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

Version: 5.0.0.0
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 as low anterior resection and abdominoperineal resection, total, partial, or segmental resection</td>
</tr>
</tbody>
</table>

Tumor Type Description

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated neuroendocrine tumor</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>Excision biopsy (transanal disk excision or polypectomy)</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>Poorly-differentiated neuroendocrine carcinoma including small cell and large cell neuroendocrine carcinoma (consider the Colon and Rectum Carcinoma protocol)</td>
</tr>
<tr>
<td>Other epithelial carcinoma of the colon and rectum including mixed neuroendocrine-non-neuroendocrine neoplasm (consider the Colon and Rectum Carcinoma protocol)</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (consider the GIST protocol)</td>
</tr>
<tr>
<td>Non-GIST sarcoma (consider the Soft Tissue protocol)</td>
</tr>
</tbody>
</table>

Authors
Dhanpat Jain, MD*; William V. Chopp, MD*; Rondell P. Graham, MBBS*.
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 5.0.0.0
- 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: (COLON AND RECTUM NEUROENDOCRINE TUMOR)

Standard(s): AJCC-UICC 9

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

SPECIMEN (Note A)

Procedure
___ Right hemicolectomy
___ Transverse colectomy
___ Left hemicolectomy
___ Sigmoidectomy
___ Low anterior resection
___ Total abdominal colectomy
___ Abdominoperineal resection
___ Transanal disk excision / Endoscopic mucosal resection (local excision)
___ Endoscopic mucosal dissection (local excision)
___ Polypectomy
___ Other (specify): _________________
___ Not specified

TUMOR

Tumor Site (Note B) (select all that apply)
___ Cecum: _________________
___ Right (ascending) colon: _________________
___ Hepatic flexure: _________________
___ Transverse colon: _________________
___ Splenic flexure: _________________
___ Left (descending) colon: _________________
___ Sigmoid colon: _________________
___ Rectosigmoid junction: _________________
___ Rectum: _________________
___ Ileocecal valve: _________________
___ Colon, not otherwise specified: _________________
___ Cannot be determined (explain): _________________

Histologic Type and Grade# (Notes C,D)
# For poorly differentiated neuroendocrine carcinomas, the College of American Pathologists (CAP) checklist for carcinoma of the colon and rectum 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 Type and Grade Comment: ____________________

**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)**

___ Greatest dimension in Centimeters (cm) (specify size of largest tumor if multiple tumors are present): ____________________ cm

+Additional Dimension in Centimeters (cm): _____ x _____ cm
___ Cannot be determined (explain): ____________________

**Tumor Focality**

___ Unifocal
___ Multifocal

**Number of Tumors**

___ Specify number: ____________________
___ Other (specify): ____________________
___ Cannot be determined: ____________________
___ Cannot be determined: ____________________

**Multiple Primary Sites (e.g., hepatic flexure and transverse colon)**

___ Not applicable (no additional primary site(s) present)
___ Present: ____________________

*Please complete a separate checklist for each primary site*

**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 (Note F)**
___ Not identified
___ Present
___ Cannot be determined: _____________________

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

**+Tumor Comment: _____________________**

**MARGINS (Note G)**

**Margin Status**
___ All margins negative for tumor
___ Closest Margin(s) to Tumor (select all that apply)
   ___ Proximal: _____________________
   ___ Distal: _____________________
   ___ Radial: _____________________
   ___ Mesenteric: _____________________
   ___ Mucosal: _____________________
   ___ Deep: _____________________
   ___ 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: _____________________
___ Mucosal: _____________________
Deep: _________________
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): _________________
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 H)
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(#); 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 the mucosa or submucosa, and is less than or equal to 2 cm in greatest dimension
   ___ pT1a: Tumor is less than or equal to 1 cm in greatest dimension
   ___ pT1b: Tumor is greater than 1 cm but less than or equal to 2 cm in greatest dimension
   ___ pT1 (subcategory cannot be determined)
___ pT2: Tumor invades the muscularis propria, or is greater than 2 cm in greatest dimension with invasion of the mucosa or submucosa
___ pT3: Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
___ pT4: Tumor invades the visceral peritoneum (serosa), 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 regional lymph node(s)

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 I)

+Additional Findings (select all that apply)
___ None identified
___ Tumor necrosis
___ Other (specify): ______________________
COMMENTS

Comment(s): _________________
Explanatory Notes

A. Application and Tumor Location
This protocol applies to well-differentiated neuroendocrine tumors (carcinoid tumors) of the colon and rectum. Poorly differentiated neuroendocrine carcinomas (including small cell carcinomas and large cell neuroendocrine carcinomas) and tumors with mixed glandular/neuroendocrine differentiation are not included.1

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.2

Table 1. Site of Origin of Gastrointestinal Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Site</th>
<th>Foregut Tumors</th>
<th>Midgut Tumors</th>
<th>Hindgut Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Stomach, Proximal Duodenum</td>
<td>Jejunum, ileum, Appendix, Proximal Colon</td>
<td>Distal Colon, Rectum</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<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% +</td>
<td>45%-83% +</td>
</tr>
<tr>
<td>Other Immunohistochemical</td>
<td>Rarely, + for pancreatic polypeptide, histamine, gastrin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)</td>
<td>Prostatic acid phosphatase + in 20%-40% 6,10</td>
<td>Prostatic acid phosphatase + in 20%-82% 3,4,5,6,7,8</td>
</tr>
<tr>
<td>Markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Rare</td>
<td>5%-39% 10,11</td>
<td>Rare</td>
</tr>
</tbody>
</table>

References


B. Site-Specific Features
Rectal neuroendocrine tumors are not uncommon, constitute approximately one-quarter of GI neuroendocrine tumors. They are usually small, solitary, and clinically silent, most commonly occurring 4 cm to 13 cm from the anal verge. Mitotically inactive rectal neuroendocrine tumors or those smaller than 2.0 cm are almost always clinically indolent. Metastases and carcinoid syndrome are very rare. L-cell NETs are usually seen in the rectum. Colonic neuroendocrine tumors outside the ileocecal region and rectum are extremely rare; most are large, bulky, highly invasive tumors that are metastatic at presentation. Two-thirds of them arise within the cecum or right colon. Many well-differentiated neuroendocrine tumors involving the ileocecal valve represent tumors arising in the terminal ileum, rather than in the large bowel. Colonic tumors are biologically more aggressive and similar to jejunoileal tumors, while rectal tumors are more indolent.

References


3. AJCC Version 9 Neuroendocrine Tumors of the Colon and Rectum Cancer Staging System. Copyright 2023 American College of Surgeons.

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.

Similar to appendix, colorectal neuroendocrine tumors composed of L-cell have been considered of low malignant potential and represent most (60-80%) of the rectal tumors. Immunohistochemistry for glucagon like peptide 1 or peptide YY that identifies these tumors is not widely available and is not
recommended for routine clinical practice. These tumors can be negative for chromogranin, which is a known diagnostic pitfall and use of other additional endocrine markers is suggested in suspected cases. Studies suggest that L-cell phenotype is associated with lower histologic grade, smaller tumor size, and lower T-stage, as well as absence of LVI, nodal metastasis and distant metastasis.6,7

Although specific histologic patterns in well-differentiated neuroendocrine tumors, such as trabecular, insular, and glandular, roughly correlate with tumor location8 these patterns have not been clearly shown independently to predict response to therapy or risk of nodal metastasis and are rarely reported in clinical practice. 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 CD56.3,9,10 Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended, although INSM1 is also emerging as a good marker for endocrine differentiation. It should be noted that hindgut neuroendocrine tumors often do not express appreciable amounts of chromogranin A. Rectal neuroendocrine tumors express prostatic acid phosphatase, a potential diagnostic pitfall for tumors arising in male patients.11

References
5. AJCC Version 9 Neuroendocrine Tumors of the Colon and Rectum Cancer Staging System. Copyright 2023 American College of Surgeons.

12

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 fields (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 10mm² Using Microscopes with Different Field Diameters

<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”\textsuperscript{3,4} Automated counting is not widely available and requires careful modification of the software to circumvent the inaccuracies.\textsuperscript{3} Eye-ballling 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.\textsuperscript{1}

Similar to other sites, histologic grade remains prognostically important for colorectal tumors. Even in low risk tumors (≤2cm or even ≤1cm) tumor that metastasize are invariably G2 tumors.\textsuperscript{5,6} It is also 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.\textsuperscript{7} In addition, these tumors do not have the genetic abnormalities seen in poorly differentiated neuroendocrine carcinomas.\textsuperscript{8} Furthermore, unlike poorly differentiated neuroendocrine carcinomas, they are less responsive to platinum-based chemotherapy.\textsuperscript{9} In WHO-2019 blue book of digestive system tumors 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 are increasingly being recognized at all sites.\textsuperscript{10,11}

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Rate (per 2mm)</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>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>Well-differentiated neuroendocrine tumor, G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

References


10. AJCC Version 9 Neuroendocrine Tumors of the Colon and Rectum 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. Rectal carcinoids smaller than 1.0 cm are almost always clinically indolent, and local excision is generally considered sufficient for tumors 1.0 cm or smaller, as well as many tumors between 1.0 cm and 2.0 cm. Metastasis in tumors ≤2cm is uncommon, and those that metastasize tend to be histologically higher grade (>G1). More extensive procedures (e.g., right hemicolectomy and abdominoperineal resection) are usually reserved for patients with rectal tumors larger than 2.0 cm, rectal tumors with regional metastasis, and most colonic neuroendocrine tumors.

Determination of size remains of colorectal tumors on resection specimens, including local excision, is performed similar to any other tumor. However, many of the rectal tumors are detected incidentally on biopsies or on digital rectal examination. In such situations, the size and depth of invasion are assessed clinically based on imaging, especially endoscopic ultrasound that has been shown to be highly sensitive for lesions between 0.5-2 cm, and can detect lesions as small as 0.2cm. Staging examinations using imaging (CT or MRI) are typically performed in tumors ≥1cm or higher grade tumors (>G1).

References


2. AJCC Version 9 Neuroendocrine Tumors of the Colon and Rectum Cancer Staging System. Copyright 2023 American College of Surgeons.

F. Lymphatic and/or Vascular Invasion

Lymphovascular invasion (LVI) has been associated recurrence and nodal metastasis. Studies show that LVI correlated with larger tumor size (>0.5cm), but not grade and use of vascular endothelial immunohistochemical markers can enhance their detection. However, the overall risk of recurrence at 5-years is so low that in the absence of any other high-risk features follow-up rather than radical resection has been suggested.
References


G. Surgical Resection Margin

For resection specimens, 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 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., transverse colon) (Figure A). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface.

For local excisions (endoscopic mucosal resections/ transanal disc excisions/ submucosal dissection), reliable assessment is only possible for specimens that are removed without any fragmentation. In such specimens, lateral mucosal and deep margins should be assessed and reported. However, incomplete removal of rectal NETs, especially with conventional EMR, is not infrequent. Positive margins in some studies have been associated with local recurrence and nodal metastasis, although the vast majority of patients with positive margins neither recur nor progress. The overall risk of recurrence or progression in these patients remains very low, and studies show no difference in risk of recurrence or survival in patients with positive margins who underwent salvage local resections versus those who opted for only follow-up.
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.

References

H. pTNM Classification
The TNM staging system for neuroendocrine tumors of the colon and rectum of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended. 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 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
The regional lymph nodes of the colon and rectum are as follows:

**Cecum:** Pericolic, anterior cecal, posterior cecal, ileocolic, right colic  
**Ascending colon:** Pericolic, ileocolic, right colic, middle colic  
**Hepatic flexure:** Pericolic, middle colic, right colic  
**Transverse colon:** Pericolic, middle colic  
**Splenetic flexure:** Pericolic, middle colic, left colic, inferior mesenteric  
**Descending colon:** Pericolic, left colic, inferior mesenteric, sigmoid  
**Sigmoid colon:** Pericolic, inferior mesenteric, superior rectal (hemorrhoidal), sigmoidal, sigmoid mesenteric  
**Rectosigmoid:** Pericolic, perirectal, left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal (hemorrhoidal), middle rectal (hemorrhoidal)  
**Rectum:** Perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory (Gerota’s), internal iliac, superior rectal (hemorrhoidal), middle rectal (hemorrhoidal), inferior rectal (hemorrhoidal)

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

I. Additional Findings
Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior and should be reported.

References