Protocol for the Examination of Specimens from Patients with Well-Differentiated Neuroendocrine Tumors (Carcinoid Tumors) of the Jejunum and Ileum

Version: 2.0.0.0
Protocol Posting Date: December 2023
CAP Laboratory Accreditation Program Protocol Required Use Date: September 2024

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>Includes specimens designated segmental resection – small intestine and ileocolicectomy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated tumor of the jejunum and ileum</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>Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Recurrent tumor</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

The following tumor types should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated tumor of the duodenum and ampulla (consider the Duodenum and Ampulla Carcinoma protocol)</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine carcinoma including small cell and large cell neuroendocrine carcinoma (consider the Small Intestine protocol)</td>
</tr>
<tr>
<td>Other epithelial carcinomas including mixed neuroendocrine-non-neuroendocrine neoplasms (consider the Small Intestine protocol)</td>
</tr>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (GIST) (consider the GIST protocol)</td>
</tr>
<tr>
<td>Non-GIST sarcoma (consider the Soft Tissue protocol)</td>
</tr>
</tbody>
</table>

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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 (i.e., 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 2.0.0.0

- Update to AJCC Version 9 pTNM Staging Classifications
- WHO 5th Edition update to content and explanatory notes
- "Lymphovascular Invasion" question updated to "Lymphatic and / or Vascular Invasion"
CASE SUMMARY: (JEJUNUM AND ILEUM NEUROENDOCRINE TUMOR)
Standard(s): AJCC-UICC 9

SPECIMEN

Procedure
___ Segmental resection, small intestine
___ Ileocolic resection
___ Other (specify): ____________________
___ Not specified

TUMOR

Tumor Site (Notes A,B)
___ Jejunum: ____________________
___ Ileum: ____________________
___ Small intestine, not otherwise specified: ____________________
___ Other (specify): ____________________

Histologic Type and Grade# (Notes C,D)
# For poorly differentiated (high-grade) neuroendocrine carcinomas arising in the small intestine or ampulla, the checklists for carcinomas of those organ sites should be used.
___ G1, well-differentiated neuroendocrine tumor
___ G2, well-differentiated neuroendocrine tumor
___ G3, well-differentiated neuroendocrine tumor
___ GX, grade cannot be assessed
___ Other (specify): ____________________
___ Not applicable: ____________________

Histologic Grade Determination (Note D)
Mitotic rate and / or Ki-67 labeling index is required to determine histologic grade. Mitotic Rate (required only when Ki-67 labeling index is not reported)#
# Mitotic rate should be reported as number of mitoses per 2 mm2, by evaluating at least 10 mm2 in the most mitotically active part of the tumor (e.g., if using a microscope with a field diameter of 0.55 mm, count 42 high power fields (10 mm2) and divide the resulting number of mitoses by 5 to determine the number of mitoses per 2 mm2 needed to assign tumor grade).
___ Not applicable (Ki-67 labeling index is reported)
___ Specify number of mitoses per 2 mm2: ________________ mitoses per 2 mm2
___ Less than 2 mitoses per 2 mm2
___ 2 to 20 mitoses per 2 mm2
___ Greater than 20 mitoses per 2 mm2
___ Cannot be determined (explain): ____________________

Ki-67 Labeling Index (required only when mitotic rate is not reported)
___ Not applicable (mitotic rate is reported)
___ Specify Ki-67 percentage: ________________ %
___ Less than 3%
___ 3% to 20%
___ Greater than 20%
___ Cannot be determined (explain): ____________________

**Tumor Size (Note E)**
*Specify size of largest tumor if multiple tumors are present*

___ Greatest dimension in Centimeters (cm): _________________ cm

+**Additional Dimension in Centimeters (cm): ____ x ____ cm**

___ Cannot be determined(84,622),(224,629) (explain): ____________________

**Tumor Focality**
___ Unifocal
___ Multifocal

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

**Tumor Extent**
___ Invades lamina propria
___ Invades submucosa
___ Invades muscularis propria
___ Invades through muscularis propria into subserosal tissue without penetration of overlying serosa
___ Invades visceral peritoneum (serosa)
___ Invades other organ(s) or adjacent structure(s) (specify): ____________________
___ Cannot be determined: ____________________
___ No evidence of primary tumor

**Lymphatic and / or Vascular Invasion**
___ Not identified
___ Present
___ Cannot be determined: ____________________

+**Perineural Invasion**
___ Not identified
___ Present
___ Cannot be determined: ____________________

**Large Mesenteric Masses (greater than 2 cm) (Note G)**
___ Not identified
___ Present

+**Number of Large Mesenteric Masses**
___ Specify number: ____________________
___ Other (specify): ____________________
___ Cannot be determined: ____________________
___ Cannot be determined: ____________________

+Tumor Comment: ____________________

MARGINS (Note F)

Margin Status
___ All margins negative for tumor

+Closest Margin(s) to Tumor (select all that apply)
   ___ Proximal: ____________________
   ___ Distal: ____________________
   ___ Radial: ____________________
   ___ Mesenteric: ____________________
   ___ Other (specify): ____________________
   ___ Cannot be determined: ____________________

+Distance from Tumor 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: ____________________
   ___ Tumor present at margin

Margin(s) Involved by Tumor (select all that apply)
   ___ Proximal: ____________________
   ___ Distal: ____________________
   ___ Radial: ____________________
   ___ Mesenteric: ____________________
   ___ Other (specify): ____________________
   ___ Cannot be determined: ____________________
   ___ Other (specify): ____________________
   ___ Cannot be determined (explain): ____________________
   ___ Not applicable

+Margin Comment: ____________________

REGIONAL LYMPH NODES

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): __________________________
Cannot be determined (explain): __________________
Other (specify): __________________________
Cannot be determined (explain): __________________

**Number of Lymph Nodes Examined**

- Exact number (specify): __________________________
- At least (specify): __________________________
- Other (specify): __________________________
- Number cannot be determined (explain): __________________

Regional Lymph Node Comment: __________________

**DISTANT METASTASIS**

**Distant Site(s) Involved, if applicable (select all that apply)**

- Not applicable
- Liver: __________________________
- Lung: __________________________
- Ovary: __________________________
- Nonregional lymph node(s): __________________________
- Peritoneum: __________________________
- Bone: __________________________
- Other (specify): __________________________
- Cannot be determined: __________________________

**pTNM CLASSIFICATION (AJCC Version 9) (Note G)**

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**

# Multiple tumors should be designated as such (the largest tumor should be used to assign T category). Use T(#) or T(m); e.g., pT3(4) N0 M0, OR use the m suffix, T(m); e.g., pT3(m) N0 M0.

- pT not assigned (cannot be determined based on available pathological information)
- pT0: No evidence of primary tumor
- pT1: Tumor invades mucosa or submucosa, and is less than or equal to 1 cm in greatest dimension
- pT2: Tumor invades muscularis propria or greater than 1 cm in greatest dimension
- pT3: Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
- pT4: Tumor invades the visceral peritoneum (serosal) or other organs or adjacent structures
T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No tumor involvement of regional lymph node(s)
___ pN1: Tumor involvement of less than 12 regional lymph nodes

# Mesenteric masses less than or equal to 2 cm should be stated in the pathology report as being present and collected by registrars but do not affect the stage.
___ pN2: Tumor involvement of large mesenteric masses (greater than 2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels#

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)

pM1: Microscopic confirmation of distant metastasis
___ pM1a: Microscopic confirmation of metastasis confined to liver
___ pM1b: Microscopic confirmation of metastasis in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
___ pM1c: Microscopic confirmation of both hepatic and extrahepatic metastases
___ pM1 (subcategory cannot be determined)

ADDITIONAL FINDINGS (Note H)

+Additional Findings (select all that apply)
___ None identified
___ Tumor necrosis
___ Mesenteric tumor deposit(s) less than or equal to 2 cm
___ Intestinal ischemia / necrosis
___ Mesenteric vascular elastosis
___ Other (specify): _______________________

COMMENTS

Comment(s): ______________________
Explanatory Notes

A. Application and Tumor Location
This protocol applies to well-differentiated neuroendocrine tumors (carcinoid tumors) of the jejunum and ileum.

This protocol can be used for tumors involving overlapping sites in the small intestine or when the site is unclear. For tumors of the duodenum and ampulla use separate protocol created for these sites. Poorly differentiated neuroendocrine carcinomas (small cell carcinomas and large cell neuroendocrine carcinomas) and tumors with mixed glandular/neuroendocrine differentiation are not included.\(^1\) Neuroendocrine tumors of the duodenum and ampulla of Vater use a separate CAP cancer protocol\(^2\).

Because of site-specific similarities in histology, immunohistochemistry, and histochemistry, neuroendocrine tumors of the digestive tract have traditionally been subdivided into those of foregut, midgut, and hindgut origin (Table 1). In general, the distribution pattern along the gastrointestinal (GI) tract parallels that of the progenitor cell type, and the anatomic site of origin of GI neuroendocrine tumors is an important predictor of clinical behavior.\(^3\)

<table>
<thead>
<tr>
<th>Immunochemical Marker</th>
<th>Foregut Tumors</th>
<th>Midgut Tumors</th>
<th>Hindgut Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromogranin A</td>
<td>86%-100% +</td>
<td>82%-92% +</td>
<td>40%-58% +</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>50% +</td>
<td>95%-100% +</td>
<td>94%-100% +</td>
</tr>
<tr>
<td>Serotonin</td>
<td>33% +</td>
<td>86% +(^4)</td>
<td>45%-83% + (\text{&amp;}4,5,6,7,8)</td>
</tr>
<tr>
<td>Other Immunohistochemical Markers</td>
<td>Rarely, + for pancreatic polypeptide, histamine, gastrin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)</td>
<td>Prostatic acid phosphatase + in 20%-40%(^9,10)</td>
<td>Prostatic acid phosphatase + in 20%-82%(^4,5,6,7,8,9,10)</td>
</tr>
<tr>
<td>Carcinoid Syndrome</td>
<td>Rare</td>
<td>5%-39%(^11,12)</td>
<td>Rare</td>
</tr>
</tbody>
</table>

References


B. Site-Specific Features
The small intestine is the most common primary site for neuroendocrine tumors.1,2,3 Most small intestine neuroendocrine tumors occur in the distal ileum. Multiple tumors are found in 25% to 40% of cases and may be associated with a worse outcome.4 Primary jejunal and ileal tumors are often small and asymptomatic. However, extensive fibrosis can form when they invade deep soft tissue (e.g., mesenteric soft tissue), causing small bowel obstruction and small bowel ischemia due to encasement of the superior mesenteric vessels. In addition, about 50% of patients with jeunoileal neuroendocrine tumor have liver metastasis as the initial presentation, and patients with liver metastasis can have carcinoid syndrome (e.g., flushing, diarrhea, and wheezing). Metastatic risk is increased by tumor size >2 cm, involvement of the muscularis propria, and mitotic activity.5,6

References

C. Histologic Type
The World Health Organization (WHO) classifies neuroendocrine neoplasms as well-differentiated neuroendocrine tumors (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas. Historically, well-differentiated neuroendocrine tumors have been referred to as “carcinoid tumors,” a term which may cause confusion because clinically a carcinoid tumor is a serotonin-producing tumor associated with functional manifestations of carcinoid syndrome. The use of the term “carcinoid” for neuroendocrine tumor reporting is therefore discouraged for these reasons.

Classification of neuroendocrine tumors is based upon size, functionality, site, and invasion. Functioning tumors are those associated with clinical manifestations of hormone production or secretion of measurable amounts of active hormone; immunohistochemical demonstration of hormone production is not equivalent to clinically apparent functionality.

Immunohistochemistry and other ancillary techniques are generally not required to diagnose well-differentiated neuroendocrine tumors. Specific markers that may be used to establish neuroendocrine differentiation include chromogranin A, synaptophysin, INSM1 and CD56. Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended, although INSIM1 is also emerging as a good marker for endocrine differentiation.

References

D. Histologic Grade
Cytologic atypia in well-differentiated neuroendocrine tumors has no impact on clinical behavior of these tumors.

The WHO classification and others use mitotic rate and/or Ki-67 index as one of the criteria for potential for aggressive behavior. Mitotic rate should be reported as number of mitoses per 2 mm², by evaluating at least 10 mm² in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Because of variations in field size, the number of high-power field (HPF) (at 40X magnification) for 10 mm² (thereby 2 mm²) must be determined for each microscope (Table 2). For example, if using a microscope with a field diameter of 0.55 mm, count 42 HPF and divide the resulting number of mitoses by 5 to determine the number of mitoses per 2 mm² needed to assign tumor grade.
Table 2. Number of HPF Required for 10 mm² Using Microscopes With Different Field Diameter

<table>
<thead>
<tr>
<th>Field Diameter (mm)</th>
<th>Area (mm²)</th>
<th>Number of HPF for 10 mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>0.125</td>
<td>80</td>
</tr>
<tr>
<td>0.41</td>
<td>0.132</td>
<td>75</td>
</tr>
<tr>
<td>0.42</td>
<td>0.139</td>
<td>70</td>
</tr>
<tr>
<td>0.43</td>
<td>0.145</td>
<td>69</td>
</tr>
<tr>
<td>0.44</td>
<td>0.152</td>
<td>65</td>
</tr>
<tr>
<td>0.45</td>
<td>0.159</td>
<td>63</td>
</tr>
<tr>
<td>0.46</td>
<td>0.166</td>
<td>60</td>
</tr>
<tr>
<td>0.47</td>
<td>0.173</td>
<td>58</td>
</tr>
<tr>
<td>0.48</td>
<td>0.181</td>
<td>55</td>
</tr>
<tr>
<td>0.49</td>
<td>0.189</td>
<td>53</td>
</tr>
<tr>
<td>0.50</td>
<td>0.196</td>
<td>50</td>
</tr>
<tr>
<td>0.51</td>
<td>0.204</td>
<td>49</td>
</tr>
<tr>
<td>0.52</td>
<td>0.212</td>
<td>47</td>
</tr>
<tr>
<td>0.53</td>
<td>0.221</td>
<td>45</td>
</tr>
<tr>
<td>0.54</td>
<td>0.229</td>
<td>44</td>
</tr>
<tr>
<td>0.55</td>
<td>0.238</td>
<td>42</td>
</tr>
<tr>
<td>0.56</td>
<td>0.246</td>
<td>41</td>
</tr>
<tr>
<td>0.57</td>
<td>0.255</td>
<td>39</td>
</tr>
<tr>
<td>0.58</td>
<td>0.264</td>
<td>38</td>
</tr>
<tr>
<td>0.59</td>
<td>0.273</td>
<td>37</td>
</tr>
<tr>
<td>0.60</td>
<td>0.283</td>
<td>35</td>
</tr>
<tr>
<td>0.61</td>
<td>0.292</td>
<td>34</td>
</tr>
<tr>
<td>0.62</td>
<td>0.302</td>
<td>33</td>
</tr>
<tr>
<td>0.63</td>
<td>0.312</td>
<td>32</td>
</tr>
<tr>
<td>0.64</td>
<td>0.322</td>
<td>31</td>
</tr>
<tr>
<td>0.65</td>
<td>0.332</td>
<td>30</td>
</tr>
<tr>
<td>0.66</td>
<td>0.342</td>
<td>29</td>
</tr>
<tr>
<td>0.67</td>
<td>0.353</td>
<td>28</td>
</tr>
<tr>
<td>0.68</td>
<td>0.363</td>
<td>28</td>
</tr>
<tr>
<td>0.69</td>
<td>0.374</td>
<td>28</td>
</tr>
</tbody>
</table>

Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling (“hot spot”), although the precise method of assessment has not been standardized. A number of methods have used to assess Ki-67 index, including automatic counting and “eyeballing.” Automated counting is not widely available and requires careful modification of the software to circumvent the inaccuracies. Eye-balling can be used for most tumors; however, for tumors with Ki-67 index close to grade cut-offs, it is recommended to perform the manual count on the print of camera-captured image of the hot spot. It has been recommended that a minimum of 500 tumor cells be counted to determine the Ki-67 index, and a notation is made if less cells are available. Grade assigned based on Ki-67 index is typically higher than that based on mitotic count, and the case is assigned to the higher of the 2 if both methods are performed.

It is important to note that there are a small group of well-differentiated neuroendocrine tumors with a Ki-67 index >20% and a mitotic rate usually <20 per 10 HPF. In WHO-2010, these tumors were considered as G3 poorly differentiated neuroendocrine carcinomas. However, they have typical morphology of well-differentiated tumors.
Previous studies (most on pancreatic neuroendocrine tumors) have demonstrated that these tumors have a worse prognosis than grade 2 (Ki-67=3-20% and mitosis <20/10 HPF) neuroendocrine tumors, but they are not as aggressive as poorly differentiated neuroendocrine carcinomas. In addition, these tumors do not have the genetic abnormalities seen in poorly differentiated neuroendocrine carcinomas. Furthermore, unlike poorly differentiated neuroendocrine carcinomas, they are less responsive to platinum-based chemotherapy. In the WHO-2019 blue book of digestive system tumor and AJCC Version 9, those with typical morphology of well-differentiated tumors are classified as “well differentiated neuroendocrine tumor” but as grade 3 (Table 3) and increasingly recognized, even in small intestine.

Table 3. Recommended Grading System for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Rate (per 2mm²)</th>
<th>Ki-67 Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated neuroendocrine tumor, G1</td>
<td>&lt;2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Well-differentiated neuroendocrine tumor, G2</td>
<td>2 to 20</td>
<td>3 to 20</td>
</tr>
<tr>
<td>Well-differentiated neuroendocrine tumor, G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

References

8. AJCC Version 9 Neuroendocrine Tumors of the Jejunum and Ileum Cancer Staging System. Copyright 2023 American College of Surgeons.

E. Tumor Size

For neuroendocrine tumors in any part of the gastrointestinal tract, size greater than 2.0 cm is associated with a higher risk of lymph node metastasis. For jejunoleal tumors, nodal metastases occur in about 12% of patients with tumors smaller than 1.0 cm and in most patients with tumors larger than 1.0 cm. Thus, treatment for small intestine neuroendocrine tumor includes complete resection with regional lymphadenectomy.
References

F. Circumferential (Radial or Mesenteric) Margin
In addition to addressing the proximal and distal margins, assessment of the circumferential (radial) margin is necessary for any segment of gastrointestinal tract either unencased (Figure, C) or incompletely encased by peritoneum (Figure, B). The circumferential margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect, respectively. The distance between the tumor and circumferential (radial) margin should be reported, if applicable. The circumferential (radial) margin is considered positive if the tumor is present at the inked nonperitonealized surface. This assessment includes tumor within a lymph node as well as direct tumor extension, but if circumferential (radial) margin positivity is based solely on intranodal tumor, this should be so stated.

The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum (e.g., jejunum and ileum) (Figure, A). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface.

A: Mesenteric margin in viscus completely encased by peritoneum (dotted line). B: Circumferential (radial) margin (dotted line) in viscus incompletely encased by peritoneum. C: Circumferential (radial) margin (dotted line) in viscus completely unencased by peritoneum.

G. pTNM Classification
The TNM staging system for neuroendocrine tumors of the jejunum and ileum of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.1

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary
tumor has been completely removed. If a biopsied tumor is not resected for any reason (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**TNM Descriptors**
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” 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 following 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 prior to 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.

The “a” prefix designates the stage determined at autopsy: aTNM.

**N Category Considerations**
For ileal and jejunal tumors, the regional lymph nodes are the cecal (for tumors arising in the terminal ileum), superior mesenteric, and mesenteric nodes. Metastases to celiac nodes are considered distant metastases.

Mesenteric masses are defined as discrete but irregular mesenteric tumor nodules frequently located adjacent to neurovascular bundles and discontinuous from the primary neoplasm. Mesenteric masses result from extranodal extension or vascular/perineural spread of the tumor and are often associated with dense fibrosis, causing ecasement of large mesenteric vessels. The presence of mesenteric masses and nodal deposits in 12 or more nodes has been associated with frequent liver metastasis and a poor prognosis.

**M Category Considerations**
The liver is the most common metastatic site. Metastases to extrahepatic sites, such as lung, ovary, peritoneum, and bone, are rare. Involvement of the celiac, para-aortic, and other nonregional lymph nodes is also considered M1 disease. In the AJCC Version 9, M is subcategorized into M1a (hepatic only), M1b (extrahepatic only), and M1c (both hepatic and extrahepatic).

**References**
1. AJCC Version 9 Neuroendocrine Tumors of the Jejunum and Ileum Cancer Staging System. Copyright 2023 American College of Surgeons.


H. Additional Findings
Mesenteric fibrosis is seen in about 50% of small intestinal neuroendocrine tumors and leads to intestinal obstruction, intestinal ischemia, malabsorption, and malnutrition. Mesenteric vascular changes (elastic vascular sclerosis) associated with midgut carcinoids may produce arterial luminal narrowing due to concentric accumulation of elastic tissue in the adventitia. These vascular changes may lead to intestinal ischemia and frank necrosis. While mesenteric fibrosis in stage IV tumors by itself does not significantly impact the overall, presence of mesenteric fibrosis along with vascular changes is indicative of an aggressive tumor biology and when leads to intestinal ischemia is associated with poor prognosis.

References
2. AJCC Version 9 Neuroendocrine Tumors of the Jejunum and Ileum Cancer Staging System. Copyright 2023 American College of Surgeons.