Protocol for the Examination of Specimens from Patients with Neuroendocrine Tumors (Carcinoid Tumors) of the Appendix

Protocol applies to well-differentiated neuroendocrine tumors of the appendix. Goblet cell carcinoids, poorly differentiated carcinomas with neuroendocrine features, and small cell carcinomas are not included.

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Procedures
• Excision (Appendectomy)
• Appendectomy with Segmental Resection (Right Hemicolectomy)

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: February 2010

APPENDIX: Excision (Appendectomy) or Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Appendix
___ Cecum
___ Right colon
___ Terminal ileum
___ Other (specify): ________________________
___ Not specified

Procedure
___ Appendectomy
*Length: ___ cm
___ Appendectomy and right colectomy
*Length of appendix: ___ cm
*Length of colonic segment: ___ cm
___ Other (specify): ______________________________

Specimen Integrity
___ Intact
___ Fragmented
*Number of pieces in fragmented specimens: ___
___ Other (specify): ______________________________

***Specimen Size (if applicable)**
*Specify: ___ (length) x ___ x ___ cm

Tumor Site
___ Proximal half of appendix
___ Distal half of appendix
___ Diffusely involving appendix
___ Appendix, not otherwise specified
___ Unknown
___ Other (specify): ____________________________

Tumor Size (Note B)
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see “Comment”)

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Histologic Type (Note C)
___ Carcinoid
___ Atypical carcinoid
___ Other (specify): ___________________________

***Alternate Histologic Classification (Note C)**
*___ Well-differentiated endocrine tumor, benign behavior
*___ Well-differentiated endocrine tumor, uncertain behavior
*___ Well-differentiated endocrine carcinoma

***Histologic Grade (Note D)**[#]
*___ Not applicable
*___ GX: Cannot be assessed
*___ G1: Low grade
*___ G2: Intermediate grade
*___ Other (specify): _____________________________

[#] *For poorly differentiated neuroendocrine carcinomas, the College of American Pathologists (CAP) checklist for carcinoma of the appendix*[1] *should be used.*

Mitotic Rate (Note D)
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 submucosa
___ Tumor invades muscularis propria
___ Tumor invades subserosal tissue without involvement of visceral peritoneum
___ Tumor extends into mesoappendix
___ 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: _____________________)

Margins (Note E)

<u>Proximal Margin</u>
___ Cannot be assessed
___ Uninvolved by tumor
___ Involved by tumor

<u>Distal Margin</u> (not applicable for appendectomy specimens)
___ Not applicable
___ Cannot be assessed
___ Uninvolved by tumor
___ Involved by tumor

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Mesenteric (Mesoappendiceal) Margin
___ Cannot be assessed
___ Uninvolved by tumor
Distance of tumor from closest mesenteric margin: ___ mm *or* ___ cm
___ Involved by tumor

*Circumferential (Radial) Margin
*___ Not applicable
*___ Cannot be assessed
*___ Uninvolved by tumor
*___ Involved by tumor (tumor present 0 to 1 mm from margin)

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

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

***Perineural Invasion**
*___ Not identified
*___ Present
*___ Indeterminate

Pathologic Staging (pTNM) (Note F)

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 2 cm or less in greatest dimension
___ pT1a: Tumor 1 cm or less in greatest dimension
___ pT1b: Tumor more than 1 cm but not more than 2 cm
___ pT2: Tumor more than 2 cm but not more than 4 cm or with extension to the cecum
___ pT3: Tumor more than 4 cm or with extension to the ileum
___ pT4: Tumor directly invades other adjacent organs or structures, eg, abdominal wall and skeletal muscle

Regional Lymph Nodes
___ Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in regional lymph nodes
Specify: Number examined: ___
Number involved: ___

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Distant Metastasis
___ Not applicable
___ pM1: Distant metastasis
  *Specify site(s), if known: ___________________________

***Ancillary Studies (select all that apply) (Notes D and G)**
*___ Ki-67 index
  *___ ≤2%
  *___ >2% to 20%
  *___ >20%
*___ Other (specify): ____________________________
*___ Not performed

***Additional Pathologic Findings (select all that apply) (Note H)**
*___ Tumor necrosis
*___ Acute appendicitis
*___ Other (specify): ____________________________

***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Explanatory Notes

A. Application and Tumor Location

This protocol applies to well-differentiated neuroendocrine neoplasms (carcinoid tumors) of the appendix. Poorly differentiated neuroendocrine carcinomas, small cell carcinomas, and goblet cell carcinoids are not included.

The appendix is a common site of gastrointestinal neuroendocrine tumors, usually presenting as small solitary lesions incidentally discovered after appendectomy. A separate staging system for appendiceal neuroendocrine tumors (NETs) is included in the *AJCC Cancer Staging Manual*[2] because of the substantial differences in behavior between appendiceal carcinomas and NETs and between appendiceal NETs and other gastrointestinal (GI) NETs. Neuroendocrine tumors arising in the appendix have no *in situ* state and arise in the deep mucosa or submucosa. Unlike for adenocarcinomas, for appendiceal NETs, tumor size is a more important predictor of patient outcome than depth of tumor invasion.

B. Tumor Size

Appendiceal neuroendocrine tumors smaller than 1.0 cm do not recur or metastasize, whereas those between 1.0 and 2.0 cm rarely do.[3] Tumor size >2.0 cm and mesoappendiceal invasion[4] have been correlated with nodal metastasis, but not with poor outcome.[5] For these reasons, appendectomy is sufficient for tumors 1.0 cm or smaller, as well as many tumors between 1.0 and 2.0 cm. More extensive procedures (eg, right hemicolectomy) are usually reserved for patients with tumors larger than 2.0 cm or with invasion beyond the muscularis propria.

C. Histologic Type

Most appendiceal NETs are low grade, with few mitoses and no necrosis, and have traditionally been classified as "carcinoids." While the term "atypical carcinoid" is not well defined for GI NETs, the *AJCC Cancer Staging Manual*[2] recommends using this terminology for appendiceal NETs with a mitotic count of 2 to 10 mitoses per 10 high-power fields and/or focal necrosis. Although the term "carcinoid tumor" remains in widespread use, this term may cause confusion for clinicians, who might view a carcinoid tumor as a serotonin-producing tumor associated with functional manifestations of carcinoid syndrome.

Alternate classification schemes based upon the World Health Organization (WHO) classification categorize neuroendocrine neoplasms as well-differentiated neuroendocrine tumors, well-differentiated neuroendocrine carcinomas, and poorly differentiated neuroendocrine carcinomas.[6-9] 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.

Alternative Classification Based Upon WHO Classification: Neuroendocrine Tumors of the Appendix

Well-Differentiated Neuroendocrine Tumor

Benign: Nonfunctioning cytologically bland tumors measuring not more than 1 cm in greatest dimension, without extension into mesoappendix.

Uncertain malignant potential: Nonfunctioning cytologically bland tumors measuring 1 to 2 cm with extension into mesoappendix.

Well-differentiated Neuroendocrine Carcinoma

Low-grade malignant potential: Nonfunctioning tumors measuring greater than 2 cm and deeply invading the mesoappendix; functioning tumors of any type.

Histologic Patterns

Although specific histologic patterns in well-differentiated neuroendocrine neoplasms, such as trabecular, insular, and glandular, roughly correlate with tumor location,[10] 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.

Most appendiceal neuroendocrine tumors are derived from enterochromaffin cells. Rarely, L-cell neuroendocrine tumors of the appendix are encountered; because of their distinctive growth pattern of tear-dropped shaped tubules embedded in a fibrous stroma,[11] these lesions are sometimes called tubular neuroendocrine tumors. It should be noted that these tumors are negative for chromogranin A but express enteroglucagon, peptide YY, and pancreatic polypeptide. Tubular neuroendocrine tumors are usually small lesions confined to the appendix and are found in female patients. These lesions exhibit benign behavior and should not be confused with adenocarcinoma.

D. Histologic Grade

Cytologic atypia in low-grade neuroendocrine tumors has no impact on clinical behavior of these tumors. The following grading system is recommended:

Grade	Mitotic Count (per 10 HPF) #	Ki-67 Index (%)##
G1	<2	≤2
G2	2 to 10	>2 to 20
G3	>10	>20

Mitotic count should be based upon counting 50 high-power (40x objective) fields and 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[12]; however, this practice may not be practical for routine clinical purposes, and it is acceptable to estimate the labeling index.

This grading system, while based upon that proposed by Rindi and colleagues, differs from their system in the designation of G2 tumors as showing mitotic counts of up to 10 per 10 HPF, rather than 20 per 10 HPF,[13] in order to harmonize criteria for “atypical carcinoid” tumors as proposed in the seventh edition of the *AJCC TNM Cancer Staging Manual*[2] with criteria for G2 designation.

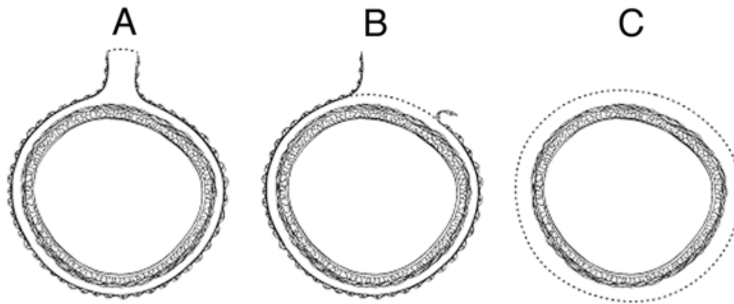
G1 and G2 are well-differentiated tumors with diffuse intense chromogranin/synaptophysin positivity. Punctate necrosis is more typical of G2 tumors. G3 tumors are high-grade neuroendocrine carcinomas (the CAP carcinoma checklist for appendiceal carcinoma[1] should be used for poorly differentiated neuroendocrine carcinomas of appendix).

E. Margins

Margins in a simple appendectomy specimen include the proximal and mesenteric or radial margin. It is recommended that the proximal margin on a simple appendectomy specimen should be taken en face in order to evaluate the entire appendiceal mucosa and muscularis circumferentially. In the vast majority of cases, the appendix is entirely peritonealized, and the closest distance between the invasive carcinoma and the mesenteric resection margin represents the radial margin and should be measured. Even retrocecal appendices are usually invested by peritoneum but have adhered to the posterior cecum, either because of inflammation or tumor. Exceptionally, a retrocecal appendix may be retroperitoneal, in which case the distance between the tumor and the nonperitonealized radial resection margin is the "surgical clearance" and should be measured.

In general, the circumferential (radial) margin must be assessed for any segment of gastrointestinal tract either incompletely encased or unencased by peritoneum (Figure, B and C). The posterior surface of the ascending colon portion of a right hemicolectomy specimen lacks a peritoneal covering and thus constitutes a circumferential margin, which in rare cases may be relevant in right hemicolectomy specimens resected for treatment of appendiceal neuroendocrine tumors. The circumferential (radial) 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 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, appendix and cecum) (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.
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F. TNM and Anatomic Stage/Prognostic Groupings
The TNM staging system for appendiceal NETs of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.[2]

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.

<u>The "m" suffix</u> indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

<u>The "y" prefix</u> indicates those cases in which classification is performed during or following 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 prior to 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.

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

T Category Considerations
Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically the classification should be pT1 to pT3.

N Category Considerations
The regional lymph nodes for the appendix are the ileocolic lymph nodes.

pTNM Pathological Classification
The pT, pN, and pM categories correspond to the T, N, and M categories except that pM0 (no distant metastasis) does not exist as a category.

pN0. Histologic examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph node results are negative, but the number ordinarily examined is not met, classify as pN0.

Histopathologic Grading
Histologic grading is not required for carcinoid tumors, but a mitotic count of 2 to 10 per 10 HPF and/or focal necrosis are features of atypical carcinoids (well-differentiated neuroendocrine carcinomas), a type seen much more commonly in the lung than in the appendix.

Goblet cell carcinoids are classified according to the carcinoma scheme.

TNM Anatomic Stage/Prognostic Groupings

Stage I	T1	N0	M0
Stage II	T2 or T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

G. 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.[9] 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.[14]

Immunohistochemistry for Ki-67 may be useful in establishing tumor grade (Note D) and prognosis[12] but is not currently considered standard of care.[9]

H. Additional Pathologic Findings

Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior[13] and should be reported. Appendiceal NETs are often an incidental finding in specimens removed for acute appendicitis.

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