Protocol for the Examination of Specimens From Patients With Neuroendocrine Tumors (Carcinoid Tumors) of the Colon and Rectum

Protocol applies to well-differentiated neuroendocrine tumors of the large bowel and rectum. Carcinomas with mixed endocrine/glandular differentiation, poorly differentiated carcinomas with neuroendocrine features, and small cell carcinomas are not included.

Based on AJCC/UICC TNM, 7th Edition
Protocol web posting date: June 2012

Procedures
• Local Excision (Transanal Disk Excision)
• Colectomy (Total, Partial, or Segmental Resection)
• Rectal Resection

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CAP Colon and Rectum NET Protocol Revision History

**Version Code**
The definition of the version code can be found at www.cap.org/cancerprotocols.

**Version:** ColonRectumNET 3.2.0.0

**Summary of Changes**
The following changes have been made since the February 2011 release.

**Resection, Including Transanal Disk Excision of Rectal Neoplasms**
The word “neoplasm” was replaced with “tumor.”

**Tumor Location**
This element was added as follows:

+ **Tumor Location**
  + ___ Tumor is located above peritoneal reflection
  + ___ Tumor is located below the peritoneal reflection
  + ___ Not specified

**Histologic Type; Alternate Histologic Classification; Histologic Grade**
These three reporting elements were combined into one, and the word “checklist” was changed to “protocol” as follows:

**Histologic Type and Grade**
___ Not applicable
___ Well-differentiated neuroendocrine tumor; GX: Grade cannot be assessed
___ Well-differentiated neuroendocrine tumor; G1: Low grade
___ Well-differentiated neuroendocrine tumor; G2: Intermediate grade
___ Other (specify): _________

* For poorly differentiated (high-grade) neuroendocrine carcinomas (G3), the College of American Pathologists (CAP) protocol for carcinoma of the colon and rectum¹ should be used.

**Ancillary Studies**
Reporting on Ki-67 was updated, as follows:
+ ___ Ki-67 labeling index (specify: _____)
  + ___ ≤2%
  + ___ 3% to 20%
  + ___ >20%

**Explanatory Notes**
The word “neoplasm” was replaced with “tumor.”

**D. Histologic Type**
The first sentence of the first paragraph was changed to read:
The World Health Organization (WHO) classifies neuroendocrine tumors as well-differentiated neuroendocrine tumors (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas.

Third paragraph: deleted “none are classified as benign or low-malignant-potential neuroendocrine tumors.”
Alternative Classification Based Upon WHO Classification: Neuroendocrine Tumors of the Appendix
This section was deleted.

E. Histologic Grade
The word “checklist” was changed to “protocol.”
“Mitotic count” was changed to “mitotic rate.”
Ki-67 Index (%): >2 was changed to 3.

References
Reference #6 was updated.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

COLON AND RECTUM: Resection, Including Transanal Disk Excision of Rectal Tumors (Note A)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Large intestine
   ___ Cecum
   ___ Ascending colon
   ___ Transverse colon
   ___ Descending colon
   ___ Sigmoid colon
___ Rectum
___ Anus
___ Terminal ileum
___ Appendix
___ Other (specify): ___________________________
___ Not specified

Procedure
___ Right hemicolecctiony
___ Transverse colectomy
___ Left hemicolecctiony
___ Sigmoidectomy
___ Rectal/rectosigmoid colon (low anterior resection)
___ Total abdominal colectomy
___ Abdominoperineal resection
___ Transanal disk excision (local excision)
___ Other (specify): ___________________________
___ Not specified

+ Specimen Size (applicable to transanal disk excision)
+ Specify: ___ (length) x ___ x ___ cm

Tumor Site (select all that apply) (Note B)
___ Large bowel
   ___ Cecum
   ___ Right (ascending) colon
   ___ Hepatic flexure
   ___ Transverse colon
   ___ Splenic flexure
   ___ Left (descending) colon
   ___ Sigmoid colon
___ Rectum
___ Other (specify): ___________________________
___ Not specified

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
+ Tumor Location
+ __ Tumor is located above peritoneal reflection
+ __ Tumor is located below the peritoneal reflection
+ __ Not specified

Tumor Size (Note C)
Greatest dimension: ___ cm (specify size of largest tumor if multiple tumors are present)
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see “Comment”)

Tumor Focality
___ Unifocal
___ Multifocal (specify number of tumors: ______)
___ Cannot be determined

Histologic Type and Grade (Notes D and E)*
___ Not applicable
___ Well-differentiated neuroendocrine tumor; Gx: Grade cannot be assessed
___ Well-differentiated neuroendocrine tumor; G1: Low grade
___ Well-differentiated neuroendocrine tumor; G2: Intermediate grade
___ Other (specify): ______________________

* For poorly differentiated neuroendocrine carcinomas (G3), the College of American Pathologists (CAP) protocol for carcinoma of the colon and rectum1 should be used.

Mitotic Rate
Specify: ___/10 high-power fields (HPF)
___ Cannot be determined

Microscopic Tumor Extension
___ Cannot be assessed
___ No evidence of primary tumor
___ Tumor invades lamina propria
___ Tumor invades into but not through muscularis mucosae
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the subserosal adipose tissue or the nonperitonealized pericolic or perirectal soft tissues but does not extend to the serosal surface (visceral peritoneum)
___ Tumor penetrates serosa (visceral peritoneum)
___ Tumor directly invades adjacent structures (specify: ________________)
___ Tumor penetrates to the surface of the visceral peritoneum (serosa) and directly invades adjacent structures (specify: ________________)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Margins

If all margins uninvolved by neuroendocrine tumor:
   Distance of tumor from closest margin: ___ mm or ___ cm
   Specify margin: ____________________________

Proximal Margin
   ___ Cannot be assessed
   ___ Uninvolved by neuroendocrine tumor
   ___ Involved by neuroendocrine tumor

Distal Margin
   ___ Cannot be assessed
   ___ Uninvolved by neuroendocrine tumor
   ___ Involved by neuroendocrine tumor

Circumferential (Radial) Margin (Note F)
   ___ Cannot be assessed
   ___ Uninvolved by neuroendocrine tumor
   ___ Involved by neuroendocrine tumor
   ___ Not applicable

Other Margin(s) (required only if applicable)
   Specify margin(s): ____________________________
   ___ Cannot be assessed
   ___ Uninvolved by neuroendocrine tumor
   ___ Involved by neuroendocrine tumor

Lymph-Vascular Invasion
   ___ Not identified
   ___ Present
   ___ Indeterminate

+ Perineural Invasion
   + ___ Not identified
   + ___ Present
   + ___ Indeterminate

Pathologic Staging (pTNM) (Note G)

   TNM Descriptors (required only if applicable) (select all that apply)
   ___ m (multiple primary tumors)
   ___ r (recurrent)
   ___ y (posttreatment)
Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor invades lamina propria or submucosa and size 2 cm or less
___ pT1a: Tumor size less than 1 cm in greatest dimension
___ pT1b: Tumor size 1 to 2 cm in greatest dimension
___ pT2: Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
___ pT3: Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
___ pT4: Tumor invades peritoneum or other organs

Regional Lymph Nodes (pN)
___ Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in regional lymph nodes
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ___
___ Number cannot be determined (explain): ________________

Number of Lymph Nodes Involved
Specify: ___
___ Number cannot be determined (explain): ________________

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
  + Specify site(s), if known: __________________________

+ Ancillary Studies (select all that apply) (Notes E and H)
+ ___ Ki-67 labeling index (specify: ____)
  + ___ ≤2%
  + ___ 3% to 20%
  + ___ >20%
+ ___ Other (specify): __________________________
+ ___ Not performed

+ Additional Pathologic Findings (select all that apply) (Note I)
+ ___ Tumor necrosis
+ ___ Other (specify): __________________________

+ Comment(s)
Explanatory Notes

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

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). 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

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>Neuron-Specific Enolase</td>
<td>90%-100% +</td>
<td>95%-100% +</td>
<td>80%-87% +</td>
</tr>
<tr>
<td>(NSE)</td>
<td>50% +</td>
<td>95%-100% +</td>
<td>94%-100% +</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>33% +</td>
<td>86% +</td>
<td>45%-83% +</td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>Rarely, + for pancreatic polypeptide, histamine, gastrin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)</td>
<td>Prostatic acid phosphatase + in 20%-40%</td>
<td>Prostatic acid phosphatase + in 20%-82%</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Rare</td>
<td>5%-39%⁶,⁷</td>
<td>Rare</td>
</tr>
</tbody>
</table>

B. Site-Specific Features
Rectal neuroendocrine tumors are common and constitute approximately one-quarter of GI neuroendocrine tumors.³ They are usually small, solitary, and clinically silent, most commonly occurring 4 to 13 cm from the anal verge. Mitotically inactive rectal neuroendocrine tumors or those smaller than 2.0 cm are almost always clinically benign.⁴ Metastases and carcinoid syndrome are very rare. Large intestinal neuroendocrine tumors outside the ileocecal region and rectum are extremely rare; most reported tumors have been large (average 5.0 cm) and high grade, with a poor prognosis. Many low-grade neuroendocrine tumors involving the ileocecal valve represent tumors arising in the terminal ileum, rather than in the large bowel.

C. 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 benign, and local excision is generally considered sufficient for tumors 1.0 cm or smaller, as well as many tumors between 1.0 and 2.0 cm. More extensive procedures (e.g., right hemicolectomy and abdominoperineal resection) are usually reserved for patients with tumors larger than 2.0 cm.
D. Histologic Type
The World Health Organization (WHO) classifies neuroendocrine tumors as well-differentiated neuroendocrine tumors (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas.\textsuperscript{5-8} 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.

Classification of neuroendocrine tumors (NETs) 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.

All colonic neuroendocrine tumors are considered potentially malignant. Most are large, bulky, high-grade, highly invasive tumors that are metastatic at presentation. Two-thirds arise within the cecum or right colon.

Rectal neuroendocrine tumors, in contrast to colonic neuroendocrine tumors, are relatively common and generally behave in a benign fashion.

Histologic Patterns
Although specific histologic patterns in well-differentiated neuroendocrine tumors, such as trabecular, insular, and glandular, roughly correlate with tumor location,\textsuperscript{4} 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.

E. Histologic Grade
Cytologic atypia in low-grade neuroendocrine tumors has no impact on clinical behavior of these tumors. However, a grading system based on mitotic activity has been proposed for NETs of the ileum, appendix, colon, and rectum:\textsuperscript{9}

| Grade | Mitotic Rate (per 10 HPF)\# | Ki-67 Index (%)\#
|-------|-----------------------------|-----------------
| G1    | <2                          | <2              |
| G2    | 2 to 20                     | 3 to 20         |
| G3    | >20                         | >20             |

\# Mitotic rate should be based upon counting 50 high-power (40x objective) fields in the area of highest mitotic activity and reported as number of mitoses per 10 HPF.

\#

Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling. It has been recommended that 2000 tumor cells be counted to determine the Ki-67 index\textsuperscript{10}; however, this practice may not be practical for routine clinical purposes, and it is acceptable to estimate the labeling index.

G1 and G2 are well-differentiated tumors with diffuse intense chromogranin/synaptophysin positivity. Punctate necrosis is more typical of G2 tumors. G3 tumors are high-grade neuroendocrine carcinomas (the CAP protocol for carcinomas of the colon and rectum\textsuperscript{1} should be used for poorly differentiated neuroendocrine carcinomas arising in these sites).

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. The circumferential (radial) margin is considered negative if the tumor is more than 1 mm from the inked nonperitonealized surface but should be recorded as positive if the tumor is located 1 mm or less from 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 (eg, transverse colon) (Figure, A). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface.


G. TNM and Anatomic Stage/Prognostic Groupings
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 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 (eg, 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
- Splenic 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)

TNM Anatomic Stage/Prognostic Groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIa</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

* M0 is defined as no distant metastasis.

H. Ancillary Studies
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, neuron-specific enolase, synaptophysin, and CD56. Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended. 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.

Immunohistochemistry for Ki-67 may be useful in establishing tumor grade (Note E) and prognosis but is not currently considered standard of care.
Immunohistochemistry for specific hormone products, such as glucagon, gastrin, and somatostatin, may be of interest in some cases. However, immunohistochemical demonstration of hormone production does not equate with clinical functionality of the tumor.

I. Additional Pathologic Findings
Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior\(^\text{10}\) and should be reported.

References