Protocol for the Examination of Specimens from Patients with Neuroendocrine Tumors (Carcinoid Tumors) of the Colon and Rectum

Protocol applies to well-differentiated neuroendocrine tumors of the large bowel and rectum. 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: February 2010

Procedures
- Local Excision (Transanal Disk Excision)
- Colectomy (Total, Partial, or Segmental Resection)
- Rectal Resection

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 Pathology, Inova Fairfax Hospital, Falls Church, VA
Lawrence J. Burgart, MD, FCAP
Allina Laboratories, Abbott Northwestern Hospital, Minneapolis, MN
David K. Carter, MD, FCAP
Department of Pathology, St. Mary's/Duluth Clinic Health System, Duluth, MN
Carolyn C. Compton, MD, PhD, FCAP
Office of Biorepositories and Biospecimen Research, National Cancer Institute, 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 Nakhleh, 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.

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CAP Colon and Rectum NET Protocol Revision History

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

Version: ColonRectumNET 3.0.0.0

Summary of Changes
No changes have been made since the February 2010 release.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: February 2010

COLON AND RECTUM: Resection, Including Transanal Disk Excision of Rectal Neoplasms (Note A)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Large intestine
    ___ Cecum
    ___ Ascending colon
    ___ Transverse colon
    ___ Descending colon
    ___ Sigmoid colon
___ Rectum
___ Anus
___ Terminal ileum
___ Appendix
___ Other (specify): ____________________________
___ Not specified

Procedure
___ Right hemicolectomy
___ Transverse colectomy
___ Left hemicolectomy
___ Sigmoidectomy
___ Rectal/rectosigmoid colon (low anterior resection)
___ Total abdominal colectomy
___ Abdominoperineal resection
___ Transanal disk excision (local excision)
___ Other (specify): _____________________________
___ Not specified

***Specimen Size (applicable to transanal disk excision)**
*Specify: ___ (length) x ___ x ___ cm

Tumor Site (select all that apply) (Note B)
____ Large bowel
    ___ Cecum
    ___ Right (ascending) colon
    ___ Hepatic flexure
    ___ Transverse colon
    ___ Splenic flexure
    ___ Left (descending) colon
    ___ Sigmoid colon
___ Rectum
___ Other (specify): _____________________________
___ Not specified

* 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.

Tumor Size (Note C)
Greatest dimension: ___ cm (specify size of largest tumor if multiple tumors are present)
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see "Comment")

Tumor Focality
___ Unifocal
___ Multifocal (specify number of tumors: ______)
___ Cannot be determined

Histologic Type (Note D)
___ 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 neuroendocrine carcinomas, the College of American Pathologists (CAP) checklist for carcinoma of the colon and rectum[1] should be used.*

Mitotic Rate
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 through the muscularis propria into the subserosal adipose tissue or the nonperitonealized pericolic or perirectal soft tissues but does not extend to the serosal surface (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

Proximal Margin

* 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.

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

Distal Margin
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

Circumferential (Radial) Margin **(Note F)**
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor
___ Not applicable

Other Margin(s) (specify): ______________________
___ Not applicable
___ Cannot be assessed
___ Uninvolved by neuroendocrine tumor
___ Involved by neuroendocrine tumor

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
___ pT1: Tumor invades lamina propria or submucosa and size 2 cm or less
___ pT1a: Tumor size less than 1 cm in greatest dimension
___ pT1b: Tumor size 1 to 2 cm in greatest dimension
___ pT2: Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
___ pT3: Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues

* 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.

___ pT4: Tumor invades peritoneum or other organs

Regional Lymph Nodes (pN)
___ Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in regional lymph nodes
Specify: Number examined: ___
Number involved: ___

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)**
*___ 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 low- and intermediate-grade neuroendocrine neoplasms (carcinoid tumors) of the colon and rectum. Poorly differentiated neuroendocrine carcinomas, small cell carcinomas, and tumors with mixed glandular/neuroendocrine differentiation are not included.

Because of site-specific similarities in histology, immunohistochemistry, and histochemistry, neuroendocrine tumors of the digestive tract have traditionally been subdivided into those of foregut, midgut, and hindgut origin (Table). In general, the distribution pattern along the gastrointestinal (GI) tract parallels that of the progenitor cell type, and the anatomic site of origin of GI neuroendocrine tumors is an important predictor of clinical behavior.[2]

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% + [13,14]	 82%-92% + 95%-100% + 95%-100% + 86% + [13,14]	 40%-58% + 80%-87% + 94%-100% + 45%-83% + [3,5,6,14]
Other Immunohistochemical Markers	Rarely, + for pancreatic polypeptide, histamine, gastrin, vasoactive intestinal peptide (VIP), or adrenocorticotropic hormone (ACTH)	Prostatic acid phosphatase + in 20%-40%[13,14]	Prostatic acid phosphatase + in 20%-82%[3,5,6,14]
Carcinoid syndrome	Rare	5%-39%[6,7]	Rare

B. Site-Specific Features

Rectal neuroendocrine tumors are common and constitute approximately one-quarter of GI neuroendocrine tumors.[3] They are usually small, solitary, and clinically silent, most commonly occurring 4 to 13 cm from the anal verge. Mitotically inactive rectal neuroendocrine tumors or those smaller than 2.0 cm are almost always clinically benign.[4] Metastases and carcinoid syndrome are very rare. Large intestinal neuroendocrine tumors outside the ileocecal region and rectum are extremely rare; most reported tumors have been large (average 5.0 cm) and high grade, with a poor prognosis. Many low-grade neuroendocrine tumors involving the ileocecal valve represent tumors arising in the terminal ileum, rather than in the large bowel.

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. Rectal carcinoids smaller than 1.0 cm are almost always clinically benign, and local excision is generally

considered sufficient for tumors 1.0 cm or smaller, as well as many tumors between 1.0 and 2.0 cm. More extensive procedures (eg, right hemicolectomy and abdominoperineal resection) are usually reserved for patients with tumors larger than 2.0 cm.

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.[5-8] 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.

All colonic neuroendocrine tumors are considered potentially malignant; none are classified as benign or low-malignant-potential neuroendocrine tumors. Most are large, bulky, high-grade, highly invasive tumors that are metastatic at presentation. Two-thirds arise within the cecum or right colon.

Rectal neuroendocrine tumors, in contrast to colonic neuroendocrine tumors, are relatively common and generally behave in a benign fashion.

Histologic Classification of Rectal Neuroendocrine Tumors, Adapted from WHO[6]

Well-Differentiated Neuroendocrine Tumor
Benign: Nonfunctioning cytologically bland tumors confined to mucosa or submucosa, with no angioinvasion, and measuring not more than 2 cm in greatest dimension.
Uncertain malignant potential: Nonfunctioning cytologically bland tumors confined to mucosa or submucosa, with angioinvasion, less than 2 cm in size.

Well-differentiated Neuroendocrine Carcinoma
Nonfunctioning tumors that are >2 cm, or invade the muscularis propria or beyond, or are metastatic. Functional tumors associated with carcinoid syndrome are included in this category.

Histologic Patterns
Although specific histologic patterns in well-differentiated neuroendocrine neoplasms, such as trabecular, insular, and glandular, roughly correlate with tumor location,[4] 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, a grading system based on mitotic activity has been proposed for NETs of the ileum, appendix, colon, and rectum[9]:

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

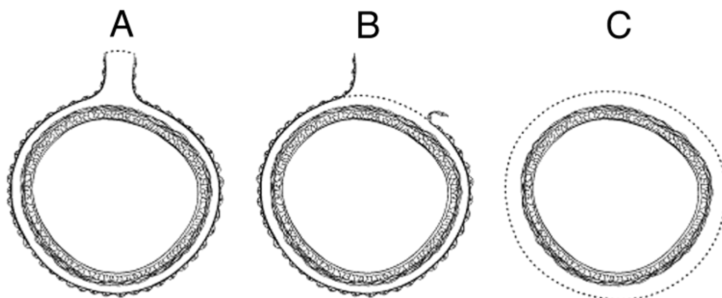
[#] Mitotic count should be based upon counting 50 high-power (40x objective) fields in the area of highest mitotic activity and reported as number of mitoses per 10 HPF.

[##] Ki-67 index is reported as percent 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[10]; 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 checklist for carcinomas of the colon and rectum[1] should be used for poorly differentiated neuroendocrine carcinomas arising in these sites).

F. Circumferential (Radial or Mesenteric) Margin
In addition to addressing the proximal and distal margins, assessment of the circumferential (radial) margin is necessary for any segment of gastrointestinal tract either unencased (Figure, C) or incompletely encased by peritoneum (Figure, B). The circumferential margin represents the adventitial soft-tissue margin closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect, respectively. The distance between the tumor and circumferential (radial) margin should be reported. The circumferential (radial) margin is considered negative if the tumor is more than 1 mm from the inked nonperitonealized surface but should be recorded as positive if the tumor is located 1 mm or less from the nonperitonealized surface. This assessment includes tumor within a lymph node as well as direct tumor extension, but if circumferential (radial) margin positivity is based solely on intranodal tumor, this should be so stated.

The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum (eg, transverse colon) (Figure, A). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface.



A, Mesenteric margin in viscus completely encased by peritoneum (dotted line). B, Circumferential (radial) margin (dotted line) in viscus incompletely encased by peritoneum. C, Circumferential (radial) margin (dotted line) in viscus completely unencased by peritoneum.
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G. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system for neuroendocrine tumors of the colon and rectum 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 regional lymph nodes of the colon and rectum are as follows:
Cecum: Pericolic, anterior cecal, posterior cecal, ileocolic, right colic
Ascending colon: Pericolic, ileocolic, right colic, middle colic
Hepatic flexure: Pericolic, middle colic, right colic
Transverse colon: Pericolic, middle colic
Splenic flexure: Pericolic, middle colic, left colic, inferior mesenteric
Descending colon: Pericolic, left colic, inferior mesenteric, sigmoid

Sigmoid colon: Pericolic, inferior mesenteric, superior rectal (hemorrhoidal), sigmoidal, sigmoid mesenteric
Rectosigmoid: Pericolic, perirectal, left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal (hemorrhoidal), middle rectal (hemorrhoidal)
Rectum: Perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory (Gerota's), internal iliac, superior rectal (hemorrhoidal), middle rectal (hemorrhoidal), inferior rectal (hemorrhoidal)

TNM Anatomic Stage/Prognostic Groupings

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.[7] Because of their relative sensitivity and specificity, chromogranin A and synaptophysin are recommended. It should be noted that hindgut neuroendocrine tumors often do not express appreciable amounts of chromogranin A. Rectal neuroendocrine tumors express prostatic acid phosphatase, a potential diagnostic pitfall for tumors arising in male patients.[12]

Immunohistochemistry for Ki-67 may be useful in establishing tumor grade (Note E) and prognosis[12] but is not currently considered standard of care.[7]

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
Coagulative tumor necrosis, usually punctate, may indicate more aggressive behavior[10] and should be reported.

References
1. Washington MK, Berlin J, Branton PA, et al. Protocol for the examination of specimens from patients with primary carcinomas of the colon and rectum. *Arch Pathol Lab Med.* 2008;132(7):1182-1193.
2. Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol.* 2005;89(3):151-160.
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003;97(4):934-959.
4. Soga J. Carcinoids of the colon and ileocecal region: a statistical evaluation of 363 cases collected from the literature. *J Exp Clin Cancer Res.* 1998;17(2):139-148.

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. Solcia E, Kloppel G, Sobin LH, et al. Histological typing of endocrine tumours. In: Solcia E, Kloppel G, Sobin LH, eds. *World Health Organization International Histological Classification of Tumours.* 2nd ed. New York, NY: Springer; 2000. *World Health Organization International Histological Classification of Tumours.*
7. Williams GT. Endocrine tumours of the gastrointestinal tract: selected topics. *Histopathology.* 2007;50(1):30-41.
8. 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.
9. Rindi G, Kloppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2007;451(4):757-762.
10. 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.
11. Edge SB, Byrd DR, Carducci MA, Compton CC. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
12. Sobin LH, Hjermstad BM, Sesterhenn IA, Helwig EB. Prostatic acid phosphatases activity in carcinoid tumors. *Cancer.* 1986;58(1):136-138.
13. Kimura N, Sasano N. Prostate-specific acid phosphatase in carcinoid tumors. *Virchows Arch A Pathol Anat Histopathol.* 1986;410(3):247-251.
14. 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.