COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Carcinoma of the Appendix

Protocol applies to all carcinomas arising in the vermiform appendix, including goblet cell carcinoid tumors. Other carcinoid tumors (well-differentiated neuroendocrine tumors) are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2013

Procedures
- Excision (Appendectomy)
- Appendectomy with Segmental Resection (Right Hemicolectomy)

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CAP Appendix Protocol Revision History

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

Version: Appendix 3.3.0.0

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

Resection (Appendectomy With or Without Right Hemicolectomy)

Histologic Type
"Goblet cell" was changed to "Typical goblet cell" and "Adenocarcinoma ex goblet cell carcinoid" was added, as follows:

Histologic Type (Note C)
___ Adenocarcinoma
___ Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)
___ Signet-ring cell carcinoma (greater than 50% signet-ring cells)
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Typical goblet cell carcinoid
___ Adenocarcinoma ex goblet cell carcinoid
___ Other (specify): _____
___ Carcinoma, type cannot be determined (see Comment)

+ Additional Pathologic Findings
Deleted "Low-grade neuroendocrine tumor (carcinoid tumor)."

Explanatory Notes

C. Histologic Type
The following sentence was added:
The family of goblet cell carcinoid tumors have the potential to transform to an adenocarcinoma phenotype and the preferred terminology for these tumors are "typical goblet cell carcinoid" or "adenocarcinoma ex goblet cell carcinoid."[4]

D. Histologic Grade
Deleted "the WHO criteria for" from the last sentence of the first paragraph.

J. Additional Pathologic Findings
Added, "Incidental well-differentiated neuroendocrine tumors (typical carcinoid tumor) of any size should be reported using the CAP protocol for neuroendocrine tumors of the appendix."

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

APPENDIX: Resection (Appendectomy With or Without Right Hemicolectomy)

Select a single response unless otherwise indicated.

Specimen (Note A) (select all that apply)
___ Appendix
___ Cecum
___ Right colon
___ Terminal ileum
___ Other (specify): _____
___ Not specified

Procedure
___ Appendectomy
___ Appendectomy and right colectomy
___ Other (specify): _____

Specimen Integrity
___ Intact
___ Fragmented
    + Number of pieces in fragmented specimens: ___
___ Other (specify): _____

+ Specimen Size
+ Specify: ___ (length) x ___ x ___ cm

Tumor Site (select all that apply) (Note B)
___ Proximal half of appendix
    ___ Base of appendix involved by tumor
    ___ Base of appendix uninvolved by tumor
    ___ Involvement of base of appendix cannot be assessed
___ Distal half of appendix
___ Diffusely involving appendix
___ Appendix, not otherwise specified
___ Unknown
___ Other (specify): _____

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Histologic Type (Note C)

___ Adenocarcinoma
___ Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)
___ Signet-ring cell carcinoma (greater than 50% signet-ring cells)
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Typical goblet cell carcinoid
___ Adenocarcinoma ex goblet cell carcinoid
___ Other (specify): _____
___ Carcinoma, type cannot be determined (see Comment)

Histologic Grade (Note D)

___ Not applicable
___ GX: Cannot be assessed
___ Grade 1 (well differentiated)
___ Grade 2 (moderately differentiated)
___ Grade 3 (poorly differentiated)
___ Grade 4 (undifferentiated)

Microscopic Tumor Extension

___ Cannot be assessed
___ No evidence of primary tumor
___ Intraepithelial carcinoma (no invasion)
___ Intramucosal carcinoma (invasion of lamina propria)
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the subserosa or mesoappendix but does not extend to the serosal surface
___ 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) (Note E)

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

Proximal Margin

___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Adenoma not identified at proximal margin (for appendectomy specimens)
___ Adenoma present at proximal margin (for appendectomy specimens)
    Specify grade of dysplasia: _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Mesenteric Margin
___ Not applicable (appendectomy specimen)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest mesenteric margin: ___ mm *or* ___ cm
___ Involved by invasive carcinoma

Other Margin(s) (required only if applicable)
Specify margin(s): _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Lymph-Vascular Invasion (Note F)
___ Not identified
___ Present
___ Indeterminate

Satellite Peritumoral Nodules (tumor deposits) (Note G)
___ Not identified
___ Present
Specify number identified: ____
___ Cannot be determined

+ Perineural Invasion (Note H)
+ ___ Not identified
+ ___ Present
+ ___ Indeterminate

Pathologic Staging (pTNM) (Note I)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ: intraepithelial or invasion of lamina propria
___ pT1: Tumor invades submucosa
___ pT2: Tumor invades muscularis propria
___ pT3: Tumor invades through the muscularis propria into the subserosa or mesoappendix
___ pT4: Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant or directly invades other organs or structures
___ pT4a: Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant
___ pT4b: Tumor directly invades other organs or structures

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in 1 to 3 regional lymph nodes
___ pN2: Metastases in 4 or more 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
___ pM1a: Intraperitoneal metastasis beyond the right lower quadrant, including pseudomyxoma peritonei
___ pM1b: Nonperitoneal metastasis
+ Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply) (Note J)
+ ___ None identified
+ ___ Appendicitis
+ ___ Perforation, not at tumor
+ ___ Chronic ulcerative colitis
+ ___ Crohn disease
+ ___ Diverticulosis
+ ___ Other (specify): _____

+ Ancillary Studies (Note K)
+ Specify: _____
+ ___ Not performed

+ Clinical History(select all that apply) (Note L)
+ ____ Chronic ulcerative colitis
+ ____ Crohn disease
+ ____ Other (specify): _____
+ ____ Not known

+ Comment(s)

Explanatory Notes

A. Anatomic Site

The protocol applies to all carcinomas arising in the vermiform appendix.

Tumors located at the base of the appendix must be distinguished from cecal carcinomas extending into the appendix, a distinction based primarily on a careful gross examination of the specimen with determination of the location of the bulk of the tumor. Microscopic examination may reveal a precursor lesion, and its location may indicate the primary site of origin.

B. Tumor Location

Some authors have suggested that appendiceal tumors that are located in the base of the appendix may cause obstruction of the lumen early in their course,[1] resulting in acute appendicitis and their early recognition, and therefore tumors located at the base would be expected to have a better prognosis than tumors located either in the colon or distal appendix. However, others have found that the site of the tumor within the appendix has no bearing on survival.[2]

C. Histologic Type

For consistency in reporting, the histologic classification of appendiceal carcinomas proposed by the World Health Organization (WHO) is recommended and is shown below.[3] However, this protocol does not preclude the use of other systems of classification or histologic types. The family of goblet cell carcinoid tumors have the potential to transform to an adenocarcinoma phenotype and the preferred terminology for these tumors are "typical goblet cell carcinoid" or "adenocarcinoma ex goblet cell carcinoid."[4] The latter has also been designated as mixed adenoneuroendocrine carcinoma by WHO.

WHO Classification of Appendiceal Carcinoma

Adenocarcinoma
Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)#
Signet-ring cell carcinoma (greater than 50% signet-ring cells)##
High-grade neuroendocrine carcinoma
    Large cell neuroendocrine carcinoma
    Small cell neuroendocrine carcinoma
Undifferentiated carcinoma
Other (specify)

In many studies, appendiceal carcinomas are classified as "mucinous carcinomas" or "adenocarcinoma, colonic type." Some studies have shown that mucinous carcinomas in the appendix have a better prognosis than nonmucinous adenocarcinomas[5,6] and are less likely to demonstrate lymphatic or hematogenous spread.[5,7]

The distinction between a carcinoma that is cystic (ie, cystadenocarcinoma) and one that is not cystic has not been shown to be of biologic significance. Therefore, the prefix "cyst" is a descriptive term rather than a clinically significant characteristic of appendiceal carcinomas.

#For purposes of this protocol, only invasive mucinous carcinomas are considered here. Although the distinction between adenoma or cystadenoma and carcinoma may be difficult on cytologic grounds, mucinous tumors with either mural invasion or peritoneal spread qualify for the diagnosis of appendiceal mucinous carcinoma.[3] Widespread pseudomyxoma peritonei is generally due to a low-grade mucinous appendiceal carcinoma. Because the most critical prognostic factor in mucinous appendiceal neoplasms is the presence or absence of mucinous epithelial cells in extra-appendiceal mucin,[8,9] their presence or absence should be clearly noted in the surgical pathology report. Several

studies have documented that the degree of architectural and cytologic atypia of the mucinous epithelium in peritoneal mucin has prognostic significance.[9-11]

##By convention, signet-ring cell carcinomas are grade 3. It should be noted that some signet-ring cell carcinomas have areas that are nested and may have a component that morphologically resembles goblet cell carcinoid. Some authors have proposed that these tumors be classified as adenocarcinoma ex goblet cell carcinoid or mixed adenoneuroendocrine carcinoma and have suggested that some appendiceal signet-ring cell carcinomas may arise from goblet cell carcinoids.[4,12] In contrast to pure goblet cell carcinoids, mixed carcinoid-adenocarcinomas and signet-ring cell carcinomas behave aggressively. Goblet cell carcinoids have a less favorable prognosis than pure appendiceal carcinoids and should be staged using the TNM system for appendiceal carcinoma, whereas pure carcinoids (low-grade neuroendocrine tumors) of the appendix should be staged using the TNM system for appendiceal carcinoids (see Protocol for Examination of Specimens with Neuroendocrine Tumors of the Appendix).

D. Histologic Grade

A uniform grading system for appendiceal carcinomas has not been developed, and the few studies examining histologic grade as a prognostic factor in appendiceal carcinoma have used inconsistent grading systems. Although rigorous criteria for grading have not been applied, histologic grade has been shown to be a prognostic factor in several series of appendiceal carcinoma.[9,10,13,14] Therefore, histologic grade probably has prognostic significance and appears to be especially important in pseudomyxoma peritonei. For uniformity, 4 grades are suggested.[3]

Grade			Gland formation (intestinal type adenocarcinomas)
G1	Well-differentiated adenocarcinoma	Mucinous low grade	Tumor exhibits >95% gland formation
G2	Moderately differentiated adenocarcinoma	Mucinous high grade	Tumor exhibits 50% to 95% gland formation
G3	Poorly differentiated adenocarcinoma	Mucinous high grade; signet-ring cell carcinoma	Tumor exhibits 5% to 50% gland formation
G4	Undifferentiated carcinoma	High grade by convention	Tumor exhibits <5% gland formation

Low-grade appendiceal mucinous carcinomas demonstrate low-grade cytologic changes resembling those of adenomas and minimal architectural complexity, displaying a villiform or flat appearance or forming small papillary excrescences. These lesions penetrate into or through the appendiceal wall, usually with a broad pushing front, and pools of acellular mucin may be present in the wall. Abundant thick mucinous material containing few cells may be found on the peritoneal surface.

Invasive colonic-type adenocarcinomas are characterized by destructive invasion of the appendiceal wall, with associated desmoplasia. These adenocarcinomas are of moderate or high cellularity and display high-grade cytologic changes and complex architecture, such as cribriform glandular spaces and complex papillary structures.[15]

E. Margins

Margins in a simple appendectomy specimen include the proximal and, in some cases, radial margin. It is recommended that the proximal margin on a simple appendectomy specimen be taken en face in

order to evaluate the entire appendiceal mucosa and muscularis circumferentially. In the vast majority of cases, the appendix is entirely peritonealized, and the closest distance between the invasive carcinoma and the mesenteric resection margin represents the radial margin and should be measured. Even retrocecal appendices are usually invested by peritoneum but have adhered to the posterior cecum, either because of inflammation or tumor. Exceptionally, a retrocecal appendix may be retroperitoneal, in which case the distance between the invasive carcinoma and the nonperitonealized resection margin is the "surgical clearance" and should be measured.

In right hemicolectomy specimens, the ileal and colonic margins are the proximal and distal margins, respectively. The distance between the tumor and the ileal and colonic margins should be measured, and these margins are considered to be grossly negative if they are greater than 5 cm from the tumor.

F. Vascular Invasion

The prognostic significance of lymphatic vessel (small vessel) and venous (large vessel) invasion has not been established in appendiceal carcinoma. However, given their significance in other human cancers (and colorectal carcinoma in particular) and the fact that they are routinely sought in cancer specimens, their presence or absence should be reported in all cases.

G. Satellite Peritumoral Nodules

Irregular tumor deposits (satellite peritumoral nodules) in periappendiceal fat are considered discontinuous extramural extension and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, perineural invasion. Tumor deposits with a smooth contour that can be identified as completely replaced lymph nodes should be counted as positive nodes. The number of irregular tumor deposits should be separately recorded.[16]

H. Perineural Invasion

The prognostic significance of perineural invasion has not been established in appendiceal carcinomas. However, given its prognostic significance in other human cancers, and in colorectal cancer in particular, its presence or absence should be recorded for appendiceal carcinomas.

I. TNM Anatomic Staging/Prognostic Groupings

A TNM staging system has been developed by the American Joint Committee on Cancer (AJCC) for the 7th edition of the *AJCC Cancer Staging Manual*[16]; formerly, the staging system for colorectal carcinomas was applied to appendiceal cancers. This system also incorporates tumor grade to subclassify stage IV tumors.

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 after 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 before 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.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through muscularis propria into subserosa or into mesoappendix
T4 Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant and/or directly invades other organs or structures
T4a Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant
T4b Tumor directly invades other organs or structures

Regional Lymph Nodes (N)#

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastases in 4 or more regional lymph nodes**#**

The regional lymph nodes for the appendix include the anterior cecal, posterior cecal, ileocolic, and right colic lymph nodes.

The presence of lymph node metastasis is relatively rare in appendiceal carcinoma[13] but has been shown to be an adverse prognostic finding.[2] Among patients with high-stage disease (peritoneal spread of appendiceal carcinoma), lymph node status appears to have less impact on overall survival.[7,17] In a study of 501 patients with peritoneal dissemination of appendiceal carcinoma who received cytoreductive surgery and perioperative intraperitoneal chemotherapy, lymph node status did not make a significant difference in survival by either univariate or multivariate analysis.[7]

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis#
M1a Intraperitoneal metastasis beyond the right lower quadrant, including pseudomyxoma peritonei
M1b Nonperitoneal metastasis

#Seeding of peritoneum or abdominal organs is considered distant metastasis.

Stage Groupings

Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	
	T2	N0	M0	
Stage IIA	T3	N0	M0	
IIB	T4a	N0	M0	
IIC	T4b	N0	M0	
Stage IIIA	T1	N1	M0	
	T2	N1	M0	
IIIB	T3	N1	M0	
	T4	N1	M0	
Stage IVA	Any T	N0	M1a	G1
IVB	Any T	N0	M1a	G2, 3, 4
	Any T	N1	M1a	Any G

	Any T	N2	M1a	Any G
Stage IVC	Any T	Any N	M1b	Any G

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Lymph-Vascular Invasion
Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

J. Additional Pathologic Findings
Most studies have not found an association between appendiceal perforation and prognosis.[18,19] However, Didolkar and Fanous demonstrated that perforation at the site of the tumor was associated with a worse prognosis, whereas appendiceal perforation due to appendicitis away from the tumor was not.[2] Gonzalez-Moreno and Sugarbaker also found on univariate analysis that tumor perforation was an adverse prognostic finding.[7]

Diverticula are a common finding in appendices containing low-grade mucinous neoplasms and may represent a route of egress for mucin.[9]

Incidental well-differentiated neuroendocrine tumors (typical carcinoid tumor) of any size should be reported using the CAP protocol for neuroendocrine tumors of the appendix.

K. Ancillary Studies
A minority of appendiceal carcinomas show high levels of microsatellite instability, and testing is not currently recommended as standard of care for these tumors.[20] Loss of chromosome 18q has been reported in more than half of the appendiceal carcinomas tested, but the clinical significance of this finding is unknown.[21]

L. Clinical History
Predisposing factors for sporadic appendiceal carcinoma have not been identified. However, these tumors have been reported in the setting of inflammatory bowel disease, although causation has not been established.[22]

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