

## Protocol for the Examination of Specimens From Patients With Neuroendocrine Tumors (Carcinoid Tumors) of the Small Intestine and Ampulla

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

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Based on AJCC/UICC TNM, 7<sup>th</sup> Edition

Protocol web posting date: October 2013

### Procedures

- Segmental Resection, Small Intestine
- Ampullectomy
- Pancreaticoduodenectomy, Partial or Complete, With or Without Partial Gastrectomy (Whipple Resection)

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## **CAP Small Bowel NET Protocol Revision History**

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### **Version Code**

The definition of the version code can be found at [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).

**Version:** SmallBowelNET 3.3.0.0

### **Summary of Changes**

The following changes have been made since the June 2012 release.

### **Segmental Resection, Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)**

#### **Specimen**

"Not specified" was deleted.

#### **Histologic Type; Histologic Grade**

Deleted "(G3)" from the note and moved the note from Histologic Grade to Histologic Type.

#### **Mitotic Rate**

A note regarding high-power fields was added, as follows:

#### **Mitotic Rate**

Specify: \_\_\_/10 high-power fields (HPF)#

\_\_\_ Cannot be determined

*# Published criteria that rely upon determination of mitotic rate for grading of gastrointestinal and pancreatic neuroendocrine tumors have been reported using counts per HPF, and do not specify microscopic field size or number of mitoses per mm<sup>2</sup>.*

### **Explanatory Notes**

#### **D. Histologic Type**

##### **Neuroendocrine Tumors of the Small Bowel**

This section was deleted.

##### **Histologic Patterns**

This section was deleted.

#### **E. Histologic Grade**

First paragraph, deleted the following sentence: However, grading systems based on mitotic activity have been shown to have utility for foregut tumors.

The second note was changed, as follows:

## Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling although the precise method of assessment has not been standardized.<sup>12</sup> It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index.<sup>8,11</sup> Published criteria that rely upon determination of mitotic count for grading of GI and pancreatic NETs have been reported using counts per high power field and do not specify microscopic field size or number of mitoses per mm<sup>2</sup>. Grade assigned based on Ki-67 index may be higher than that based on mitotic count. Thus, reporting the higher grade by either method is preferred if both are performed.<sup>10</sup>

#### **References**

Reference #11 was deleted and reference #12 was added.

## Surgical Pathology Cancer Case Summary

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Protocol web posting date: October 2013

### SMALL INTESTINE AND AMPULLA: Segmental Resection, Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Select a single response unless otherwise indicated.

#### Specimen (select all that apply) (Note A)

- Duodenum  
 Ampulla of Vater  
 Small intestine  
     +  Jejunum  
     +  Ileum  
     +  Unknown

Other organs received:

- Stomach  
 Head of pancreas  
 Common bile duct  
 Gallbladder  
 Cecum  
 Right colon  
 Appendix  
 Other (specify): \_\_\_\_\_

#### Procedure

- Segmental resection  
 Ampullectomy  
 Pancreaticoduodenectomy (Whipple resection)  
 Other (specify): \_\_\_\_\_  
 Not specified

#### + Specimen Size (if applicable)

+ Specify: \_\_\_ (length) x \_\_\_ x \_\_\_ cm

#### Tumor Site (select all that apply) (Note B)

- Duodenum  
 Ampulla  
 Small bowel  
     +  Jejunum  
     +  Ileum  
 Other (specify): \_\_\_\_\_  
 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 (Note D)#**

- Well-differentiated neuroendocrine tumor (carcinoid tumor)  
+  Somatostatinoma  
+  Gastrinoma  
+  Gangliocytic paraganglioma  
+  Other (specify): \_\_\_\_\_

# For poorly differentiated (high-grade) neuroendocrine carcinomas arising in the small intestine or ampulla, the College of American Pathologists (CAP) protocols for carcinomas of those organ sites should be used.<sup>1,2</sup>

**Histologic Grade (Note E)**

- Not applicable  
 GX: Cannot be assessed  
 G1: Low grade  
 G2: Intermediate grade  
 Other (specify): \_\_\_\_\_

**Mitotic Rate (Note E)**

- Specify: \_\_\_\_/10 high-power fields (HPF)#  
 Cannot be determined

# Published criteria that rely upon determination of mitotic rate for grading of gastrointestinal and pancreatic neuroendocrine tumors have been reported using counts per HPF, and do not specify microscopic field size or number of mitoses per mm<sup>2</sup>.

**Microscopic Tumor Extension: Small Intestine**

- 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 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: \_\_\_\_\_)

**Microscopic Tumor Extension: Ampulla**

- Cannot be assessed  
 No evidence of primary tumor  
 Tumor limited to ampulla of Vater or sphincter of Oddi  
 Tumor invades duodenal wall  
 Tumor invades pancreas  
 Tumor invades peripancreatic soft tissues  
 Tumor invades common bile duct  
 Tumor invades other adjacent organs or 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**

Small Intestine Resection Specimen

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

*Mesenteric (Radial) Margin (Note F)*

\_\_\_ Cannot be assessed

\_\_\_ Uninvolved by neuroendocrine tumor

\_\_\_ Involved by neuroendocrine tumor

*Other Margin(s) (required only if applicable)*

Specify margin(s): \_\_\_\_\_

\_\_\_ Cannot be assessed

\_\_\_ Uninvolved by neuroendocrine tumor

\_\_\_ Involved by neuroendocrine tumor

Ampullectomy Specimen (required only if applicable)

\_\_\_ Margins cannot be assessed

\_\_\_ Margins uninvolved by neuroendocrine tumor

Distance of neuroendocrine tumor from closest margin: \_\_\_ mm or \_\_\_ cm

Specify margin (if possible): \_\_\_\_\_

\_\_\_ Margin(s) involved by neuroendocrine tumor

Specify margin(s) (if possible): \_\_\_\_\_

Pancreaticoduodenal Resection Specimen (for ampullary tumors) (required only if applicable)

If all margins uninvolved by neuroendocrine tumor:

Distance of tumor from closest margin: \_\_\_ mm or \_\_\_ cm

Specify margin: \_\_\_\_\_

*Proximal Mucosal Margin (Gastric or Duodenal)*

\_\_\_ Cannot be assessed

\_\_\_ Uninvolved neuroendocrine tumor

\_\_\_ Involved by neuroendocrine tumor

*Distal Margin (Distal Duodenal or Jejunal)*

\_\_\_ Cannot be assessed

\_\_\_ Uninvolved by neuroendocrine tumor

\_\_\_ Involved by neuroendocrine tumor

+ 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.

*Pancreatic Retroperitoneal (Uncinate) Margin*

- Not applicable
- Cannot be assessed
- Uninvolved by neuroendocrine tumor
- Involved by neuroendocrine tumor (present 0-1 mm from margin)

*Bile Duct Margin*

- Not applicable
- Cannot be assessed
- Margin uninvolved by neuroendocrine tumor
- Margin involved by neuroendocrine tumor

*Distal Pancreatic Resection Margin*

- Not applicable
- Cannot be assessed
- Margin uninvolved by neuroendocrine tumor
- Margin 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 1 cm or less (small intestinal tumors); tumor 1 cm or less (ampullary tumors)
- pT2: Tumor invades muscularis propria or tumor size >1 cm (small intestinal tumors); tumor size >1 cm (ampullary tumors)
- pT3: Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into nonperitonealized tissues
- pT4: Tumor penetrates visceral peritoneum (serosa) or invades 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) (Note H)**

- +  Ki-67 labeling index (specify: \_\_\_\_\_)  
     +  ≤2%  
     +  3% to 20%  
     +  >20%  
 +  Other (specify): \_\_\_\_\_  
 +  Not performed

**+ Additional Pathologic Findings (select all that apply) (Note I)**

- +  Endocrine cell hyperplasia  
 +  Tumor necrosis  
 +  Psammoma bodies  
 +  Mesenteric vascular elastosis  
 +  Other (specify): \_\_\_\_\_

**+ Comment(s)**

## Explanatory Notes

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### A. Application and Tumor Location

This protocol applies to well-differentiated neuroendocrine tumors (carcinoid tumors) of the small intestine and ampulla of Vater. 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.<sup>3</sup>

#### Site of Origin of Gastrointestinal Neuroendocrine Tumors

	Foregut Tumors	Midgut Tumors	Hindgut Tumors
Site	<i>Stomach, Proximal Duodenum</i>	<i>Jejunum, Ileum, Appendix, Proximal Colon</i>	<i>Distal Colon, Rectum</i>
Immunohistochemistry			
Chromogranin A	86%-100% +	82%-92% +	40%-58% +
Neuron-Specific Enolase (NSE)	90%-100% +	95%-100% +	80%-87% +
Synaptophysin	50% +	95%-100% +	94%-100% +
Serotonin	33% + <sup>17</sup>	86% + <sup>17</sup>	45%-83% + <sup>4-6,17</sup>
Other Immunohistochemical Markers	Rarely, + for pancreatic polypeptide, histamine, gastrin, vasoactive intestinal peptide (VIP), or adrenocorticotrophic hormone (ACTH)	Prostatic acid phosphatase + in 20%-40% <sup>16,17</sup>	Prostatic acid phosphatase + in 20%-82% <sup>4-6,16,17</sup>
Carcinoid Syndrome	Rare	5%-39% <sup>7,8</sup>	Rare

### B. Site Specific Features

Duodenal NETs are relatively uncommon, accounting for roughly 4% of GI NETs.<sup>4</sup> The most common subtype is the gastrin-secreting NET, or gastrinoma, associated with Zollinger-Ellison syndrome in one-third of cases.<sup>5</sup> These gastrin-secreting tumors are often associated with multiple endocrine neoplasia type 1 (MEN1) syndrome, but sporadic tumors also occur.<sup>6</sup> Duodenal somatostatin-producing tumors (somatostatinomas) are less common, accounting for about 1% of GI NETs, and are seldom associated with the functional syndrome of mild diabetes mellitus, cholelithiasis, and steatorrhea. These tumors often have a pure glandular growth pattern with scattered psammoma bodies and may be confused with conventional adenocarcinomas.<sup>7</sup> They arise almost exclusively in the ampulla or periampullary duodenum and are often associated with MEN1 and with neurofibromatosis type 1.<sup>8</sup>

Most small bowel 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.<sup>9</sup> Metastatic risk is increased by tumor size >2 cm, involvement of the muscularis propria, and mitotic activity.<sup>3</sup>

### 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. For jejunoileal 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.<sup>3</sup> Thus,

treatment for small bowel carcinoid tumor includes complete resection with regional lymphadenectomy.

#### 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.<sup>5,7,10</sup> Historically, well-differentiated neuroendocrine neoplasms 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 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.

#### E. Histologic Grade

Cytologic atypia in low-grade neuroendocrine tumors has no impact on clinical behavior of these tumors. The following grading system is recommended by the European Neuroendocrine Tumor Society (ENETS) and the WHO<sup>10,11</sup>:

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.

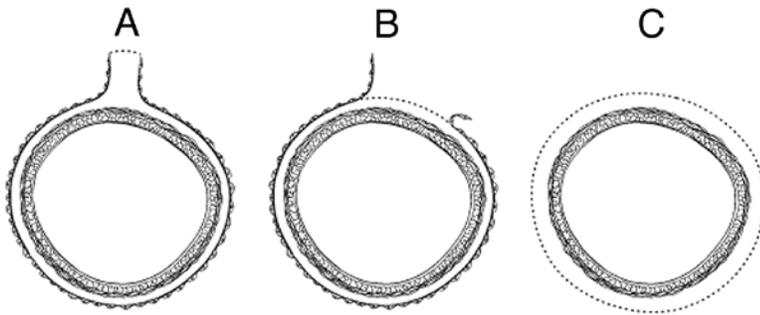
## Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling although the precise method of assessment has not been standardized.<sup>12</sup> It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index.<sup>8,11</sup> Published criteria that rely upon determination of mitotic count for grading of GI and pancreatic NETs have been reported using counts per high power field and do not specify microscopic field size or number of mitoses per mm<sup>2</sup>. Grade assigned based on Ki-67 index may be higher than that based on mitotic count. Thus, reporting the higher grade by either method is preferred if both are performed.<sup>10</sup>

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 protocol for the appropriate organ system should be used for poorly differentiated neuroendocrine carcinomas of the small intestine<sup>1</sup> and ampulla<sup>2</sup>).

#### 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 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, jejunum and ileum) (Figure 1, 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. From Washington et al.<sup>18</sup> Copyright 2008. College of American Pathologists. Reproduced with permission.

### G. TNM and Stage Groupings

The TNM staging system for neuroendocrine tumors of the duodenum, ampulla, and small bowel of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.<sup>13</sup>

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 (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.

### N Category Considerations

The regional lymph nodes for the small intestine vary with site. For duodenal tumors, the regional lymph nodes are duodenal, hepatic, pancreaticoduodenal, infrapyloric, gastroduodenal, pyloric, superior mesenteric, and pericholedochal nodes. 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.

The regional nodes for the ampulla may be subdivided as follows:

Superior: Lymph nodes superior to head and body of pancreas

Inferior: Lymph nodes inferior to head and body of pancreas

Anterior: Anterior pancreaticoduodenal, pyloric, and proximal mesenteric lymph nodes

Posterior: Posterior pancreaticoduodenal, common bile duct or pericholedochal, and proximal mesenteric nodes

### TNM Anatomic Stage/Prognostic Groupings

Stage I	T1	N0	M0 <sup>#</sup>
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

<sup>#</sup> 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.<sup>7</sup> Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended.

Immunohistochemistry for Ki-67 may be useful in establishing tumor grade (Note E) and prognosis<sup>11</sup> but is not currently considered standard of care.<sup>7</sup>

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

**Psammoma bodies** are commonly found in duodenal neuroendocrine tumors, especially periampullary tumors<sup>14</sup> expressing somatostatin and associated with von Recklinghausen disease.<sup>5</sup>

**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.<sup>15</sup>

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