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

Version: 4.3.0.0
Protocol Posting Date: December 2022
CAP Laboratory Accreditation Program Protocol Required Use Date: September 2023

The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures and tumor types:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td></td>
</tr>
<tr>
<td>Tumor Type</td>
<td>Description</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td></td>
</tr>
</tbody>
</table>

This protocol is NOT required for accreditation purposes for the following:

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>Local excision</td>
</tr>
<tr>
<td>Primary resection specimen with no residual tumor (eg, following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

Authors
Julie C. Fanburg-Smith, MD, FCAP*; Andrew M. Bellizzi, MD*; Julia A. Bridge, MD, FCAP*; Paari Murugan, MD, FCAP*; Javier A. Laurini, MD; Markku Miettinen, MD.
With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.
Accreditation Requirements
This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- **Core data elements** are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- **Conditional data elements** are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- **Optional data elements** are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
  - Anatomic site or specimen, laterality, and procedure
  - Pathologic Stage Classification (pTNM) elements
  - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.
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%
- Updated pTNM Classification
Reporting Template
Protocol Posting Date: December 2022
Select a single response unless otherwise indicated.

CASE SUMMARY: (GASTROINTESTINAL STROMAL TUMOR (GIST): Resection)
Standard(s): AJCC-UICC 8

CLINICAL

+Associated Syndrome
___ Carney triad
___ Carney-Stratakis syndrome
___ Neurofibromatosis type 1
___ Familial GIST syndrome
___ Other (specify): _________________
___ Not specified

+Preresection Treatment (select all that apply)
___ No known preresection therapy
___ Previous biopsy or surgery (specify): _________________
___ Systemic therapy performed (specify type): _________________
___ Therapy performed, type not specified
___ Not specified

SPECIMEN

Procedure
___ Local excision
___ Resection (specify type, eg., partial gastrectomy): _________________
___ Metastasectomy
___ Other (specify): _________________
___ Not specified

TUMOR

Tumor Focality
___ Unifocal
___ Multifocal

Number of Tumors
___ Specify number: _________________
___ Other (specify): _________________
___ Cannot be determined: _________________

Sizes of Tumors: _________________
___ Cannot be determined: _________________

Multiple Primary Sites (eg., stomach and small intestine)
___ Not applicable (no additional primary site(s) present)
Please complete a separate checklist for each primary site

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 presurgical 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 malignant / metastatic
___ Cannot be determined: _________________

+Tumor Comment: _________________
MARGINS

Margin Status
___ All margins negative for GIST

Closest Margin(s) to GIST (select all that apply)
___ Proximal: __________________
___ Distal: __________________
___ Omental (radial): ___________
___ Mucosal: __________________
___ Deep: ___________________
___ Other (specify): ___________
___ Cannot be determined: _______

Distance from GIST to Closest Margin
Specify in Centimeters (cm)
___ Exact distance in cm: __________ cm
___ Greater than 1 cm

Specify in Millimeters (mm)
___ Exact distance in mm: __________ mm
___ Greater than 10 mm

Other
___ Other (specify): ______________
___ Cannot be determined: ___________
___ GIST present at margin

Margin(s) Involved by GIST (select all that apply)
___ Proximal: _________________
___ Distal: _________________
___ Omental (radial): _________________
___ Mucosal: _________________
___ Deep: _________________
___ Other (specify): _________________
___ Cannot be determined: _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________
___ Not applicable

+Margin Comment: _________________

REGIONAL LYMPH NODES (Note E)

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)

Number of Lymph Nodes with Tumor
___ Exact number (specify): __________
___ At least (specify): __________
___ Other (specify): __________
Number of Lymph Nodes Examined
___ Exact number (specify): __________________
___ At least (specify): __________________
___ Other (specify): __________________
___ Cannot be determined (explain): __________________

Regional Lymph Node Comment: __________________

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Liver: __________________
___ Other (specify): __________________
___ Cannot be determined

pTNM CLASSIFICATION (AJCC 8th Edition) (Note F)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of 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

T Suffix (required only if applicable)
___ Not applicable
___ (m) Multiple primary synchronous tumors in a single organ

pN Category (Notes E,F)
# When no lymph nodes are present (as is often the case with resection for GIST), the pathologic 'N' category is not assigned (pNX is not used for GIST) and should not be reported.
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
pM Category (required only if confirmed pathologically) (Notes E,F)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

ADDITIONAL FINDINGS

+Additional Findings (specify): _________________

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

+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 extravesical locations, which include the omentum, mesentery, pelvis, and retroperitoneum. Typically, these tumors 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 mucosa. 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.

References

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 mm².

GX: Grade cannot be assessed
G1: Low grade; mitotic rate ≤5/5 mm²
G2: High grade; mitotic rate >5/5 mm²

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 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 an actual number of fields required to be counted on individual microscopes to encompass 5 mm².

References


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 seen. Because all of these histologic features can be seen in untreated GIST, it is not possible to know whether they 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 mm²) for mitotic counting and may not sample mitotic “hot spots”. Furthermore, the risk for metastasis or tumor 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. Because GIST can recur many years after initial excision, 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. 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 Table 1. 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 are more unpredictable. 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 Disease* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitotic Rate</strong></td>
<td><strong>Size</strong></td>
</tr>
<tr>
<td>≤5 per 5 mm²</td>
<td>≤2 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;2 - ≤5 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;5 - ≤10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
</tr>
<tr>
<td>&gt;5 per 5 mm²</td>
<td>≤2 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;2 - ≤5 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;5 - ≤10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
</tr>
</tbody>
</table>

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

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

* Defined as metastasis or tumor-related death

## Denotes small number of cases

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

References


E. Regional Lymph Nodes, Metastasis
Gastrointestinal stromal tumors generally metastasize to a very limited subset of anatomic sites. These tumors 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, GIST metastasize to the lungs. This situation is associated with rectal location or very advanced disease. Metastasis to bone has also been documented, but it is very rare.

References

F. Pathologic Stage Classification
The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) GIST staging system is recommended. The staging system should not be applied to pediatric GIST, familial GIST (germline mutant *KIT* or *PDGFRA*) or syndromic GIST (GIST arising in the setting of neurofibromatosis type 1, Carney triad, or Carney dyad also known as Carney-Stratakis syndrome).

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 (i.e., 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 (i.e., 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
Regional nodal metastasis is extremely rare in GIST, and there is no routine indication for lymph node biopsy or lymph node dissection. When no lymph nodes are resected or present in the specimen (as is often the case with resections for GIST), the pathologic ‘N’ category is not assigned; pNX should not be used.

M Category Considerations
Most GIST metastasizes 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 GIST at different GI locations have been reported. In the absence of a primary gastrointestinal GIST, solitary omental, mesenteric, pelvic, or retroperitoneal GIST should be considered primary tumors because extra-gastrointestinal GIST has been described. Liver metastasis implies the presence of metastatic tumor inside the liver parenchyma as one or more nodules. Adherence to liver capsule, even if extensive, as sometimes seen in gastric GIST, should not be considered liver metastasis.

Stage Groupings:
Although T, N, and M definitions are identical for all GIST, separate stage grouping schemes are provided for gastric and small intestinal tumors. Primary omental GIST should follow the gastric GIST staging group scheme. GIST arising in other locations (i.e., mesentery, esophagus, colon, and rectum) are to follow the small intestinal group staging scheme.

References

G. 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. Immunohistochemistry is instrumental in the work up of GIST. For the initial workup 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%). 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. 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. Approximately 70% of GIST are 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).
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, has 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 in all independent of the SDH-subunit that is inactivated.\textsuperscript{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.\textsuperscript{12,13} Patients with SDH-deficient GIST should be referred to a genetic counselor for appropriate work up.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure_1}
\caption{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)}
\end{figure}

\textbf{Molecular Analysis}

Approximately 75% of GIST possess activating mutations in the \textit{KIT} gene, whereas another 10% have activating mutations in the \textit{PDGFRA} gene.\textsuperscript{14,15,16,17} These mutations result in virtually full-length \textit{KIT} proteins that exhibit ligand-independent activation. \textit{KIT} and \textit{PDGFRA} each contain 21 exons. However, mutations cluster within “hotspots”: exons 9, 11, 13, and 17 in \textit{KIT}, and exons 12, 14, and 18 in \textit{PDGFRA} (Figure 2). About 5\% to 10\% of GIST appear to be negative for both \textit{KIT} and \textit{PDGFRA} mutations. The most recent NCCN Task Force on GIST strongly encourages that \textit{KIT} and \textit{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. \textit{KIT} and \textit{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 \textit{KIT} exons 13, 14, and 17.\textsuperscript{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 (SDH)-competent and SDH-deficient GIST, both of which can arise in the sporadic or familial setting. SDH-competent GIST include tumors with mutations of \textit{KIT} and \textit{PDGFRA} as well as a subset of wild-type GIST with mutations mainly in \textit{NF1} and \textit{BRAF} genes or rarely fusion gene events involving \textit{FGFR1} or \textit{BRAF}. 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 represents 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 are 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 arises almost exclusive in the stomach, affects predominantly female patients, and tends 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 lead to paragangliomas/pheochromocytomas, 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 \textit{KIT} and \textit{PDGFRA} mutations in GIST. Adapted with permission from Heinrich et al. Copyright 2003 by the American Society of Clinical Oncology. All rights reserved.

\textit{KIT} and \textit{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. SDH-deficient GIST is usually resistant to imatinib but may have a higher probability of response to sunitinib. 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, because this may influence which drug the patient receives. Secondary resistance mutations may also affect drug selection as their significance is further defined.

References


