

# Protocol for the Examination of Specimens from Patients with Gastrointestinal Stromal Tumor (GIST)

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Based on AJCC/UICC TNM, 7<sup>th</sup> edition

Protocol web posting date: October 8, 2010

## Procedures

- Biopsy
- Resection

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## **CAP GIST Protocol Revision History**

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### **Version Code**

The definition of the version code can be found at [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).

**Version:** GIST 3.0.1.0

### **Summary of Changes**

#### **Biopsy and Resection Checklists**

##### **Mitotic Rate**

and

##### **Explanatory Notes**

##### **Note B. Histologic Grade**

##### **Note C. Risk Assessment, Table 1**

The following note was added:

Note: The required total count of mitoses is per 5 mm<sup>2</sup> on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm<sup>2</sup>. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm<sup>2</sup>. 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<sup>2</sup>.

**Surgical Pathology Cancer Case Summary (Checklist)**

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**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 mm<sup>2</sup> on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm<sup>2</sup>. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm<sup>2</sup>. 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<sup>2</sup>.

**\*Necrosis**

- \* \_\_\_ Not identified  
 \* \_\_\_ Present  
     \*Extent: \_\_\_ %  
 \* \_\_\_ Cannot be determined

\* Data elements with asterisks 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  $\leq 5/50$  HPF  
 G2: High grade; mitotic rate  $> 5/50$  HPF

**Risk Assessment (Note C)**

- None  
 Very low risk  
 Low risk  
 Intermediate risk  
 High risk  
 Overtly 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)**

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**Surgical Pathology Cancer Case Summary (Checklist)**

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Protocol web posting date: October 8, 2010

**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 mm<sup>2</sup> on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm<sup>2</sup>. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm<sup>2</sup>. 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<sup>2</sup>.

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**\*Necrosis**

- \* \_\_\_ Not identified
- \* \_\_\_ Present
  - \*Extent: \_\_\_%
- \* \_\_\_ Cannot be determined

**Histologic Grade (Note B)**

- \_\_\_ GX: Grade cannot be assessed
- \_\_\_ G1: Low grade; mitotic rate  $\leq 5/50$  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: \_\_\_ 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)

- \_\_\_ 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: \_\_\_\_\_

\* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**\*Additional Pathologic Findings**

\*Specify: \_\_\_\_\_

**Ancillary Studies (select all that apply) (Note E)**Immunohistochemical Studies KIT (CD117) Positive Negative Others (specify): \_\_\_\_\_ Not performedMolecular 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 with asterisks 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.<sup>1-3</sup> 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.<sup>4</sup>

### 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  $\leq 5/50$  HPF  
G2: High grade; mitotic rate  $>5/50$  HPF

Note: The required total count of mitoses is per 5 mm<sup>2</sup> on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm<sup>2</sup>. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm<sup>2</sup>. 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<sup>2</sup>.

### 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.<sup>1</sup> More specific data generated by large follow-up studies refined the biologic potential assessment.<sup>4-8</sup> Criteria obtained from those data were adopted in a National Cancer Care Network (NCCN) Task Force report on GIST.<sup>9</sup> We have adopted the criteria for risk stratification, as indicated in the Table.<sup>4-8</sup> 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, 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)**

Tumor Parameters		Risk of Progressive Disease <sup>#</sup> (%)			
Mitotic Index	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5 per 50 high-power fields (HPF)	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 50 HPF	≤2 cm	None <sup>##</sup>	(Insufficient data)	High <sup>##</sup>	High (54%)
	>2 - ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

<sup>#</sup> Defined as metastasis or tumor-related death.

<sup>##</sup> 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.<sup>4-6,8</sup>

Note: The required total count of mitoses is per 5 mm<sup>2</sup> on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm<sup>2</sup>. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm<sup>2</sup>. 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<sup>2</sup>.

Adapted with permission from Miettinen and Lasota.<sup>7</sup> Copyright 2006 by Elsevier.

#### D. Metastasis

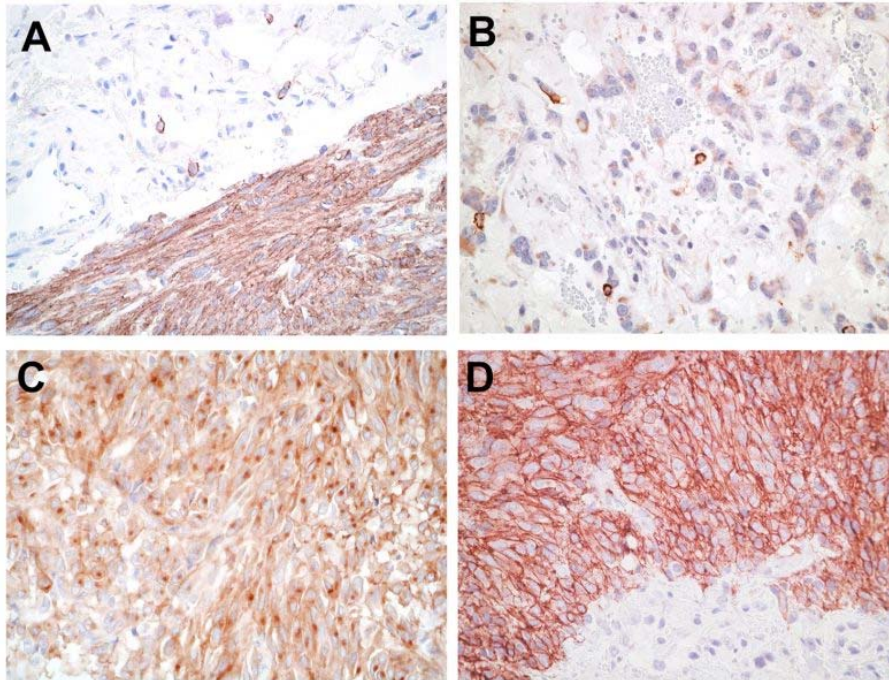
Gastrointestinal stromal tumors generally metastasize to a very limited subset of anatomic sites.<sup>1</sup> They rarely metastasize to lymph nodes, which is important to note because lymphadenectomy is unnecessary except in rare circumstances when an enlarged or otherwise suspicious lymph node is encountered. 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.<sup>5</sup> 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.<sup>10,11</sup> Immunohistochemistry is instrumental in the workup of GIST. Approximately 95% of GISTs are immunoreactive for KIT (CD117).<sup>12</sup> Most KIT-negative

GISTs are gastric or extra-visceral GISTs that are positive for the *platelet-derived growth factor receptor A (PDGFRA)* mutation.<sup>13</sup> 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).<sup>1</sup>

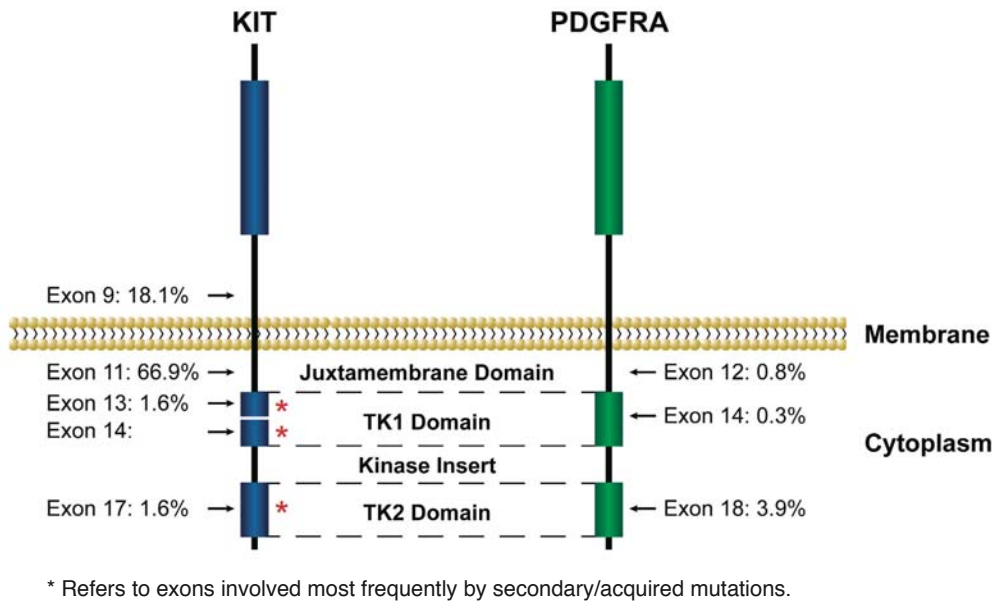


**Figure 1.** Patterns of KIT staining in gastrointestinal stromal tumor (GIST). A, Diffuse and strong immunoreactivity in a typical GIST. B, Focal and weak pattern in an epithelioid gastric GIST with a *PDGFRA* mutation. C, Dot-like perinuclear staining. D, Membranous pattern. (Original magnification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

### Molecular Analysis

Approximately 85% of GISTs possess activating mutations in the *KIT* gene, whereas another 10% have activating mutations in the *PDGFRA* gene.<sup>14-17</sup> 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.<sup>18</sup> 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.<sup>14</sup> 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.<sup>9,19,20</sup> 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.<sup>14,21</sup> 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.<sup>22</sup>

**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**

				<u>Mitotic Rate</u>
Stage IA	T1 or T2	N0	M0 <sup>#</sup>	Low
Stage IB	T3	N0	M0	Low
Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate

Any T      Any N      M1      Any rate

# M0 denotes no distant metastasis.

### Stage Grouping: Small Intestinal GISTs

				<u>Mitotic Rate</u>
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

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