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

Version: 4.3.0.0
Protocol Posting Date: December 2022
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Biopsy	
Tumor Type	**Description**
Gastrointestinal stromal tumor	

The following should NOT be reported using this protocol:

Procedure
Resection
Cytologic specimens

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Accreditation Requirements
The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 4.3.0.0

- Added Associated Syndrome under Clinical
- Reformatted Tumor Site
- Added BRAF to Special Studies
- Updated Note D Table 1 correction of Gastric moderate rate changed from 10% to 12%

Reporting Template

Protocol Posting Date: December 2022

Select a single response unless otherwise indicated.

CASE SUMMARY: (GASTROINTESTINAL STROMAL TUMOR (GIST): Biopsy)

Standard(s): AJCC-UICC 8

This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

CLINICAL

+Associated Syndrome

___ Carney triad
___ Carney-Stratakis syndrome
___ Neurofibromatosis type1
___ Familial GIST syndrome
___ Other (specify): _____
___ Not specified

+Prebiopsy Treatment (select all that apply)

___ No known prebiopsy therapy
___ Systemic therapy performed (specify type): _____
___ Therapy performed, type not specified
___ Not specified

SPECIMEN

Procedure

___ Core needle biopsy
___ Endoscopic biopsy
___ Fine needle aspiration biopsy
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (Note A)

___ Esophagus (specify location): _____
___ Gastroesophageal junction: _____
___ Stomach (specify location): _____
___ Small intestine
  ___ Duodenum
  ___ Jejunum
  ___ Ileum (excluding ileocecal valve)
  ___ Meckel diverticulum (site of neoplasm)
  ___ Small intestine, NOS
___ Appendix: _____
___ Ileocecal valve: _____

___ Large intestine
  ___ Cecum
  ___ Ascending colon
  ___ Hepatic flexure of colon
  ___ Transverse colon
  ___ Splenic flexure of colon
  ___ Descending colon
  ___ Sigmoid colon
  ___ Rectosigmoid junction: _____
  ___ Rectum: _____
  ___ Large intestine, NOS
___ Retroperitoneum: _____
___ Peritoneum / abdomen (specify site): _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Not specified

Histologic Type
___ Gastrointestinal stromal tumor, spindle cell type
___ Gastrointestinal stromal tumor, epithelioid type
___ Gastrointestinal stromal tumor, mixed
___ Gastrointestinal stromal tumor, other (specify): _____
  +Histologic Type Comment: _____

Tumor Size (based on clinicoradiologic estimate)
___ Greatest dimension in Centimeters (cm): _____ cm
  +Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Mitotic Rate (Note B)
The mitotic rate should be determined in 5 mm2 of tumor. With the use of older model microscopes, 50 HPF is equivalent to 5 mm2. Most modern microscopes with wider fields require approximately 20 to 25 HPF to encompass 5 mm2. If necessary, please measure a field of view to accurately determine actual number of fields required to be counted on individual microscopes to encompass 5 mm2.
___ Specify mitotic rate per 5 mm2: _____ mitoses per 5 mm2
___ Other (specify): _____
___ Cannot be determined (explain): _____

Histologic Grade (Note B)
___ G1, low grade (mitotic rate less than or equal to 5 per 5 mm2)
___ G2, high grade (mitotic rate greater than 5 per 5 mm2)
___ Other (specify): _____
___ GX, cannot be assessed: _____

+Necrosis
___ Not identified
___ Present

+Extent of Necrosis
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined: _____

Treatment Effect (Note C)
___ No known prebiopsy therapy
___ Not identified
___ Present
+Percentage of Viable Tumor
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined: _____

Risk Assessment (Note D)
___ None
___ Very low risk
___ Low risk
___ Moderate risk
___ High risk
___ Overtly metastatic
___ Cannot be determined: _____

+Tumor Comment: _____

ADDITIONAL FINDINGS

+Additional Findings (specify): _____

SPECIAL STUDIES (Note E)
The CAP GIST Biomarker Template can be used for reporting biomarkers.

+Immunohistochemical Studies (select all that apply)
___ Not performed
___ KIT (CD117)
KIT (CD117)
___ Positive
___ Negative
___ Pending
___ DOG1 (ANO1)
DOG1 (ANO1)
___ Positive
___ Negative
___ Pending
___ SDHA

SDHA
___ Intact
___ Deficient
___ Pending
___ SDHB
SDHB
___ Intact
___ Deficient
___ Pending
___ BRAF
BRAF
___ Positive
___ Negative
___ Pending
___ Other (specify): _____

+Molecular Genetic Studies (eg., KIT, PDGFRA, SDHA / B / C / D, RAS or NF1 mutational analysis or BRAF or FGFR1 fusion gene analysis)
___ Performed, see biomarker report: _____
___ Performed (specify method(s) and result(s)): _____
___ Pending
___ Not performed

COMMENTS

Comment(s): _____

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.[1,2,3,4,5,6] 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 mucosa 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.[5,6]

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B. Histologic Grade

Histologic grading in GIST, unlike in soft tissue sarcoma, only takes mitotic rate into account. GIST is generally less proliferative than many other soft tissue tumors and the threshold for separating low from high-grade tumors occurs at 5 mitotic figures per 5 mm^2.[1,2,3]

GX: Grade cannot be assessed
G1: Low grade; mitotic rate ≤5/5 mm^2
G2: High grade; mitotic rate >5/5 mm^2

The mitotic count should be initiated in an area that on screening magnification reveals the highest level of mitotic activity and be performed as consecutive high-power fields (HPF). Stringent criteria should be applied when counting mitotic figures; pyknotic or apoptotic nuclei should not be regarded as mitosis.

Note: Mitoses should be counted in 5 mm^2 of tumor.[2,3] With the use of older model microscopes, 50 HPF is equivalent to 5 mm^2. Most modern microscopes with wider fields require approximately 20 to 25 HPF to

encompass 5 mm^2. If necessary, please measure a field of view to accurately determine actual number of fields required to be counted on individual microscopes to encompass 5 mm^2.

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C. 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 observed. Because all of these histologic features can be demonstrated in untreated GIST, it is not possible to know whether these changes are due to treatment or not. As a practical compromise, it is best to report the percentage of viable tumor after treatment.

D. Risk Assessment

Biopsies are suboptimally positioned for GIST risk stratification as these may not include sufficient tumor (i.e., 5 mm^2) for mitotic counting and may not sample mitotic “hot spots”. Furthermore, the risk for metastasis or tumor related death presumes that the GIST has been removed. On biopsy, one may attempt to risk stratify a GIST, using location, available material for mitotic count, and clinicoradiologic size into account.

Biopsies are more predictive if overtly high mitotic count/high grade/high risk on biopsy, based on mitoses and clinicoradiologic size yet low mitotic count/low grade on biopsy may underestimate actual mitoses on resection and not be accurate due to sampling. Most GIST is now regarded 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.[1] More specific data generated by large follow-up studies refined the biologic potential assessment.[2,3,4,5,6,7] Criteria obtained from those data were adopted in a National Cancer Care Network (NCCN) Task Force report on GIST.[8] We have adopted the criteria for risk stratification, as indicated in Table 1.[2,3,4,5,6,7] The scheme includes anatomic site as a factor because small bowel GIST carries a higher risk of progression than gastric GIST of similar size and mitotic activity. This prognostic assessment applies best to *KIT/PDGFRA* mutant GIST whereas SDH-deficient GIST is more unpredictable.[9] 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)

Tumor Parameters		**Risk of Progressive Disease[#](%)**			
Mitotic Rate	***Size***	***Gastric***	***Duodenum***	***Jejunum/Ileum***	***Rectum***
≤5 per 5 mm²	≤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 (12%)	High (34%)	High (52%)	High (57%)
>5 per 5 mm²	≤2 cm	None	(Insufficient data##)	High	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%)

Adapted with permission from Miettinen and Lasota.[5] Copyright 2006 by Elsevier.

 # 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 GIST from the pre-imatinib era.[2,3,4,6]

Note: See Note B, "Histologic Grade," regarding the number of high-power fields to evaluate

References

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E. Ancillary Studies

Immunohistochemistry

Because small-molecule kinase inhibitor therapy is highly effective in the treatment of GIST, it has become imperative to distinguish GIST from its histologic mimics, mainly leiomyoma, leiomyosarcoma, schwannoma, and desmoid fibromatosis.[1,2] Immunohistochemistry is instrumental in the workup of GIST. For the initial work up of GIST, a basic immunohistochemical panel including CD117 (KIT), DOG1 (Ano1), Desmin, S100 protein, and CD34 is recommended. GIST is immunoreactive for KIT (CD117) (approximately 95%) and/or DOG1(>99%).[3,4,5] 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 GIST 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. Most KIT-negative/DOG1-positive GIST is gastric or extra-visceral GIST and almost invariably harbor a platelet-derived growth factor receptor A (*PDGFRA*) mutation.[6] DOG1 expression is not related to mutational status in GIST, and it may be a useful marker to identify a subset of patients with CD117-negative GIST, who might benefit from targeted therapy.[4,5] Approximately 70% of GIST is positive for CD34, 30% to 40% are positive for smooth muscle actin, 5% are positive for S100 protein (usually focal), 5% are positive for desmin (usually focal), and 1% to 2% are positive for keratin (weak/focal).[7]

Note: PanTrk immunohistochemistry may be positive in GIST, a tumor typically negative for *NTRK* fusion and this immunostain is not recommended.

Since succinate dehydrogenase (SDH)-deficient GIST may be familial, have specific implications (see the following), it is recommended that all gastric GIST be screened for loss of SDH by immunohistochemistry, best accomplished by immunostaining for SDHB, which is lost independent of the SDH-subunit that is inactivated.[8,9,10,11] Mutations in SDHA are detected in 30% of SDH-deficient GIST and loss of expression of SDHA specifically identifies tumors with SDHA mutations; other SDH-deficient GIST show normal (intact) cytoplasmic staining for SDHA.[12,13] Patients with SDH-deficient GIST should be referred to a genetic counselor for appropriate workup.

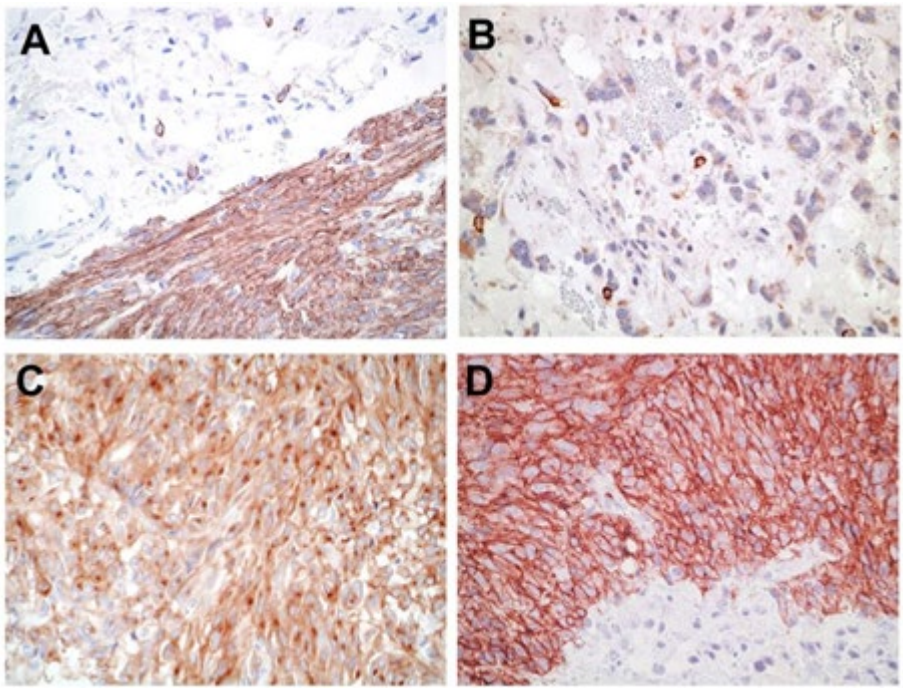

Figure 1. Patterns of KIT staining in gastrointestinal stromal tumor (GIST). A. Diffuse and strong immunoreactivity in a typical GIST. B. Focal and weak pattern in an epithelioid gastric GIST with a *PDGFRA* mutation. C. Dot-like perinuclear staining. D. Membranous pattern. (Original magnification X400)

Molecular Analysis

Approximately 75% of GIST possess activating mutations in the *KIT* gene, whereas another 10% have activating mutations in the *PDGFRA* gene.[14,15,16,17] 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 GIST 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 tyrosine kinase inhibitors (TKIs) are considered as part of the treatment plan 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.

Recent studies focusing on the molecular classification of GIST recognized two major subgroups: succinate dehydrogenase (SHD)-competent and SDH-deficient GIST, both of which can arise in the sporadic or familial setting.[8,9] SDH-competent GIST include tumors with mutations of *KIT* and *PDGFRA* as well of a subset of wild-type GIST with mutations mainly in *NF1* and *BRAF* genes or rarely fusion gene events involving *FGFR1* or *BRAF*.[19,20,21,22,23,24] On the other hand, SDH-deficient GIST includes tumors with a genetic alteration in any of the SDH subunits leading to SDH dysfunction.

SDH-deficient GIST represent approximately 8% of GIST; although, these may arise sporadically. The majority of pediatric GIST, arise in Carney triad and Carney-Stratakis syndrome and are SDH-deficient. SDH is a mitochondrial enzyme comprising four subunits (SDHA, SDHB, SDHC and SDHD) that is involved in the Krebs cycle. Genetic alteration of any of the four subunits results in SDH dysfunction and subsequent loss of SDHB expression by immunohistochemistry. SDH deficient GIST arise almost exclusively in the stomach, affect predominantly female patients and tend to manifest at a young age. Pathologic features associated with SDH-deficient tumors include multinodular and/or plexiform growth pattern, epithelioid morphology, lymphovascular invasion, nodal involvement and frequent metastasis to the liver and peritoneum. Importantly, germline mutations in the genes coding for any of the SDH subunits can also lead to paraganglioma/pheochromocytoma, SDH-deficient renal cell carcinoma and pituitary tumors in addition to GIST. It is recommended that all gastric GIST be screened for loss of SDHB by immunohistochemistry. All patients with SDH-deficient GIST identified by loss of SDHB immunostain should be referred to a genetic counselor.

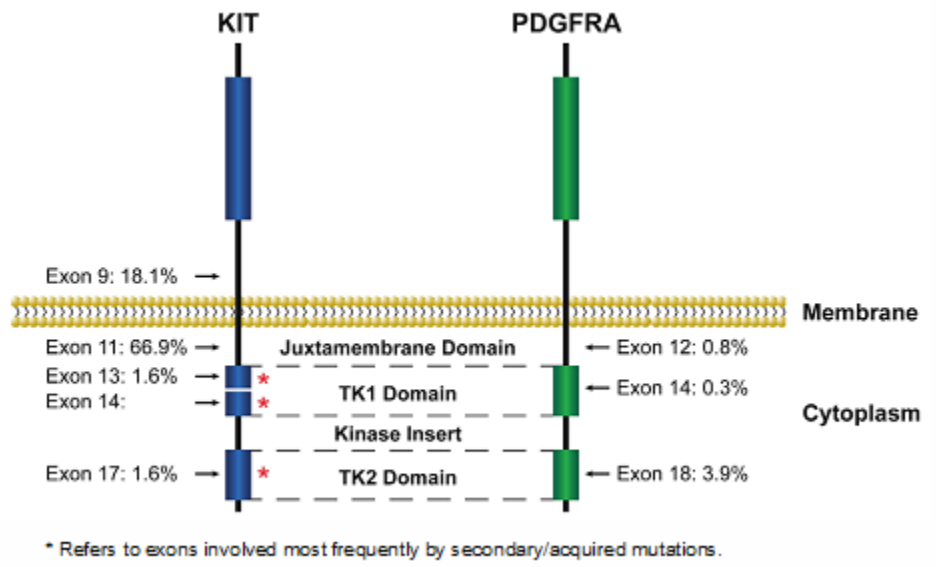

Figure 2. Locations and frequency of activating *KIT* and *PDGFRA* mutations in GIST. Adapted with permission from Heinrich et al.[14] Copyright 2003 by the American Society of Clinical Oncology. All rights reserved.

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), avapritinib (Ayvakit, PDGFRA D842V (exon 18) mutant, may be resistant to standard therapy), regornfenib (3rd line), ripretinib (4th line, Qinlock) have shown efficacy in clinical trials and have been approved by the US Food and Drug Administration for the treatment of GIST.[25,26,27,28] SDH-deficient GIST are usually resistant to imatinib but may have a higher probability of response to sunitinib.[8,29] Because different tyrosine kinase inhibitors (TKIs) may have differential efficacy depending on the type of mutation present in GIST, oncologists may want to know the mutation status of each GIST[30], because this may influence which drug the patient receives.[14] Secondary resistance mutations may also affect drug selection as their significance is further defined.

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