Protocol for the Examination of Specimens from Patients with Well-Differentiated Neuroendocrine Tumors (Carcinoid Tumors) of the Stomach

Version: 5.0.0.0
Protocol Posting Date: December 2023
CAP Laboratory Accreditation Program Protocol Required Use Date: September 2024
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Gastrectomy (Partial or Complete)	
Tumor Type	**Description**
Well-differentiated neuroendocrine tumors of the stomach	

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Excisional biopsy (includes endoscopic resection and polypectomy)
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Recurrent tumor
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Poorly differentiated neuroendocrine carcinoma including small cell and large cell neuroendocrine carcinoma (consider Stomach protocol)
Other epithelial carcinomas including mixed neuroendocrine-non-neuroendocrine neoplasms (consider Stomach protocol)
Lymphoma (consider Hodgkin or non-Hodgkin Lymphoma protocols)
Gastrointestinal stromal tumor (GIST) (consider GIST protocol)
Non-GIST sarcoma (consider Soft Tissue protocol)

Authors
Dhanpat Jain, MD*; William V. Chopp, MD*; Rondell P. Graham, MBBS*.
With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.

© 2023 College of American Pathologists (CAP). All rights reserved. For Terms of Use please visit www.cap.org/cancerprotocols .

Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (i.e., secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 5.0.0.0

- Update to AJCC Version 9 pTNM Staging Classifications
- WHO 5th Edition update to content and explanatory notes
- “Lymphovascular Invasion” question updated to “Lymphatic and / or Vascular Invasion"

Reporting Template
Protocol Posting Date: December 2023
Select a single response unless otherwise indicated.

CASE SUMMARY: (STOMACH NEUROENDOCRINE TUMOR)
Standard(s): AJCC-UICC 9

SPECIMEN (Note A)
Author's Note: A major determinant of natural history, including outcomes, of well differentiated gastric neuroendocrine tumors is the milieu in which the tumor arises. This is likely more influential than tumor stage in most cases and is well described in Explanatory Note E. Tumor stage and underlying gastric milieu are complementary, and both should be reported in support of proper management of these tumors.

Procedure
___ Endoscopic resection
___ Partial gastrectomy, proximal
___ Partial gastrectomy, distal
___ Partial gastrectomy, other (specify): _____
___ Total gastrectomy
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (Note B) (select all that apply)
___ Gastric cardia / fundus: _____
___ Gastric body: _____
___ Gastric antrum: _____
___ Gastric pylorus: _____
___ Lesser curvature: _____
___ Greater curvature: _____
___ Other (specify): _____
___ Stomach, not otherwise specified: _____

Histologic Type and Grade# (Notes C,D)
 # For poorly differentiated (high-grade) neuroendocrine carcinomas, the College of American Pathologists (CAP) checklist for carcinoma of the stomach should be used.
___ G1, well-differentiated neuroendocrine tumor
___ G2, well-differentiated neuroendocrine tumor
___ G3, well-differentiated neuroendocrine tumor
___ GX, grade cannot be assessed
___ Other (specify): _____
___ Not applicable: _____
+Histologic Type and Grade Comment: _____
Histologic Grade Determination (Note D)
Mitotic rate and / or Ki-67 labeling index is required to determine histologic grade
Mitotic Rate (required only when Ki-67 labeling index is not reported)#
 # Mitotic rate should be reported as number of mitoses per 2 mm2, by evaluating at least 10 mm2 in the most mitotically active part of the tumor (e.g., if using a microscope with a field diameter of 0.55 mm, count 42 high

power fields (10 mm2) and divide the resulting number of mitoses by 5 to determine the number of mitoses per 2 mm2 needed to assign tumor grade).

___ Not applicable (Ki-67 labeling index is reported)
___ Specify number of mitoses per 2 mm2: _____ mitoses per 2 mm2
___ Less than 2 mitoses per 2 mm2
___ 2 to 20 mitoses per 2 mm2
___ Greater than 20 mitoses per 2 mm2
___ Cannot be determined (explain): _____

Ki-67 Labeling Index (required only when mitotic rate is not reported)

___ Not applicable (mitotic rate is reported)
___ Specify Ki-67 percentage: _____ %
___ Less than 3%
___ 3% to 20%
___ Greater than 20%
___ Cannot be determined (explain): _____

Tumor Size (Note E)

___ Greatest dimension in Centimeters (cm) (specify size of largest tumor if multiple tumors are present): _____ cm

+Additional Dimension in Centimeters (cm): ____ x ____ cm

___ Cannot be determined (explain): _____

Tumor Focality

___ Unifocal
___ Multifocal

Number of Tumors

___ Specify number: _____
___ Other (specify): _____
___ Cannot be determined: _____

___ Cannot be determined: _____

Tumor Extent

___ Invades lamina propria
___ Invades submucosa
___ Invades muscularis propria
___ Invades through muscularis propria into subserosal tissue without penetration of overlying serosa
___ Penetrates visceral peritoneum (serosa)
___ Invades other organ(s) or adjacent structure(s) (specify): _____
___ Cannot be determined: _____
___ No evidence of primary tumor

Lymphatic and / or Vascular Invasion

___ Not identified
___ Present
___ Cannot be determined: _____

+Perineural Invasion
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note F)

Margin Status
___ All margins negative for tumor
+Closest Margin(s) to Tumor (select all that apply)
___ Proximal: _____
___ Distal: _____
___ Omental (radial): _____
___ Mucosal: _____
___ Deep: _____
___ Other (specify): _____
___ Cannot be determined: _____
+Distance from Tumor to Closest Margin
Specify in Centimeters (cm)
___ Exact distance in cm: _____ cm
___ Greater than 1 cm
Specify in Millimeters (mm)
___ Exact distance in mm: _____ mm
___ Greater than 10 mm
Other
___ Other (specify): _____
___ Cannot be determined: _____
___ Tumor present at margin
Margin(s) Involved by Tumor (select all that apply)
___ Proximal: _____
___ Distal: _____
___ Omental (radial): _____
___ Mucosal: _____
___ Deep: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Liver: _____
___ Lung: _____
___ Ovary: _____
___ Nonregional lymph node(s): _____
___ Peritoneum: _____
___ Bone: _____
___ Other (specify): _____
___ Cannot be determined: _____

pTNM CLASSIFICATION (AJCC Version 9) (Note G)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category#
 # Multiple tumors should be designated as such (the largest tumor should be used to assign T category). Use T(#); e.g., pT3(4) N0 M0, OR use the m suffix, T(m); e.g., pT3(m) N0 M0.

___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pT1: Tumor invades the mucosa or submucosa, and is less than or equal to 1 cm in greatest dimension
___ pT2: Tumor invades the muscularis propria or is greater than 1 cm in greatest dimension
___ pT3: Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
___ pT4: Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No tumor involvement of regional lymph node(s)
___ pN1: Tumor involvement of regional lymph node(s)

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
pM1: Microscopic confirmation of distant metastasis
___ pM1a: Microscopic confirmation of metastasis confined to liver
___ pM1b: Microscopic confirmation of metastasis in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone), but not liver
___ pM1c: Microscopic confirmation of both hepatic and extrahepatic metastases
___ pM1 (subcategory cannot be determined)

ADDITIONAL FINDINGS (Note H)

+Additional Findings (select all that apply)
___ None identified
___ Gastric atrophy
+___ Multifocal gastric atrophy
+___ Diffuse gastric atrophy
___ Autoimmune gastritis
___ Intestinal metaplasia of gastric mucosa
___ Glandular dysplasia of gastric mucosa
___ Endocrine cell hyperplasia
___ Absence of parietal cells
___ Tumor necrosis
___ Other (specify): _____

COMMENTS

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 and large cell neuroendocrine carcinoma) and tumors with mixed glandular/neuroendocrine differentiation are not included.[1]

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 Synaptophysin Serotonin	 86%-100% + 50% + 33% + [3]	 82%-92% + 95%-100% + 86% + [3]	 40%-58% + 94%-100% + 45%-83% +[3,4,5,6]
Other Immunohistochemical Markers	Rarely, + for pancreatic polypeptide, histamine, gastrin, somatostatin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)	Prostatic acid phosphatase + in 20%-40%[7,8]	Prostatic acid phosphatase + in 20%-82%[3,4,5,2,6,7,8]
Carcinoid Syndrome	Rare	5%-39%[9,10]	Rare

References

1. Burghart LJ, Chopp WV, Jain D. Protocol for the Examination of Specimens From Patients with Carcinoma of the Stomach. 2021. Available at www.cap.org/cancerprotocols.
2. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol.* 2005;89(3):151-160.
3. Eckhauser FE, Argenta LC, Strodel WE, et al. Mesenteric angiopathy, intestinal gangrene, and midgut carcinoids. *Surgery.* 1981;90(4):720-728.
4. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003;97(4):934-959.
5. Graeme-Cook F. Neuroendocrine tumors of the GI tract and appendix. In: Odze RD, Goldblum JR, Crawford JM, eds. *Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas*. Philadelphia, PA: Saunders; 2004: 483-504.
6. Anlauf, M., N. Garbrecht, T. Henopp, A. Schmitt, R. Schlenger, A. Raffel, M. Krausch, et al. 'Sporadic Versus Hereditary Gastrinomas of the Duodenum and Pancreas: Distinct Clinico-Pathological and Epidemiological Features.' *World J Gastroenterol* 12, no. 34 (Sep 14 2006): 5440-5446.
7. Kimura N, Sasano N. Prostate-specific acid phosphatese in carcinoid tumors. *Virchows Arch A*

Pathol Anat Histopathol. 1986;410(3):247-251.
8. Nash SV, Said JW. Gastroenteropancreatic neuroendocrine tumors: a histochemical and immunohistochemical study of epithelial (keratin proteins, carcinoembryonic antigen) and neuroendocrine (neuron-specific enolase, bombesin and chromogranin) markers in foregut, midgut, and hindgut tumors. *Am J Clin Pathol.* 1986;86(2):415-422.
9. Williams GT. Endocrine tumours of the gastrointestinal tract: selected topics. *Histopathology.* 2007;50(1):30-41.
10. Garbrecht N, Anlauf M, Schmitt A, et al. Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. *Endocr Rel Cancer.* 2008;15(1):229-241.

B. Site-Specific Features

Well-differentiated gastric neuroendocrine tumors are divided into 3 types (Table 2).[1] Type 1 enterochromaffin like (ECL)-cell tumors arising in the setting of chronic atrophic gastritis (often autoimmune) with associated hypergastrinemia are the most common. These lesions are composed of enterochromaffin-like (ECL) cells and are usually found as multiple small nodules/polyps in the body of the stomach and limited to the mucosa and submucosa. Type 1 lesions are generally indolent 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 ECL-cell 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, 10% to 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, hypergastrinemia, or endocrine cell hyperplasia. These tumors may occur anywhere in the stomach. Metastasis is common and is associated with larger mean size, angioinvasion, and invasion of muscularis propria. Surgical resection is usually advised for solitary gastric neuroendocrine tumors, particularly those larger than 2.0 cm, but tumors smaller than 1.0 cm have been rarely reported to metastasize.[2] Recently amongst type 3 gastric NETs a subset has been recognized that is associated with long-term proton pump inhibitors (PPI) use. Long term PPI use has been defined as >1 year in most studies and the background gastric mucosa in such cases typically shows parietal cell hyperplasia and endocrine cell hyperplasia in the gastric body as well as the antrum. Such tumors are typically G1 or G2, rarely metastasize and have much better prognosis compared to those that are not associated with PPI.[3,4]

In addition to the above 4 types that represent mostly ECL-cell tumors, based on the cell of origin other rare variants include: 1) Serotonin-producing enterochromaffin (EC)-cell neuroendocrine tumors, which have morphologic features similar to those of ileal EC-cell neuroendocrine tumors; 2) Gastrin-producing G-cell neuroendocrine tumor and gastrinoma; and 3) Somatostatin-producing D-cell neuroendocrine tumors.[1]

References

1. WHO Classification of Tumours Editorial Board. *Digestive system tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th

ed.; vol. 1).
2. Xie SD, Wang LB, Song XY, Pan T. Minute gastric carcinoid with regional lymph node metastasis: a case report and review of the literature. *World J Gastroenterol.* 2004;10(16):2461-2463
3. Rais, R., N. A. Trikalinos, J. Liu, and D. Chatterjee. 'Enterochromaffin-Like Cell Hyperplasia-Associated Gastric Neuroendocrine Tumors May Arise in the Setting of Proton Pump Inhibitor Use.' *Arch Pathol Lab Med* 146, no. 3 (Mar 1 2022): 366-371.
4. Trinh, V. Q., C. Shi, and C. Ma. 'Gastric Neuroendocrine Tumours from Long-Term Proton Pump Inhibitor Users Are Indolent Tumours with Good Prognosis.' *Histopathology* 77, no. 6 (Dec 2020): 865-867.

C. 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.[1,2,3,4] 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. The use of the term “carcinoid” for neuroendocrine tumor reporting is therefore discouraged for these reasons.

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.

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.

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, synaptophysin, and CD56.[2] Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended, although INSM1 is also emerging as a good marker for endocrine differentiation.[5,6] Immunohistochemistry for specific hormone products, such as gastrin, may be of interest in some cases. However, immunohistochemical demonstration of hormone production does not equate with clinical functionality of the tumor.

References

1. Graeme-Cook F. Neuroendocrine tumors of the GI tract and appendix. In: Odze RD, Goldblum JR, Crawford JM, eds. *Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas*. Philadelphia, PA: WB Saunders; 2004:483-504.
2. Williams GT. Endocrine tumours of the gastrointestinal tract: selected topics. *Histopathology*. 2007;50(1):30-41
3. Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci.* 2004;1014:13-27.
4. WHO Classification of Tumours Editorial Board. *Digestive system tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th

ed.; vol. 1).
5. Zhang Q, Huang J, He Y, Cao R, Shu J. Insulinoma-associated protein 1(INSM1) is a superior marker for the diagnosis of gastroenteropancreatic neuroendoerine neoplasms: a meta-analysis. *Endocrine*. 2021;74(1):61-71.
6. McHugh KE, Mukhopadhyay S, Doxtader EE, Lanigan C, Allende DS. INSM1 Is a Highly Specific Marker of Neuroendocrine Differentiation in Primary Neoplasms of the Gastrointestinal Tract, Appendix, and Pancreas. *Am J Clin Pathol*. 2020;153(6):811-820.

D. Histologic Grade

Cytologic atypia in well-differentiated neuroendocrine tumors has no impact on clinical behavior of these tumors. The WHO classification[1] and others[2] use mitotic rate and/or Ki-67 index as one of the criteria for potential for aggressive behavior. Mitotic rate should be reported as number of mitoses per 2 mm^2, by evaluating at least 10 mm^2 in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Because of variations in field size, the number of high-power fields (HPF) (at 40X magnification) for 10 mm^2 (thereby 2 mm^2) must be determined for each microscope (Table 3). For example, if using a microscope with a field diameter of 0.55 mm, count 42 HPF and divide the resulting number of mitoses by 5 to determine the number of mitoses per 2 mm^2 needed to assign tumor grade.

Table 3. Number of HPF Required for 10 mm^2 Using Microscopes With Different Field Diameter

Field Diameter (mm)	Area (mm^2)	Number of HPF for 10mm^2
0.40	0.125	80
0.41	0.132	75
0.42	0.139	70
0.43	0.145	69
0.44	0.152	65
0.45	0.159	63
0.46	0.166	60
0.47	0.173	58
0.48	0.181	55
0.49	0.189	53
0.50	0.196	50
0.51	0.204	49
0.52	0.212	47
0.53	0.221	45
0.54	0.229	44
0.55	0.238	42
0.56	0.246	41
0.57	0.255	39
0.58	0.264	38
0.59	0.273	37
0.60	0.283	35
0.61	0.292	34
0.62	0.302	33
0.63	0.312	32
0.64	0.322	31
0.65	0.332	30
0.66	0.342	29

0.67	0.353	28
0.68	0.363	28
0.69	0.374	28

Ki-67 index is reported as percent positive tumor cells in area of highest nuclear labeling ("hot spot"), although the precise method of assessment has not been standardized. A number of methods have been used to assess Ki-67 index, including automatic counting and "eyeballing." [3,4] Automated counting is not widely available and requires careful modification of the software to circumvent the inaccuracies.[3] Eye-balling can be used for most tumors; however, for tumors with Ki-67 index close to grade cut-offs, it is recommended to perform the manual count on the print of camera-captured image of the hot spot. It has been recommended that a minimum of 500 tumor cells be counted to determine the Ki-67 index, and a notation is made if less cells are available. Grade assigned based on Ki-67 index is typically higher than that based on mitotic count, and the case is assigned to the higher of the 2 if both methods are performed.[1]

It is important to note that there are a small group of well-differentiated neuroendocrine tumors with a Ki-67 index >20% and a mitotic rate usually <20 per 10 HPF. In WHO-2010, these tumors were considered as G3 poorly differentiated neuroendocrine carcinomas. However, they have typical morphology of well-differentiated tumors.

Previous studies (most on pancreatic neuroendocrine tumors) have demonstrated that these tumors have a worse prognosis than grade 2 (Ki-67=3-20 % and mitosis <20/10 HPF) neuroendocrine tumors, but they are not as aggressive as poorly differentiated neuroendocrine carcinomas.[5] In addition, these tumors do not have the genetic abnormalities seen in poorly differentiated neuroendocrine carcinomas.[6] Furthermore, unlike poorly differentiated neuroendocrine carcinomas, they are less responsive to platinum-based chemotherapy.[7] In the WHO-2019 blue book of digestive system tumors,[1] and AJCC Version 9,[8] those with typical morphology of well-differentiated tumors are classified as "well differentiated neuroendocrine tumor" but as grade 3 (Table 4).

Table 4. Recommended Grading System for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors

Grade	Mitotic Rate (per 2mm^2)	Ki-67 index (%)
Well-differentiated neuroendocrine tumor, G1	<2	<3
Well-differentiated neuroendocrine tumor, G2	2-20	3-20
Well-differentiated neuroendocrine tumor, G3	>20	>20

References

1. WHO Classification of Tumours Editorial Board. *Digestive system tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1).
2. Rindi G, Kloppel G, Alhman H, et al; and all other Frascati Consensus Conference participants; European Neuroendocrine Tumor Society (ENETS). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006;449(4):395-401.
3. Tang LH, Gonen M, Hedvat C, Modlin I, Klimstra DS. Objective quantification of the Ki67 proliferative index in neuroendocrine tumors of gastroenteropancreatic system: a comparison of digital image analysis with manual methods. *Am J Surg Pathol.* 2012;36(12):1761-1770.

4. Reid MD, Bagci P, Ohike N, Saka B, Erbarut Seven I, Dursun N et al. Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies. *Mod Pathol*. 2015;28(5):686-9411.
5. Shi C, Klimstra DS. Pancreatic neuroendocrine tumors: pathologic and molecular characteristics. *Semin Diagn Pathol*. 2014;31(6):498-511.
6. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012;36(2):173-184.
7. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer*. 2014;120(18):2814-2823.
8. AJCC Version 9 Neuroendocrine Tumors of the Stomach Cancer Staging System. Copyright 2023 American College of Surgeons.

E. Tumor Size

For well-differentiated 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 neuroendocrine tumors are significantly larger than type 1 tumors,[1] which usually measure 1 cm or less[2,3] (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. Regardless of size, any nodules with invasion are defined as neuroendocrine tumors; lesions without invasion can be regarded as neuroendocrine cell dysplasia or hyperplasia.[4]

Table 2. Types of Well-Differentiated Gastric Neuroendocrine Tumors

	Type 1	**Type 2**	**Type 3**	**PPI-associated**
Frequency	65% of cases	2%	13% of cases	20%
Multiplicity	Multifocal	Multifocal	Solitary	Single or multifocal
Size	0.5-1.0 cm	~1.5 cm or less	Variable; one-third are larger than 2 cm	Generally small in size
Location	Corpus	Corpus	Anywhere in stomach	Corpus
Hypergastrinemia	Present	Present	Absent	Present
Acid secretion	Low or absent	High	Normal	Unknown
Association	Chronic atrophic gastritis	Multiple endocrine type 1 (MEN-1)	Sporadic	Long-term PPI use
Background gastric mucosa	Enterochromaffin-like (ECL) cell hyperplasia, partial or complete loss of parietal cells, intestinal metaplasia	Parietal cell hyperplasia; ECL cell hyperplasia	Usually normal	Parietal cell hyperplasia; ECL cell hyperplasia, antral neuroendocrine cell hyperplasia
Clinical Behavior	Usually indolent: ~100% 5-year survival	10-30% metastasize	71% of tumors >2 cm with muscularis propria and vascular invasion have lymph node metastases	Rarely metastasize, ~100% 5-year survival
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	Equally in males and females, in their 50s and 60s

References
1. Borch K, Ahren B, Ahlman H, Falkmer S, Granerus G, Grimelius L. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Ann Surg.* 2005;242(1):64-73.
2. Graeme-Cook F. Neuroendocrine tumors of the GI tract and appendix. In: Odze RD, Goldblum JR, Crawford JM, eds. *Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas*. Philadelphia, PA: WB Saunders; 2004:483-504.
3. Williams GT. Endocrine tumours of the gastrointestinal tract: selected topics. *Histopathology.* 2007;50(1):30-41.
4. WHO Classification of Tumours Editorial Board. *Digestive system tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 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. pTNM Classification

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.[1]

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 (e.g., 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 (i.e., 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 (i.e., 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.[2]

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

Pancreatic and splenic areas:
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 retropancreatic, mesenteric, and para-aortic, is classified as distant metastasis.[2]

M Category Considerations

The liver is the most common metastatic site. Metastases to extrahepatic sites, such as lung, ovary, peritoneum and bone, are rare. Involvement of the celiac, para-aortic, and other nonregional lymph nodes is also considered M1 disease. In the AJCC Version 9, M is subcategorized into M1a (hepatic only), M1b (extrahepatic only), and M1c (both hepatic and extrahepatic).

References

1. AJCC Version 9 Neuroendocrine Tumors of the Stomach Cancer Staging System. Copyright 2023 American College of Surgeons.
2. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012;36(2):173-184.

H. Additional 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,[1] which is more commonly seen in type-III gastric neuroendocrine tumors, and should be reported.

References

1. Rindi G, Kloppel G, Alhman H, et al; and all other Frascati Consensus Conference participants; European Neuroendocrine Tumor Society (ENETS). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006;449(4):395-401.