

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

**Protocol applies to well-differentiated neuroendocrine tumors of the stomach. 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**

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## **Procedures**

- Endoscopic Resection
- Gastrectomy (Partial or Complete)

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**Surgical Pathology Cancer Case Summary (Checklist)**

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**STOMACH: Endoscopic Resection, Gastrectomy (Note A)**

Select a single response unless otherwise indicated.

**Specimen (select all that apply)**

- Stomach  
 Portion of stomach  
     Gastric body  
     Gastric antrum  
     Not specified  
 Distal esophagus  
 Proximal duodenum  
 Other (specify): \_\_\_\_\_  
 Not specified

**Procedure**

- Endoscopic resection  
 Partial gastrectomy, proximal  
 Partial gastrectomy, distal  
 Partial gastrectomy, other (specify): \_\_\_\_\_  
 Total gastrectomy  
 Other (specify): \_\_\_\_\_  
 Not specified

**\*Specimen Size (if applicable)**

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

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

- Gastric cardia  
 Gastric fundus  
 Gastric body  
 Gastric antrum  
 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

\* 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 D)**

- Carcinoid tumor  
 Other (specify): \_\_\_\_\_

**\*Alternative Histologic Classification (Note E)**

- \*  Well-differentiated endocrine tumor, benign behavior  
 \*  Well-differentiated endocrine tumor, uncertain behavior  
 \*  Well-differentiated endocrine carcinoma

**\*Histologic Grade (Note E)#**

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

# For poorly differentiated (high-grade) neuroendocrine carcinomas, the College of American Pathologists (CAP) checklist for carcinoma of the stomach should be used.<sup>1</sup>

**Mitotic Rate (Note E)**

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

**Margins (select all that apply)**Proximal Margin

- Cannot be assessed  
 Uninvolved by neuroendocrine tumor  
 Involved by neuroendocrine tumor  
 \*  Involved by neuroendocrine cell hyperplasia/dysplasia

Distal Margin

- Cannot be assessed  
 Uninvolved by neuroendocrine tumor  
 Involved by neuroendocrine tumor  
 \*  Involved by neuroendocrine cell hyperplasia/dysplasia

\* 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.

**Omental (Radial) Margin (Note F)**

- Cannot be assessed  
 Uninvolved by neuroendocrine tumor  
 Involved by neuroendocrine tumor

**Other Margin(s) (specify):** \_\_\_\_\_

- Not applicable  
 Cannot be assessed  
 Uninvolved by neuroendocrine tumor  
 Involved by neuroendocrine tumor  
 \*  Involved by neuroendocrine cell hyperplasia/dysplasia

If all margins uninvolved by neuroendocrine tumor:

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

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

**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  
 pTis: Carcinoma in situ/dysplasia (tumor size less than 0.5 mm), confined to mucosa  
 pT1: Tumor invades lamina propria or submucosa and 1 cm or less in size  
 pT2: Tumor invades muscularis propria or more than 1 cm in size  
 pT3: Tumor penetrates subserosa  
 pT4: Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures

**Regional Lymph Nodes (pN)**

- 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 (pM) Not applicable pM1: Distant metastasis

\*Specify site(s), if known: \_\_\_\_\_

**\*Ancillary Studies (select all that apply) (Notes E and H)**\*  Ki-67 index\*  ≤2%\*  >2% to 20%\*  >20%\*  Other (specify): \_\_\_\_\_\*  Not performed**Additional Pathologic Findings (select all that apply) (Note I)**\*  Atrophic gastritis\*  Intestinal metaplasia of gastric mucosa\*  Glandular dysplasia of gastric mucosa\*  Endocrine cell hyperplasia\*  Absence of parietal cells\*  Tumor necrosis\*  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 stomach. 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 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.<sup>2</sup>

**Table 1. 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>11,12</sup>	86% + <sup>11,12</sup>	45%-83% + <sup>3-5,12</sup>
Other Immunohistochemical Markers	Rarely, + for pancreatic polypeptide, histamine, gastrin, somatostatin, vasoactive intestinal peptide (VIP), or adrenocorticotrophic hormone (ACTH)	Prostatic acid phosphatase + in 20%-40% <sup>11,12</sup>	Prostatic acid phosphatase + in 20%-82% <sup>3-5,12</sup>
Carcinoid Syndrome	Rare	5%-39% <sup>6,7</sup>	Rare

### B. Site-Specific Features

Gastric neuroendocrine tumors are divided into 4 types.<sup>3</sup> Type 1 tumors arising in the setting of atrophic gastritis with associated hypergastrinemia are the most common. These lesions are composed of enterochromaffin-like (ECL) cells and are usually found as multiple small nodules in the body of the stomach and limited to mucosa and submucosa. Type 1 lesions are generally benign and may regress following antrectomy; lymph node metastases are very rare and occur only when the tumors are large (greater than 2 cm) and infiltrate the muscularis propria.

Type 2 gastric neuroendocrine tumors are rare. These multifocal small tumors, which are associated with multiple endocrine neoplasia (MEN) type 1 with Zollinger-Ellison syndrome, develop in the body of the stomach, are usually smaller than 1.5 cm, and are confined to the mucosa or submucosa. However, in contrast to type 1 tumors, 30% metastasize. Tumors greater than 2 cm and invading the muscularis propria and exhibiting vascular invasion are more likely to metastasize.

Type 3 gastric neuroendocrine tumors, the second most common neuroendocrine tumor in the stomach, are sporadic solitary tumors that are unassociated with atrophic gastritis or endocrine cell hyperplasia. These tumors may occur anywhere in the stomach. Metastasis is associated with larger mean size, angioinvasion, and invasion of muscularis propria. Surgical resection is usually advised for solitary gastric carcinoid tumors, particularly those larger than 2.0 cm, but tumors smaller than 1.0 cm have been rarely reported to metastasize.<sup>4</sup>

Type 4 gastric neuroendocrine tumors are rare high-grade neuroendocrine carcinomas that are usually bulky tumors with metastases at diagnosis (the CAP cancer checklist for gastric carcinoma applies<sup>1</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. In the stomach, types 3 and 4 neuroendocrine tumors are significantly larger than type 1 tumors,<sup>3</sup> which usually measure 1 cm or less<sup>5,6</sup> (Table 2). Tumor size correlates with depth of invasion for gastric neuroendocrine tumors, with larger tumors more likely to be deeply infiltrative and thus at higher risk for metastases. Nodules measuring 0.5 mm or larger are defined as neuroendocrine tumors; lesions measuring less than 0.5 mm are regarded as representing in situ tumor, neuroendocrine cell dysplasia, or hyperplasia.

**Table 2. Types of Gastric Neuroendocrine Tumors**

	<b>Type 1</b>	<b>Type 2</b>	<b>Type 3</b>	<b>Type 4</b>
Frequency	70%-80% of cases	Rare	10%-15% of cases	Rare
Multiplicity	Multifocal	Multifocal	Solitary	Solitary
Size	0.5-1.0 cm	~1.5 cm or less	Variable; one-third are larger than 2 cm	Large
Location	Corpus	Corpus	Anywhere in stomach	Anywhere in stomach
Associations	Hypergastrinemic states; chronic atrophic gastritis, enterochromaffin-like (ECL) cell hyperplasia, pernicious anemia	Multiple endocrine neoplasia (MEN) type 1, with hypergastrinemia or Zollinger-Ellison syndrome	Sporadic	Sporadic
Clinical Behavior	Usually benign	30% metastasize	71% of tumors >2 cm with muscularis propria and vascular invasion have lymph node metastases	High-grade carcinoma. Metastases common; poor prognosis

	Type 1	Type 2	Type 3	Type 4
Demographic Profile	70%-80% are females in their 50s and 60s	Equally in males and females, mean age 50 y	More common in males, mean age 55 y	More common in males

**D. Histologic Type**

The World Health Organization (WHO) classifies neuroendocrine neoplasms as well-differentiated neuroendocrine tumors, well-differentiated neuroendocrine carcinomas, and poorly differentiated neuroendocrine carcinomas.<sup>5-8</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 (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.

**Alternative Classification for Neuroendocrine Tumors of the Stomach, Adapted from WHO**

Well-Differentiated Neuroendocrine Tumor

*Benign:* Nonfunctioning cytologically bland tumors confined to mucosa or submucosa, without angiovascular invasion, and measuring not more than 1 cm in greatest dimension. Nodules of neuroendocrine cells that measure between 0.5 and 1 cm and are confined to the mucosa are classified by some as microneuroendocrine tumors.

*Uncertain malignant potential:* Nonfunctioning, cytologically bland tumors confined to mucosa or submucosa, with or without angioinvasion and measuring from 1 to 2 cm.

Well-differentiated Neuroendocrine Carcinoma

*Low-grade malignant potential:* Nonfunctioning tumors that invade the muscularis propria or beyond, or are metastatic, or measure greater than 2 cm; all sporadic gastric NETs (type 3 tumors) and some type 1 and 2 tumors. All functioning tumors of any type, including gastrinomas.

**Histologic Patterns**

Although specific histologic patterns in well-differentiated neuroendocrine neoplasms, such as trabecular, insular, and glandular, roughly correlate with tumor location, 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, grading systems based on mitotic activity have been shown to have utility for foregut tumors. The following grading system is recommended<sup>9</sup>:

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

# Mitotic count 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 percentage of 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<sup>9</sup>; 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 carcinoma checklist for carcinomas of the stomach applies<sup>1</sup>).

#### F. Circumferential (Radial) Margin

For surgical resection specimens, margins include the proximal, distal, and radial margins. The radial margins represent the nonperitonealized soft tissue margins closest to the deepest penetration of tumor. In the stomach, the lesser omental (hepatoduodenal and hepatogastric ligaments) and greater omental resection margins are the only radial margins. For endoscopic resection specimens, margins include mucosal margins and the deep margin of resection. It may be helpful to mark the margin(s) closest to the tumor with ink. Margins marked by ink should be designated in the macroscopic description.

#### G. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system for gastric neuroendocrine tumors of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.<sup>10</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 specific nodal areas of the stomach are listed below.<sup>10</sup>

Greater curvature of stomach: Greater curvature, greater omental, gastroduodenal, gastroepiploic, pyloric, and pancreaticoduodenal

Pancreatic and splenic area: Pancreaticolienal, peripancreatic, splenic

Lesser curvature of stomach: Lesser curvature, lesser omental, left gastric, cardioesophageal, common hepatic, celiac, and hepatoduodenal

Involvement of other intra-abdominal lymph nodes, such as hepatoduodenal, retropancreatic, mesenteric, and para-aortic, is classified as distant metastasis.<sup>10</sup>

### TNM Anatomic Stage/Prognostic Groupings

Stage 0	Tis	N0	M0 <sup>#</sup>
Stage I	T1	N0	M0
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>6</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>8</sup> but is not currently considered standard of care.<sup>6</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

Most gastric neuroendocrine tumors arise in the setting of chronic atrophic gastritis (see Note B). Atrophic gastritis may be associated with glandular dysplasia, and in rare cases, gastric adenocarcinoma. Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior<sup>9</sup> and should be reported.

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