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
Protocol web posting date: November 2011

Procedures
• Endoscopic Resection
• Gastrectomy (Partial or Complete)

Authors
Kay Washington, MD, PhD, FCAP*
Department of Pathology, Vanderbilt University Medical Center, Nashville, TN
Laura H. Tang, MD, PhD, FCAP†
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
Jordan Berlin, MD
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
Philip Branton, MD, FCAP
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
Lawrence J. Burgart, MD, FCAP
Department of Pathology, Inova Fairfax Hospital, Falls Church, VA
David K. Carter, MD, PhD, FCAP
Office of Biorepositories and Biospecimen Research, National Cancer Institute, Bethesda, MD
Carolyn C. Compton, MD, PhD, FCAP
Department of Pathology, National Institutes of Health, Bethesda, MD
Patrick Fitzgibbons, MD, FCAP
Department of Pathology, St. Jude Medical Center, Fullerton, CA
Wendy L. Frankel, MD, FCAP
Department of Pathology, Ohio State University Medical Center, Columbus, OH
John Jessup, MD
Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD
Sanjay Kakar, MD, FCAP
Department of Pathology, University of California San Francisco and the Veterans Affairs Medical Center, San Francisco, CA
Bruce Minsky, MD
Department of Radiation Oncology, University of Chicago, Chicago, IL
Raouf Nakhdleh, MD, FCAP
Department of Pathology, Mayo Clinic, Jacksonville, FL
For the Members of the Cancer Committee, College of American Pathologists

*denotes primary author. †denotes secondary author. All other contributing authors are listed alphabetically.
© 2011 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) Dictation from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) Copying from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a computerized system for items (1) and (2), provided that the Protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from CAP. Applications for such a license should be addressed to the SNOMED Terminology Solutions division of the CAP.

Any public dissemination of the original or modified Protocols is prohibited without a written license from the CAP.

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 (Checklist)” 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.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
CAP Stomach NET Protocol Revision History

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

Version: StomachNET 3.1.1.0

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

Endoscopic Resection, Gastrectomy Checklist

Margins
The following data elements were added:

Deep Margin (applies to endoscopic resections)
- Cannot be assessed
- Uninvolved by tumor
- Involved by tumor
- Not applicable

Lateral Mucosal Margins (applies to endoscopic resections)
- Cannot be assessed
- Uninvolved tumor
- Involved by tumor
- Not applicable
**Surgical Pathology Cancer Case Summary (Checklist)**

Protocol web posting date: November 2011

**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.

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
___ Involvesd by neuroendocrine tumor
*___ Involvesd by neuroendocrine cell hyperplasia/dysplasia

Distal Margin
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involvesd by neuroendocrine tumor
___ Involvesd by neuroendocrine tumor
*___ Involvesd 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

Deep Margin (applies to endoscopic resections)
___ Cannot be assessed
___ Uninvolved by tumor
___ Involved by tumor
___ Not applicable

Lateral Mucosal Margins (applies to endoscopic resections)
___ Cannot be assessed
___ Uninvolved tumor
___ Involved by tumor
___ Not applicable

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)

* 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.
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 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.²

Table 1. 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>Other Immunohistochemical</td>
<td>Rarely, + for pancreatic polypeptide, histamine, gastrin, somatostatin, 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>Markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoid Syndrome</td>
<td>Rare</td>
<td>5%-39%</td>
<td>Rare</td>
</tr>
</tbody>
</table>

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 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.4

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 applies1).

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 less5,6 (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

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>70%-80% of cases</td>
<td>Rare</td>
<td>10%-15% of cases</td>
<td>Rare</td>
</tr>
<tr>
<td>Multiplicity</td>
<td>Multifocal</td>
<td>Multifocal</td>
<td>Solitary</td>
<td>Solitary</td>
</tr>
<tr>
<td>Size</td>
<td>0.5-1.0 cm</td>
<td>~1.5 cm or less</td>
<td>Variable; one-third are larger than 2 cm</td>
<td>Large</td>
</tr>
<tr>
<td>Location</td>
<td>Corpus</td>
<td>Corpus</td>
<td>Anywhere in stomach</td>
<td>Anywhere in stomach</td>
</tr>
<tr>
<td>Associations</td>
<td>Hypergastrinemic states; chronic atrophic gastritis, enterochromaffin-like (ECL) cell hyperplasia, pernicious anemia</td>
<td>Multiple endocrine neoplasia (MEN) type 1, with hypergastrinemia or Zollinger-Ellison syndrome</td>
<td>Sporadic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Clinical Behavior</td>
<td>Usually benign</td>
<td>30% metastasize</td>
<td>71% of tumors &gt;2 cm with muscularis propria and vascular invasion have lymph node metastases</td>
<td>High-grade carcinoma. Metastases common; poor prognosis</td>
</tr>
<tr>
<td>Demographic Profile</td>
<td>70%-80% are females in their 50s and 60s</td>
<td>Equally in males and females, mean age 50 y</td>
<td>More common in males, mean age 55 y</td>
<td>More common in males</td>
</tr>
</tbody>
</table>
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. 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:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Count (per 10 HPF)</th>
<th>Ki-67 Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2 to 20</td>
<td>&gt;2 to 20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

# 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; 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).

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.

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.10

Greater curvature of stomach: Greater curvature, greater omental, gastroduodenal, gastroepiploic, pyloric, and pancreaticoduodenal
Pancreatic and splenic area: Pancreaticocolenal, 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.10

TNM Anatomic Stage/Prognostic Groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0#</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIa</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIb</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIa</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIb</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>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 CD56.6 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 prognosis8 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 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 and should be reported.

References