

Appendix

Protocol applies to all invasive carcinomas of the appendix. Carcinoid tumors and related lesions, lymphomas, and sarcomas are excluded.

*Protocol web posting date: July 2006
Protocol effective date: April 2007
Based on AJCC/UICC TNM, 6th edition*

Procedures

- **Excision (Appendectomy)**
- **Appendectomy with Segmental Resection (Right hemicolectomy)**

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Summary of Changes to Checklist(s)

Protocol web posting date: July 2006

Protocol effective date: April 2007

This is a new protocol.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: July 2006

Protocol effective date: April 2007

Applies to invasive carcinomas only

Based on AJCC/UICC TNM, 6th edition

Appendix: Resection

Patient name:

Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type

Appendectomy

*Length: ___ cm

Appendectomy and right colectomy

*Length of appendix: ___ cm

*Length of colonic segment: ___ cm

Other (specify): _____

Tumor Site

Proximal half of appendix

Distal half of appendix

Diffusely involving appendix

Appendix, not otherwise specified

Tumor Size

Greatest dimension: ___ cm

*Additional dimensions: ___ x ___ cm

Cannot be determined (see Comment)

*Tumor Configuration

* Ulcerative

* Polypoid

* Infiltrative

Other (specify): _____

MICROSCOPIC**Histologic Type**

- Adenocarcinoma
 Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)
 Signet-ring cell carcinoma (greater than 50% signet-ring cells)
 Small cell carcinoma
 Undifferentiated carcinoma
 Other (specify): _____
 Carcinoma, type cannot be determined (see Comment)

Histologic Grade

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

Pathologic Staging (pTNM)Primary Tumor (pT)

- pTX: Cannot be assessed
 pT0: No evidence of primary tumor
 pTis: Intraepithelial carcinoma (no invasion)
 pTis: Intramucosal carcinoma (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 directly invades other organs or structures, and/or perforates visceral peritoneum

Regional Lymph Nodes (pN)

- pNX: Cannot be assessed
 pN0: No regional lymph node metastasis
 pN1: Regional lymph node metastasis
 Specify: Number examined: ____
 Number involved: ____

Distant Metastasis (pM)

- pMX: Cannot be assessed
 pM1: Distant metastasis
 *Specify site(s): _____

* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Margins (check all that apply)Proximal Margin

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

Distal Margin

- Not applicable (appendectomy specimen)
 Cannot be assessed
 Uninvolved by invasive carcinoma
 Involved by invasive carcinoma

Mesenteric Margin

- Cannot be assessed
 Uninvolved by invasive carcinoma
 Involved by invasive carcinoma
 Distance of invasive carcinoma from closest mesenteric margin: ___ mm OR ___ cm

***Circumferential (Radial) Margin**

- * Not applicable
 * Cannot be assessed
 * Uninvolved by invasive carcinoma
 * Involved by invasive carcinoma (tumor present 0-1 mm from CRM)

Lymphatic (Small Vessel) Invasion (L) (check all that apply)

- Absent
 Present
 * Intramural
 * Extramural
 Indeterminate

Venous (Large Vessel) Invasion (V) (check all that apply)

- Absent
 Present
 * Intramural
 * Extramural
 Indeterminate

***Perineural Invasion**

- * Absent
 * Present

***Additional Pathologic Findings (check all that apply)**

- * None identified
- * Appendicitis
- * Perforation, not at tumor
- * Chronic ulcerative colitis
- * Crohn disease
- * Diverticulosis
- * Carcinoid tumor
- * Other (specify): _____

***Comment(s)**

* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Background Documentation

Protocol web posting date: July 2006

Protocol effective date: April 2007

I. Appendectomy

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history
 - (1) previous colon adenoma(s)/carcinoma(s)
 - (2) familial adenomatous polyposis syndrome
 - (3) hereditary nonpolyposis colon cancer syndrome
 - (4) familial hamartomatous polyposis syndrome
 - (5) inflammatory bowel disease
 - b. Relevant findings (eg, colonoscopic and/or imaging studies)
 - c. Clinical diagnosis
 - d. Operative findings

B. Macroscopic Examination

1. Specimen
 - a. Organ(s)/tissue(s) included
 - b. Unfixed/fixed (specify fixative)
 - c. Dimensions
 - e. Results of intraoperative consultation
2. Tumor
 - a. Location (note **B**)
 - b. Dimensions (3 dimensions)
 - c. Tumor configuration (note **B**)
 - (1) ulcerative
 - (2) polypoid
 - (3) infiltrative
 - d. Descriptive characteristics (eg, color, consistency)
 - e. Distance from margins (note **C**)
 - (1) proximal
 - (2) radial margin (nonperitonealized margin closest to deepest tumor penetration)
 - f. Estimated depth of invasion (note **D**)
 - g. Appearance of serosa overlying tumor/perforation (note **E**)
3. Lesions in noncancerous appendix (eg, carcinoid, perforation away from tumor)
4. Regional lymph nodes (note **D**)
5. Nonregional lymph nodes (note **D**)
6. Metastasis to other organ(s) or structure(s) (note **D**)
7. Other tissue(s)/organ(s)
8. Tissues submitted for microscopic evaluation (note **D**)
 - a. Carcinoma, including:
 - (1) points of deepest penetration
 - (2) interface with adjacent uninvolved appendix
 - (3) visceral serosa overlying tumor

- b. Margins (note **C**)
 - (1) proximal
 - (2) radial margin (nonperitonealized margin closest to deepest tumor penetration)
- c. All lymph nodes (note **D**)
- d. Other lesions (eg, carcinoid)
- e. Frozen section tissue fragment(s) (unless saved for special studies)
- 9. Special studies (specify) (eg, histochemistry, immunohistochemistry, morphometry, molecular studies [specify type], cytogenetic analysis)

C. Microscopic Evaluation

- 1. Tumor
 - a. Histologic type (note **F**)
 - b. Histologic grade (note **G**)
 - c. Extent of invasion (note **D**)
 - d. Perforation (note **E**)
 - e. Venous/lymphatic vessel invasion (note **H**)
 - f. Extramural venous invasion (note **H**)
 - g. Perineural invasion (note **I**)
- 2. Margins (note **C**)
 - a. Proximal
 - b. Radial (specify distance of carcinoma from closest nonperitonealized margin)
- 3. Regional lymph nodes (note **D**)
 - a. Number examined
 - b. Number involved by tumor
- 4. Additional pathologic findings, if present
 - a. Carcinoid tumor
 - b. Appendicitis
 - c. Perforation away from tumor
 - d. Inflammatory bowel disease
 - e. Diverticula
 - f. Other (specify)
- 5. Distant metastasis, specify site (note **D**)
 - a. Specify grade in peritoneal deposits of mucinous carcinoma (note **J**)
- 6. Other tissue(s)/organ(s)
- 7. Results/status of special studies (specify)
- 8. Comments
 - a. Correlation with intraoperative consultation, as appropriate
 - b. Correlation with other specimens, as appropriate
 - c. Correlation with clinical information, as appropriate

II. Appendectomy and Right Hemicolectomy

A. Clinical Information

- 1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
- 2. Responsible physician(s)
- 3. Date of procedure
- 4. Other clinical information
 - a. Relevant history
 - (1) previous colon adenoma(s)/carcinoma(s)
 - (2) familial adenomatous polyposis syndrome

- (3) hereditary nonpolyposis colon cancer syndrome
 - (4) familial hamartomatous polyposis syndrome
 - (5) inflammatory bowel disease
 - b. Relevant findings (eg, colonoscopic and/or imaging studies)
 - c. Clinical diagnosis
 - d. Operative findings
- B. Macroscopic Examination**
- 1. Specimen
 - a. Organ(s)/tissue(s) included
 - b. Unfixed/fixed (specify fixative)
 - c. Number of pieces
 - d. Dimensions
 - e. Orientation of specimen, if indicated by surgeon
 - f. Results of intraoperative consultation
 - 2. Tumor
 - a. Location (note **B**)
 - b. Dimensions (3 dimensions)
 - c. Tumor configuration (note **B**)
 - (1) ulcerative
 - (2) polypoid
 - (3) infiltrative
 - d. Descriptive characteristics (eg, color, consistency)
 - e. Distance from margins (note **C**)
 - (1) proximal
 - (2) radial (nonperitonealized margin closest to deepest tumor penetration)
 - f. Estimated depth of invasion (note **D**)
 - g. Appearance of serosa overlying tumor/perforation (note **E**)
 - 3. Lesions in noncancerous appendix (eg, carcinoid tumor, diverticulosis, perforation away from tumor site)
 - 4. Regional lymph nodes (note **D**)
 - 5. Nonregional lymph nodes (note **D**)
 - 6. Metastasis to other organ(s) or structure(s) (note **D**)
 - 7. Colon uninvolved by tumor (eg, colitis, polyps)
 - 8. Other tissue(s)/organ(s)
 - 9. Tissues submitted for microscopic evaluation
 - a. Carcinoma, including:
 - (1) points of deepest penetration (at least 3 sections; optimally 5 sections)
 - (2) interface with adjacent appendix or colon
 - (3) visceral serosa overlying tumor
 - b. Margins (note **C**)
 - (1) proximal
 - (2) distal
 - (3) radial (nonperitonealized margin closest to deepest tumor penetration)
 - c. All lymph nodes (note **D**)
 - d. Other lesions (eg, carcinoid tumor/polyps/colitis)
 - e. Frozen section tissue fragment(s) (unless saved for special studies)
 - 10. Special studies (specify) (eg, histochemistry, immunohistochemistry, morphometry, molecular studies [specify type], cytogenetic analysis)
- C. Microscopic Evaluation**
- 1. Tumor
 - a. Histologic type (note **F**)
 - b. Histologic grade (note **G**)
 - c. Extent of invasion (note **D**)

- d. Perforation (note **E**)
- e. Venous/lymphatic vessel invasion (note **H**)
- f. Extramural venous invasion (note **H**)
- g. Perineural invasion (note **I**)
- 2. Margins (note **C**)
 - a. Proximal
 - b. Distal
 - c. Radial (specify distance of carcinoma from closest nonperitonealized margin)
- 3. Regional lymph nodes (note **D**)
 - a. Number examined
 - b. Number involved by tumor
- 4. Additional pathologic findings, if present
 - a. Carcinoid tumor
 - b. Appendicitis
 - c. Perforation away from tumor
 - d. Inflammatory bowel disease
 - e. Diverticula
 - f. Dysplasia
 - g. Adenoma(s)
 - h. Other types of polyps
 - i. Other (specify)
- 5. Distant metastasis, specify site (note **D**)
 - a. Specify grade in peritoneal deposits of mucinous carcinoma (note **J**)
- 6. Other tissue(s)/organ(s)
- 7. Results/status of special studies (specify)
- 8. Comments
 - a. Correlation with intraoperative consultation, as appropriate
 - b. Correlation with other specimens, as appropriate
 - c. Correlation with clinical information, as appropriate

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. This is 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 and Configuration

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.^{2,3} Gilhorne et al suggested that polypoid tumors may have a better prognosis than either ulcerative or infiltrative tumors due to early luminal obstruction.³

C. 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 should 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 non-peritonealized 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. Histologic confirmation of a grossly negative margin is not required.

D. Depth of invasion

At present, the American Joint Committee on Cancer (AJCC) has not established a TNM classification for appendiceal tumors. Most series of appendiceal carcinoma use Duke’s staging system or modified Astler-Coller staging system.

Several studies have demonstrated an association between depth of invasion and prognosis. Didolkar and Fanous found an association between full thickness invasion and prognosis in nonmucinous appendiceal adenocarcinoma.² Other investigators have found a direct correlation between Duke’s stage and prognosis.³⁻⁷

While outcome curves based on TNM colorectal data cannot be applied to the appendix, the AJCC recommends that adenocarcinomas of the vermiform appendix be classified according to the TNM staging system and recorded separately.⁸ Therefore, for consistency, the AJCC colorectal classification for depth invasion is recommended.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Intraepithelial carcinoma (no invasion)
Tis	Intramucosal carcinoma (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 directly invades other organs or structures, and/or perforates visceral peritoneum

Regional Lymph Nodes (N)[#]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis [#]

[#] 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 has been shown to be an adverse prognostic finding in patients with appendiceal carcinoma.^{2,3,7} Among patients with high stage disease (peritoneal spread of appendiceal carcinoma), lymph node status has been shown to be an adverse prognostic factor by some authors,⁹ but not others.¹⁰⁻¹² In a recent 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.¹¹

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
 M0 No distant metastasis
 M1 Distant metastasis[#]

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

E Perforation

Most studies have not found an association between appendiceal perforation and prognosis.^{5,6,13,14} 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.¹²

F. Histologic Types

For consistency in reporting, the histologic classification of appendiceal carcinomas proposed by the World Health Organization (WHO) is recommended and is shown below.¹⁵ However, this protocol does not preclude the use of other systems of classification or histologic types.

WHO Classification of Appendiceal Carcinoma

Adenocarcinoma
 Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)[#]
 Signet-ring cell carcinoma (greater than 50% signet-ring cells)^{##}
 Small cell carcinoma
 Undifferentiated carcinoma
 Other (specify)

In many studies, appendiceal carcinomas are classified as “mucinous carcinoma” or “colonic type.” Some studies have shown that mucinous carcinomas in the appendix have a better prognosis than nonmucinous adenocarcinomas^{2,14,16} and are less likely to demonstrate lymphatic or hematogenous spread.^{12,16,17}

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 some authorities consider ruptured mucinous cystadenomas with peritoneal spread (pseudomyxoma peritonei) as well-differentiated mucinous carcinoma, that classification is not universally accepted. For mucinous cystadenomas or villous adenomas, the pathology report should state the grade of dysplasia of the mucinous epithelium (low grade or high grade), the presence or absence of appendiceal rupture,

the presence or absence of peritoneal mucin, whether or not the peritoneal mucin contains mucinous epithelial cells, and if so, the degree of epithelial architectural and cytologic atypicity. The most critical prognostic factor in mucinous cystadenomas is the presence or absence of mucinous epithelial cells in extra-appendiceal mucin,^{18,19} and thus their presence or absence should be clearly noted in the report. Several studies have documented that the degree of architectural and cytologic atypia of the mucinous epithelium in peritoneal mucin has prognostic significance.¹⁹⁻²²

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 mixed carcinoid-adenocarcinoma.²³ Others have classified these tumors as microglandular carcinoma.⁷ Others have suggested that some appendiceal signet-ring cell carcinomas may arise from goblet cell carcinoids.¹⁸ In contrast to pure goblet cell carcinoids, mixed carcinoid-adenocarcinomas and signet-ring cell carcinomas behave aggressively.

G. 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. Rigorous criteria for grading have not been applied.

Histologic grade has been shown to be a prognostic factor in several series of appendiceal carcinoma.^{6,7,13} In the largest of these series, 94 appendiceal adenocarcinomas were stratified into 3 histologic grades, and survival correlated with grade.⁶ However, the histologic criteria for grading was not specified. In one study, the tumors were stratified into 4 grades, but the grades were collapsed into a 2-tiered system for purposes of prognostication. Patients with “well-differentiated” tumors (grades 1 and 2) fared better than those with “undifferentiated” tumors (grades 3 and 4).¹³ In one series, 24 appendiceal adenocarcinomas were classified into 2 types: “well-differentiated” tumors included those that resemble colonic adenocarcinoma, and “microglandular” carcinomas included signet-ring cell carcinomas and related tumors (including cases that might be considered mixed carcinoid-adenocarcinoma or goblet cell carcinoid).⁷ In this series, only 4 patients survived longer than 5 years, and 3 of those patients had a “well-differentiated” adenocarcinoma.

Therefore, histologic grade likely has prognostic significance. Although survival data in colorectal carcinoma has shown that a 2-tiered system predicts prognosis and is reproducible,²⁴ this data has not been reproduced in the appendix. Therefore, a 4-tiered system is prudent until additional data are available to address whether a simpler, 2-tiered system is adequate for appendiceal carcinomas. For uniformity, the World Health Organizations criteria for the 4 grades are suggested.²⁵

Grade 1 (well differentiated): Tumors exhibiting > 95% gland formation

Grade 2 (moderately differentiated): Tumors exhibiting 50% to 95% gland formation

Grade 3 (poorly differentiated): Tumors exhibiting 5% to 50% gland formation

Grade 4 (undifferentiated): Tumors exhibiting < 5% gland formation

H. Vascular Invasion

The prognostic significance of lymphatic vessel (small vessel) and venous (large vessel) invasion has not been studied 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. The following L and V systems of the AJCC/UICC may be used to record lymphatic and venous invasion, respectively:

Lymphatic Vessel Invasion (L)

LX	Lymphatic vessel invasion cannot be assessed
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

Venous Invasion (V)

VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

I. Perineural Invasion

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

J. Peritoneal Tumor Deposits

Among patients with peritoneal carcinomatosis from appendiceal mucinous carcinomas, the grade of the peritoneal tumor has been shown to be of prognostic significance.²⁶

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