COLLEGE of AMERICAN PATHOLOGISTS

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.

Based on AJCC/UICC TNM, 7th Edition
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Procedures

- Endoscopic Resection
- Gastrectomy (Partial or Complete)

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

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CAP Stomach NET Protocol Revision History

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

Version: StomachNET 3.3.0.0

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

Endoscopic Resection, Gastrectomy

Specimen
"Not specified" was deleted.

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

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

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^2.

Explanatory Notes

B. Site-Specific Features: First paragraph, last sentence: Deleted "following antrectomy."

E. Histologic Grade
The second note was edited, 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.[10] It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index.[8] 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^2. 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.[8]

I. Additional Pathologic Findings
This section was edited, as follows:
Most gastric neuroendocrine tumors (type-I) arise in the setting of hypergastrinemia secondary to atrophic gastritis such as autoimmune gastritis (see Note B). Autoimmune gastritis may be also associated with, glandular dysplasia, and in rare cases, gastric adenocarcinoma. Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior,[9] which is more commonly seen in type-III gastric neuroendocrine tumors, and should be reported.

References
Reference #10 was added and the remaining references renumbered accordingly.

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

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): _____

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

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 (carcinoid)
___ Well-differentiated neuroendocrine tumor; G2: Intermediate grade (atypical carcinoid)
___ Other (specify): _____

 # For poorly differentiated (high-grade) neuroendocrine carcinomas, the College of American Pathologists (CAP) protocol for carcinoma of the stomach[1] should be used.

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[2].

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)

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

<u>Proximal Margin</u>
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor
+ ___ Involved by neuroendocrine cell hyperplasia/dysplasia

<u>Distal Margin</u>
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor
+ ___ Involved by neuroendocrine cell hyperplasia/dysplasia

<u>Omental (Radial) Margin</u> (Note F)
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Deep Margin (endoscopic resections) (required only if applicable)
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Mucosal Margins (endoscopic resections) (required only if applicable)
___ 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
+ ___ Involved by neuroendocrine cell hyperplasia/dysplasia

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

___ 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)
+ ___ 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)

Explanatory Notes

A. Application and Tumor Location

This protocol applies to well-differentiated neuroendocrine tumors (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.[2]

Table 1. Site of Origin of Gastrointestinal Neuroendocrine Tumors

	Foregut Tumors	Midgut Tumors	Hindgut Tumors
Site	*Stomach, Proximal Duodenum*	*Jejunum, Ileum, Appendix, Proximal Colon*	*Distal Colon, Rectum*
Immunohistochemistry Chromogranin A Neuron-Specific Enolase (NSE) Synaptophysin Serotonin	 86%-100% + 90%-100% + 50% + 33% + [13]	 82%-92% + 95%-100% + 95%-100% + 86% + [13]	 40%-58% + 80%-87% + 94%-100% + 45%-83% + [3-5,13]
Other Immunohistochemical Markers	Rarely, + for pancreatic polypeptide, histamine, gastrin, somatostatin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)	Prostatic acid phosphatase + in 20%-40% [12,13]	Prostatic acid phosphatase + in 20%-82% [3-5,12]
Carcinoid Syndrome	Rare	5%-39% [6,7]	Rare

B. Site-Specific Features

Gastric neuroendocrine tumors are divided into 4 types.[3] 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; 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.[4]

Type 4 gastric neuroendocrine tumors are rare high-grade neuroendocrine carcinomas that are usually bulky tumors with metastases at diagnosis (the CAP cancer protocol for gastric carcinoma applies[1]).

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,[3] which usually measure 1 cm or less[5,6] (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

	Type 1	Type 2	Type 3	Type 4
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
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 (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas.[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.

Histologic Patterns
Although specific histologic patterns in well-differentiated neuroendocrine tumors, 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 by both the European Neuroendocrine Tumor Society (ENETS) and the WHO[8,9]:

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 although the precise method of assessment has not been standardized.[10] It has been recommended that 500 to 2000 tumor cells be counted to determine the Ki-67 index.[8] 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^2. 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.[8]

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 carcinomas of the stomach applies[1]).

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.[11]

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.[11]

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.[11]

TNM Anatomic Stage/Prognostic Groupings

Stage 0	Tis	N0	M0[#]
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

[#] 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.[6] 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[8] but is not currently considered standard of care.[6]

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 (type-I) arise in the setting of hypergastrinemia secondary to atrophic gastritis such as autoimmune gastritis (see Note B). Autoimmune gastritis may be also associated with, glandular dysplasia, and in rare cases, gastric adenocarcinoma. Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior,[9] which is more commonly seen in type-III gastric neuroendocrine tumors, and should be reported.

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