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

Version: GIST Resection 4.1.0.0  Protocol Posting Date: August 2019

CAP Laboratory Accreditation Program Protocol Required Use Date: May 2020

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

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>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td></td>
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</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 cancer (eg, following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

Authors

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

* Denotes primary author. All other contributing authors are listed alphabetically.
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
Version 4.1.0.0
The following data elements were modified:
Ancillary Testing - included SDHB and SDHA
Surgical Pathology Cancer Case Summary

Protocol posting date: August 2019

GASTROINTESTINAL STROMAL TUMOR (GIST): Resection

Note: This case summary is recommended for reporting local excision specimens, but is not required for accreditation purposes.

Select a single response unless otherwise indicated.

Procedure
___ Local excision
___ Resection
   Specify type (eg, partial gastrectomy): ________________________________
___ Metastasectomy
___ Other (specify): ____________________________
___ Not specified

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

Tumor Size
Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ x ___ cm
___ Cannot be determined (explain): _______________________________

Tumor Focality
___ Unifocal
___ Multifocal
   Specify number of tumors: _____
   Specify size of tumors: ____________________________

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

Mitotic Rate
Specify: ___ /5 mm²
___ Cannot be determined (explain): _______________________________

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 approximately 20 to 25 HPF to encompass 5 mm². If necessary, please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to encompass 5 mm².

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

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
Histologic Grade (Note B)
___ G1: Low grade; mitotic rate \( \leq 5/5 \text{ mm}^2 \)
___ G2: High grade; mitotic rate \( >5/5 \text{ mm}^2 \)
___ GX: Grade cannot be assessed

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

Margins
___ Cannot be assessed
___ Uninvolved by GIST
    Distance of tumor from closest margin (millimeters or centimeters): ___ mm or ___ cm
    Specify margin (if known): ______________________
___ Involved by GIST
    Specify margin(s) (if known): ______________________

Regional Lymph Nodes (Note D)
___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in specimen)

Number of Lymph Nodes Involved: _____
___ Number cannot be determined (explain): ______________________

Number of Lymph Nodes Examined: _____
___ Number cannot be determined (explain): ______________________

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note E)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

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 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

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
Regional Lymph Nodes (pN) (Note D) (required only if lymph nodes submitted in this case)*

- **pN0**: No regional lymph node metastasis
- **pN1**: Regional lymph node metastasis

*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.

Distant Metastasis (pM) (Note D) (required only if confirmed pathologically in this case)

- **pM1**: Distant metastasis
  
  Specify site(s), if known: __________________________

+ Additional Pathologic Findings
  
  + Specify: ____________________________

Ancillary Studies (Note F)

*Note: For molecular genetic and further immunohistochemical study reporting, the CAP GIST Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.*

**Immunohistochemical Studies**

- **KIT (CD117)**
  
  - Positive
  
  - Negative

- **DOG1 (ANO1)**
  
  - Positive
  
  - Negative

- **SDHB**
  
  - Intact
  
  - Deficient

- **SDHA**
  
  - Intact
  
  - Deficient

- **Other (specify): ____________________________**

  + Pending

  + Not performed

  + **Molecular Genetic Studies (eg, KIT, PDGFRA, BRAF, SDHA/B/C/D, or NF1 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 known preresection therapy

    + Previous biopsy or surgery (specify): ____________________________

    + Systemic therapy performed (specify type): ____________________________

    + Therapy performed, type not specified

    + Not specified

**Treatment Effect (Note G)**

- **No known presurgical therapy**

- Not identified

- **Present**

  + Specify percentage of viable tumor: ____%

  + Cannot be determined

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
CAP Approved

Other • GI Stromal Tumor (GIST) 4.1.0.0
Resection

+ Comment(s)

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional 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 extravesical 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.

References

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 ≤5/5 mm²
G2: High grade; mitotic rate >5/5 mm²

The mitotic count should be initiated on an area that on screening magnification shows 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, dyskaryotic or apoptotic nuclei should not be regarded as mitosis.

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 approximately 20 to 25 HPF to encompass 5 mm². If necessary, please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to encompass 5 mm².

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 Table 1. 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 Disease# (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastric</td>
</tr>
<tr>
<td><strong>Mitotic Rate</strong></td>
<td></td>
</tr>
<tr>
<td>≤5 per 5 mm²</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 5 mm²</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>

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Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs from the pre-imatinib era.2-4,6

# 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

D. Regional Lymph Nodes, 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.2 Metastasis to bone has also been documented, but it is very rare.

References

E. 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 (GISTs 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 (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
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 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 one or more nodules. Adherence to liver capsule, even if extensive, as sometimes seen in gastric GISTs, should not be considered liver metastasis.

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

References
F. 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.\(^1\) 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. GISTs are immunoreactive for KIT (CD117) (approximately 95%) and/or DOG1 (>99%).\(^3\),\(^5\) 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 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. Most KIT-negative / DOG1 positive GISTs are gastric or extra-visceral GISTs and almost invariably harbor a *platelet-derived growth factor receptor A (PDGFRA)* mutation.\(^5\) DOG1 expression is not related to mutational status in GISTs, and it may be a useful marker to identify a subset of patients with CD117-negative GISTs, who might benefit from targeted therapy.\(^4\),\(^5\) Approximately 70% of GISTs 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).\(^7\)

Since succinate dehydrogenase (SDH)-deficient GISTs have specific implications (see the following), it is recommended to screen all gastric GISTs for loss of SDH by immunohistochemistry, usually best accomplished by staining for SDHB, which is loss in all subtypes of SDH-deficient GISTs.\(^8\) -\(^11\) Mutations in SDHA are detected in 30% of SDH-deficient GISTs and loss of expression of SDHA specifically identifies tumors with SDHA mutations; other SDH-deficient GISTs show normal (intact) cytoplasmic staining for SDHA.\(^12\),\(^13\) Patients with SDH-deficient GIST should be referred to a genetic counselor for appropriate work up.

![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.)](image)

**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 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 GISTs recognized two major subgroups: succinate dehydrogenase (SHD)-competent and SDH-deficient GISTs, both of which can arise in the sporadic or familiar setting.8,9 SDH-competent GISTs include tumors with mutations of KIT and PDGFRA as well of a subset of wild-type GISTs with mutations mainly in NF1 and BRAF genes. On the other hand, SDH-deficient GISTs include tumors with a genetic alteration in any of the SDH subunits leading to SDH dysfunction.

SDH-deficient GISTs represent approximately 8% of GISTs and comprise some sporadic cases, the majority of pediatric GISTs, and two forms of syndromic GISTs (Carney triad and Carney-Stratakis syndrome). 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 GISTs arise almost exclusive 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 SHD subunits can lead to paragangliomas/pheochromocytomas, SDH-deficient renal cell carcinoma and pituitary tumors in addition to GISTs. Since SDH-deficient GISTs typically require germline genetic testing possibly including family members as well as possible surveillance for paragangliomas/pheochromocytomas, it is recommended that all gastric GISTs be screened for loss of SDHB by immunohistochemistry. All patients with SDH-deficient GISTs identified by loss of SDHB stain 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), have shown efficacy in clinical trials and have been approved by the US Food and Drug Administration for the treatment of GIST.\textsuperscript{19-21} SDH-deficient GISTs are usually resistant to imatinib but may have a higher probability of response to sunitinib.\textsuperscript{8} Because different tyrosine kinase inhibitors (TKIs) may have more efficacy in genetic subsets of GIST, oncologists may want to know the mutation status of each GIST, because this may impact which drug each patient should receive.\textsuperscript{14,22} Secondary resistance mutations may also affect drug selection as their significance is further defined.

References


G. Treatment Effect
Gastrointestinal stromal tumors respond well to the newer targeted systemic therapies, imatinib mesylate and sunitib 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.