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 carcinoids. Low-grade neuroendocrine tumors (carcinoids) are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: January 2016

Procedures
• Excision (Appendectomy)
• Appendectomy with Segmental Resection (Right Hemicolecction)

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CAP Appendix Protocol Revision History

Version Code
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: Appendix 3.4.0.0

Summary of Changes
The following changes have been made since the October 2013 release.

The following data elements were modified:
- Tumor Size
- Histologic Type
- Microscopic Tumor Extension
- Margins
- Lymph-Vascular Invasion
- Perineural Invasion
- Distant Metastasis (changed to required only if confirmed pathologically)

The following data elements were deleted:
- Specimen Integrity
- Specimen Size
Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

**APPENDIX: Resection (Appendectomy With or Without Right Hemicolectomy)**

Select a single response unless otherwise indicated.

**Specimen** (select all that apply) (Note A)
- __ Appendix
- __ Cecum
- __ Right colon
- __ Terminal ileum
- __ Other (specify): ____________________________
- __ Not specified

**Procedure**
- __ Appendectomy
- __ Appendectomy and right colectomy
- __ Other (specify): ____________________________

**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 (explain): ____________________________

**Histologic Type** (select all that apply) (Note C)
- __ Adenocarcinoma
- __ Mucinous adenocarcinoma
- __ Low-grade appendiceal mucinous neoplasm
- __ High-grade appendiceal mucinous neoplasm
- __ Signet-ring cell carcinoma
- __ Goblet cell carcinoid
- __ Mixed adenoneuroendocrine carcinoma (mixed goblet cell carcinoid-adenocarcinoma or adenocarcinoma ex goblet cell carcinoid)
- __ High-grade neuroendocrine carcinoma
  - __ Large cell neuroendocrine carcinoma
  - __ Small cell neuroendocrine carcinoma
- __ Undifferentiated carcinoma
- __ Other (specify): ____________________________
- __ Carcinoma, type cannot be determined (explain): ____________________________

+ 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.
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
___ No invasion (high-grade dysplasia/intraepithelial carcinoma)
___ Tumor invades lamina propria or muscularis mucosa (intramucosal carcinoma)
___ 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
___ Involved by high-grade dysplasia
___ Uninvolved by low-grade appendiceal mucinous neoplasm
___ Involved by low-grade appendiceal mucinous neoplasm
___ Uninvolved by high-grade appendiceal mucinous neoplasm
___ Involved by high-grade appendiceal mucinous neoplasm

Mesenteric Margin (required only if applicable)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Involved by low-grade appendiceal mucinous neoplasm
___ Involved by low-grade appendiceal mucinous neoplasm
___ Involved by high-grade appendiceal mucinous neoplasm
___ Involved by high-grade appendiceal mucinous neoplasm

Other Margin(s) (required only if applicable)
Specify margin(s): __________________
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
Lymph-Vascular Invasion (select all that apply) (Note F)
____ Not identified
___ Present
   + ___ Small vessel lymph-vascular invasion
   + ___ Large vessel (venous) invasion
      + ___ Intramural
      + ___ Extramural
___ Cannot be determined

Tumor Deposits (Note G)
____ Not identified
___ Present (specify number of deposits): ___
___ Cannot be determined

Perineural Invasion (Note H)
+ ___ Not identified
+ ___ Present
+ ___ Cannot be determined

Pathologic Staging (pTNM) (Note I)

TNM Descriptors (required only if applicable) (select all that apply)
____ m (multiple primary tumors)
____ r (recurrent)
____ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ: 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): ______________________

+ 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.
Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM: Distinct 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, 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.

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. However, this protocol does not preclude the use of other systems of classification or histologic types. Goblet cell carcinoids can be associated with conventional adenocarcinoma or signet-ring cell carcinoma. The WHO recommends the term adenoneuroendocrine carcinoma for these tumors. Other terms that have been used are mixed goblet cell carcinoid-adenocarcinoma and adenocarcinoma ex goblet cell carcinoid.

WHO Classification of Appendiceal Carcinoma

Adenocarcinoma
Mucinous adenocarcinoma
Low-grade appendiceal mucinous neoplasm
High-grade appendiceal mucinous neoplasm
Signet-ring cell carcinoma
Goblet cell carcinoid
Mixed adenoneuroendocrine carcinoma (mixed goblet cell carcinoid-adenocarcinoma or adenocarcinoma ex goblet cell carcinoid)
Neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Undifferentiated carcinoma

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 and are less likely to demonstrate lymphatic or hematogenous spread.

The distinction between a carcinoma that is cystic 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.

This protocol is applicable to low-grade (or high-grade) appendiceal neoplasms and invasive carcinomas. Low-grade appendiceal mucinous neoplasm (LAMN) is considered a low-grade carcinoma. Adenomatous proliferation with an intact muscularis mucosa is considered an appendiceal adenoma. Tumors with obliteration of muscularis mucosa in which the adenomatous epithelium rests on fibrous tissue or if there is nondestructive mural or peritoneal involvement qualify for the diagnosis of LAMN. Tumors with destructive invasion and desmoplasia are classified as invasive adenocarcinoma. Both LAMN and invasive carcinomas should be staged as per this protocol. High-grade appendiceal neoplasms (HAMNs) are rare tumors that resemble LAMN in lacking destructive invasion but show high-grade cytologic features. This term is not part of the current WHO terminology.
Because the most critical prognostic factor in mucinous appendiceal neoplasms is the presence or absence of mucinous epithelial cells in extra-appendiceal mucin, 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.

By convention, signet-ring cell carcinomas are grade 3.

Goblet cell carcinoids (GCC) have a less favorable prognosis than pure appendiceal neuroendocrine tumors and should be staged using the TNM system for appendiceal carcinoma, whereas low-grade neuroendocrine tumors of the appendix should be staged using the TNM system for appendiceal neuroendocrine tumors (see Protocol for Examination of Specimens with Neuroendocrine Tumors of the Appendix). Some tumors show a combination of GCC and adenocarcinoma (conventional, mucinous, or signet-ring cell type). These mixed GCC-adenocarcinomas have been referred to as adenoneuroendocrine carcinoma in the WHO classification. The terms mixed goblet cell carcinoid-adenocarcinoma and adenocarcinoma ex goblet cell carcinoid have also been used for these tumors. The behavior of these mixed tumors is more aggressive compared to pure GCC.

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. Therefore, histologic grade probably has prognostic significance and appears to be especially important in pseudomyxoma peritonei. For uniformity, 4 grades are suggested.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histologic Grade</th>
<th>Gland formation (intestinal type adenocarcinomas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Well-differentiated adenocarcinoma</td>
<td>Mucinous low grade</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated adenocarcinoma</td>
<td>Mucinous high grade</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated adenocarcinoma</td>
<td>Mucinous high grade; signet-ring cell carcinoma</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated carcinoma</td>
<td>High grade by convention</td>
</tr>
</tbody>
</table>

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.

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 mesenteric resection margin represents the radial margin. The closest distance between the invasive carcinoma and this margin 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 nonperitonealized surface is the radial resection margin. The distance between the invasive carcinoma and this margin 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. Tumor Deposits**

Foci of tumor in the periappendiceal fat or mesoappendix away from the leading edge of the tumor, and showing no evidence of residual lymph node tissue or obvious vascular invasion, are considered as peritumoral deposits or satellite nodules. Such tumor deposits may represent a totally replaced lymph node or venous invasion with extravascular spread with no identifiable venous wall. If the vessel wall or its remnant is identifiable on hematoxylin-eosin, elastic, or any other stain, it should be classified as vascular (venous) invasion, and not as a tumor deposit. The number of tumor deposits should be separately recorded.

**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*; 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)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through muscularis propria into subserosa or into mesoappendix</td>
</tr>
</tbody>
</table>
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)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1 to 3 regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in 4 or more regional lymph nodes</td>
</tr>
</tbody>
</table>

*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 but has been shown to be an adverse prognostic finding. Among patients with high-stage disease (peritoneal spread of appendiceal carcinoma), lymph node status appears to have less impact on overall survival. 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.

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis*</td>
</tr>
<tr>
<td>M1a</td>
<td>Intraperitoneal metastasis beyond the right lower quadrant, including pseudomyxoma peritonei</td>
</tr>
<tr>
<td>M1b</td>
<td>Nonperitoneal metastasis</td>
</tr>
</tbody>
</table>

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

**Stage Groupings**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
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<td>T3</td>
<td>N1</td>
<td>M0</td>
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<td>T4</td>
<td>N1</td>
<td>M0</td>
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<td>Stage IVA</td>
<td>Any T</td>
<td>N0</td>
<td>M1a</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N0</td>
<td>M1a</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M1a</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N2</td>
<td>M1a</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RX</td>
<td>Presence of residual tumor cannot be assessed</td>
</tr>
<tr>
<td>R0</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
</tr>
</tbody>
</table>
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. 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. Gonzalez-Moreno and Sugarbaker also found on univariate analysis that tumor perforation was an adverse prognostic finding.

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

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. 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.

**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.

**References**


