchyma as 1 or more nodules. Adherence to liver capsule, even if extensive, as sometimes seen in gastric GISTs, should not be considered liver metastasis.

**Staging Grouping: Gastric GISTs**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Mitotic Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1 or T2</td>
<td>N0</td>
<td>M0#</td>
<td>Low</td>
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<tr>
<td>IB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Low</td>
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<td>II</td>
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<td>N0</td>
<td>M0</td>
<td>High</td>
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<td>Low</td>
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<td>N1</td>
<td>M0</td>
<td>Any rate</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any rate</td>
</tr>
</tbody>
</table>

# M0 denotes no distant metastasis.
Stage Grouping: Small Intestinal GISTs

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1 or T2</th>
<th>N0</th>
<th>M0</th>
<th>Mitotic Rate</th>
</tr>
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<tr>
<td>Stage I</td>
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<td>Stage II</td>
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<td>N0</td>
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<td>Stage IIIA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>High</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>Low</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2</td>
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</tr>
<tr>
<td>Stage IIIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>High</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
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<td>Stage IV</td>
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</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any rate</td>
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References