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

Version: 4.2.0.0
Protocol Posting Date: June 2021
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2022
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

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

Procedure	Description
Excision	Includes specimens designated appendectomy with or without segmental resection (right hemicolectomy)
Tumor Type	**Description**
Carcinoma	Includes low grade mucinous neoplasm (LAMN), adenocarcinoma (including mucinous and signet ring cell variants), goblet cell adenocarcinoma, undifferentiated carcinoma, small cell and large cell (poorly differentiated) neuroendocrine carcinoma

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

Procedure
Biopsy
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

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

Tumor Type
Well-differentiated neuroendocrine tumors (consider the Appendix NET protocol)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Gastrointestinal stromal tumor (GIST) (consider the GIST protocol)
Non-GIST sarcoma (consider the Soft Tissue protocol)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
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Accreditation Requirements
This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

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

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

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

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

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

Summary of Changes

v 4.2.0.0

- General Reformatting
- Updated Tumor Extent
- Revised Margins Section
- Revised Lymph Nodes Section
- Added Distant Metastasis Section
- Removed pTX and pNX Staging Classification

Reporting Template

Protocol Posting Date: June 2021
Select a single response unless otherwise indicated.

CASE SUMMARY: (APPENDIX: Resection)
Standard(s): AJCC-UICC 8

SPECIMEN (Note A)

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

TUMOR

+Tumor Site (Note B) (select all that apply)
___ Proximal half of appendix
+Base of Appendix Involvement
___ Not identified
___ Present
___ Cannot be determined: _____
___ Distal half of appendix
___ Diffusely involving appendix
___ Appendix, not otherwise specified
___ Other (specify): _____

Histologic Type (Note C)
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Low-grade appendiceal mucinous neoplasm
___ High-grade appendiceal mucinous neoplasm
___ Signet-ring cell carcinoma
___ Goblet cell adenocarcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Mixed neuroendocrine-non-neuroendocrine neoplasm (Mixed adenoneuroendocrine carcinoma)
___ Medullary carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated carcinoma
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined (explain): _____
+Histologic Type Comment: _____

Histologic Grade (Note D)
___ G1, well differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____

___ GX, cannot be assessed: _____
___ Not applicable

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Tumor Deposits (Note E)
___ Not identified
___ Present
Number of Deposits
___ Specify number: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Cannot be determined: _____

Tumor Extent (select all that apply)
___ Tumor invades lamina propria or muscularis mucosa
___ Tumor invades submucosa
___ Acellular mucin invades muscularis propria
___ Tumor invades muscularis propria
___ Acellular mucin invades subserosa or mesoappendix but does not extend to serosal surface
___ Tumor invades through muscularis propria into subserosa or mesoappendix but does not extend to serosal surface
___ Acellular mucin invades visceral peritoneum (serosa)
___ Tumor invades visceral peritoneum (serosa)
___ Tumor directly invades adjacent organ(s) or structure(s) (specify): _____
___ Cannot be determined: _____
___ No evidence of primary tumor

Lymphovascular Invasion (Note F)
___ Not identified
___ Present
___ Cannot be determined: _____

+Perineural Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note H)

Margin Status for Invasive Carcinoma
___ All margins negative for invasive carcinoma
+Distance from Invasive Carcinoma to Closest Mesenteric Margin
Specify in Centimeters (cm)
___ Exact distance in cm: _____ cm

___ Greater than 1 cm
Specify in Millimeters (mm)
___ Exact distance in mm: _____ mm
___ Greater than 10 mm
Other
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable
___ Invasive carcinoma present at margin
Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Proximal: _____
___ Mesenteric: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for Non-Invasive Tumor and Mucin (select all that apply)
___ All margins negative for non-invasive tumor and mucin
___ High-grade dysplasia present at proximal margin: _____
___ Low-grade appendiceal mucinous neoplasm (AMN) present at margin
Margin(s) Involved by Low-grade AMN (select all that apply)
___ Proximal: _____
___ Mesenteric: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ High-grade appendiceal mucinous neoplasm (AMN) present at margin
Margin(s) Involved by High-grade AMN (select all that apply)
___ Proximal: _____
___ Mesenteric: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Acellular mucin present at margin
Margin(s) Involved by Acellular Mucin (select all that apply)
___ Proximal: _____
___ Mesenteric: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present

___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
For specimens containing acellular mucin without identifiable tumor cells, efforts should be made to obtain additional tissue for thorough histologic examination to evaluate for cellularity.
___ Not applicable
___ Non-regional lymph node(s): _____
___ Intraperitoneal acellular mucin without identifiable tumor cells in the disseminated peritoneal mucinous deposits: _____
___ Intraperitoneal metastasis only (including peritoneal mucinous deposits containing tumor cells): _____
___ Liver: _____
___ Lung: _____
___ Site(s) other than peritoneum (specify, if known): _____
___ Cannot be determined: _____

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

TNM Descriptors (select all that apply)
___ Not applicable
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
___ pTis (LAMN): Low-grade appendiceal mucinous neoplasm confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into the muscularis propria. (T1 and T2 are not

applicable to LAMN. Acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively.)
___ pT1: Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
___ pT2: Tumor invades the muscularis propria
___ pT3: Tumor invades through the muscularis propria into the subserosa or the mesoappendix
pT4: Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and / or directly invades adjacent organs or structures
___ pT4a: Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
 # The text in parentheses is not applicable to pT determination. A tumor grossly adherent to other organs or structures is classified as cT4b; however, if no tumor is identified on pathological examination of the adhesion, the T category assigned based on the depth of wall invasion observed on microscopic examination (typically pT1-3).
___ pT4b: Tumor directly invades (or adheres to#) adjacent organs or structures
___ pT4 (subcategory cannot be determined)

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
pN1: One to three regional lymph nodes are positive (tumor in lymph node measuring greater than or equal to 0.2 mm) or any number of tumor deposits is present, and all identifiable lymph nodes are negative
___ pN1a: One regional lymph node is positive
___ pN1b: Two or three regional lymph nodes are positive
___ pN1c: No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
___ pN1 (subcategory cannot be determined)
___ pN2: Four or more regional lymph nodes are positive

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
pM1: Distant metastasis
___ pM1a: Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
___ pM1b: Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
___ pM1c: Metastasis to sites other than peritoneum
___ pM1 (subcategory cannot be determined)

ADDITIONAL FINDINGS (Note J)

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

SPECIAL STUDIES (Note K)

+Ancillary Studies
___ Performed (specify): _____
___ Not performed

COMMENTS

Comment(s): _____

Explanatory Notes

A. Anatomic Site
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
Appendiceal tumors 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, with a resultant better prognosis compared to tumors located either in the colon or distal appendix.

C. Histologic Type
For consistency in reporting, the histologic classification of appendiceal carcinomas proposed by the World Health Organization (WHO) is recommended.[1] However, this protocol does not preclude the use of other systems of classification or histologic types.

This protocol is applicable to low-grade (or high-grade) appendiceal mucinous neoplasms as well as 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 tumors with nondestructive mural or peritoneal involvement qualify for the diagnosis of LAMN.[1] Tumors with destructive invasion and desmoplasia are classified as invasive adenocarcinoma. Both LAMN and invasive carcinomas should be staged as per this protocol.[1] If the histologic features qualify for LAMN, the histologic type in the tumor synoptic should be selected as LAMN even if there is peritoneal involvement. 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, but has been recommended in a recent consensus publication and has been included in the AJCC 8th edition.[2]

High grade appendiceal mucinous neoplasm is included in WHO 2019 (5th edition) but is not included in the AJCC 8th edition. For practical purposes, these could likely be incorporated into Adenocarcinoma NOS or Mucinous adenocarcinoma depending on a given patient's specific findings. Per the WHO 5th edition, "HAMN's are rare, and there are limited data regarding when they are confined to the appendix…. HAMN's that have disseminated to the peritoneal cavity are likely to behave like other mucinous tumours that have spread to the peritoneum."

Goblet cell adenocarcinoma (WHO 5th edition) has replaced goblet cell carcinoid and mixed goblet cell carcinoid/adenocarcinoma terms, which are still listed in AJCC 8th edition.[3,4]

Adenocarcinoma subtypes are included in the menu of diagnostic terms of AJCC 8th edition but are not included as independent diagnostic options in WHO 5th edition. 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.[5,6,7] One of the most critical prognostic factors in mucinous appendiceal neoplasms is the presence or absence of mucinous epithelial cells in extra-appendiceal mucin.[8,9,10,11] Hence the presence or absence of epithelial cells in mucin should be clearly noted in the surgical pathology report.

References
1. WHO Classification of Tumours Editorial Board. *Digestive system tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1).
2. Carr NJ, Cecil TD, Mohamed F, et al; Peritoneal Surface Oncology Group International. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: the results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol*. 2016;40(1):14-26.
3. Carr NJ, Sobin LH. Neuroendocrine tumors of the appendix. *Semin Diagn Pathol.* 2004;21(2):108-119.
4. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. *Am J Surg Pathol.* 2008;32(10):1429-1443.
5. Kabbani W, Houlihan PS, Luthra R, Hamilton SR, Rashid A. Mucinous and nonmucinous appendiceal adenocarcinomas: different clinicopathological features but similar genetic alterations. *Mod Pathol.* 2002;15(6):599-605.
6. McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY. Malignancies of the appendix: beyond case series reports. *Dis Colon Rectum*. 2005;48(12):2264-2271.
7. Gonzalez-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. *Br J Surg.* 2004;91(3):304-311.
8. Carr NJ, McCarthy WF, Sobin LH. Epithelial noncarcinoid tumors and tumor-like lesions of the appendix: a clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. Cancer. 1995;75:757-768.
9. Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. *Am J Surg Pathol.* 2003;27(8):1089-1103.
10. Yantiss RK, Shia J, Klimstra DS, Hahn HP, Odze RD, Misdraji J. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. *Am J Surg Pathol.* 2009;33(2):248-55.
11. Pai RK, Beck AH, Norton JA, Longacre TA. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. *Am J Surg Pathol.* 2009;33(10):1425-1439.

D. Histologic Grade

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.[1,2,3,4,5,6]

Nonmucinous tumors: These tumors are graded as well differentiated (G1, >95% gland formation), moderately differentiated (G2, 50-95% gland formation), and poorly differentiated (G3, <50% gland formation).

Appendiceal mucinous tumors have been graded as low or high grade based on cytologic features in the WHO 2010 scheme. For mucinous tumors involving the peritoneum, the AJCC recommends a 3-tier grading scheme as the prognostic significance of three groups has been shown in multiple studies for mucinous tumors involving the peritoneum. The proposed 3-tier grading scheme by AJCC is modified from Davison et al[5] and is based on cytologic features, tumor cellularity, and presence of signet-ring component. The grade of the appendiceal and peritoneal tumors is concordant in most instances, but some cases may show discordant grades in the appendix and peritoneum. In case of discordance of grades, the highest grade should be assigned to the tumor for staging (see note I).

Table: Three-Tier Grading Scheme Recommended by AJCC[7] (based on scheme proposed by Davison et el[5])

Well-differentiated (G1)	Low-grade cytologic atypia, no signet-ring cells. Tumors involving peritoneum show acellular mucin or low cellularity (typically <20%) and lack infiltrative invasion of the peritoneum or other organs are considered G1.
Moderately differentiated (G2)	Mix of low- and high-grade cytologic atypia or diffuse high-grade cytologic atypia, no signet-ring cells.
Poorly differentiated (G3)	High-grade cytologic atypia, usually with signet-ring cell component.

In the appendix, G1 tumors usually lack typical features of invasion and are classified as LAMNs. In the peritoneum, G1 tumors may involve peritoneal surface or organs with a pushing front without desmoplasia, and lack infiltrative invasion. Perineural invasion and lymphovascular invasion are not seen. G1 tumors with peritoneal involvement have been variously termed as LAMN with peritoneal involvement, low-grade mucinous carcinoma peritonei and disseminated peritoneal adenomucinosis (DPAM). In cancer protocols, the histologic type of these tumors is best recorded as LAMN. G2 mucinous tumors in the appendix may correspond to high-grade mucinous appendiceal neoplasms (HAMN) or mucinous adenocarcinomas with destructive invasion and associated desmoplasia. The latter often shows complex architecture, such as cribriform glandular spaces and complex papillary structures. G3 mucinous tumors in the appendix are high-grade, invasive tumors that usually have a signet ring cell component. With extra-appendiceal spread, G2 and G3 tumors can show invasion (with desmoplasia) into the peritoneum or other organs, perineural invasion, and lymphovascular invasion. Most mucinous G2 and G3 tumors with peritoneal involvement would correspond to terms such as high-grade mucinous carcinoma peritonei and peritoneal mucinous adenocarcinoma.

By convention, signet-ring cell carcinomas are grade 3. The above grading schemes are not applicable to poorly differentiated neuroendocrine carcinoma and goblet cell carcinoid. Tumors with no differentiation (undifferentiated carcinomas) are categorized as grade 4 in the WHO 2010 classification, but G4 is not included in the AJCC 8th edition.

References

1. Sugarbaker PH, Chang D, Koslowe P. Prognostic features for peritoneal carcinomatosis in colorectal and appendiceal cancer patients when treated by cytoreductive surgery and intraperitoneal chemotherapy. *Cancer Treat Res.* 1996;81:89-104.
2. Ronnett BM, Yan H, Kurman RJ, Shmookler BM, Lee W, Sugarbaker PH. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. *Cancer.* 2001;92:85-91.
3. Bradley RF, Stewart JH, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. *Am J Surg Pathol.* 2006;30(5):551-559.
4. Shetty S, Natarajan B, Thomas P, Govindarajan V, Sharma P, Loggie B. Proposed classification of pseudomyxoma peritonei: influence of signet ring cells on survival. *Am Surg.* 2013;79(11):1171-1176.
5. Davison JM, Choudry HA, Pingpank JF, et al. Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. *Mod Pathol.* 2014;27(11):1521-1539.

6. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: Analysis of the National Cancer Data Base. *Cancer.* 2016;122(2):213-221.
7. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

E. Tumor Deposits

A tumor focus in the periappendiceal fat or mesoappendix, but without identifiable lymph node tissue or vascular structure, is considered a tumor deposit. If the vessel wall or its remnant is identified (H&E, elastic, or any other stain), it should be classified as vascular (venous) invasion, and not as tumor deposit. Similarly, a tumor focus is present in or around a large nerve, should be classified as perineural invasion and not as tumor deposit. Size and shape of the tumor focus are not relevant for classification as a tumor deposit. The presence of tumor deposits in the absence of any regional node involvement is categorized as N1c, irrespective of T category. The significance of tumor deposits has not been specifically examined in appendiceal tumors. In view of the established prognostic significance of tumor deposits in colorectal cancer, this feature has been adopted into the AJCC staging scheme for the appendix.[1]

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

F. Lymph-Vascular Invasion

Lymph-vascular invasion (LVI) includes small vessel (lymphatic or vascular) invasion and large vessel (venous) invasion. The prognostic significance of lymph-vascular invasion has not been widely studied in appendiceal carcinoma. However, given their significance in colorectal carcinoma, this feature should be reported in all cases.

G. Perineural Invasion

The prognostic significance of perineural invasion has not been widely studied in appendiceal carcinomas. Based on limited studies[1] and its prognostic significance in colorectal cancer, its presence or absence should be recorded for appendiceal carcinomas.

References

1. Davison JM, Choudry HA, Pingpank JF, et al. Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. *Mod Pathol.* 2014;27(11):1521-1539.

H. 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.

I. Pathologic Stage Classification

A revised TNM staging system has been developed by the American Joint Committee on Cancer (AJCC) for the 8th edition of the *AJCC Cancer Staging Manual.*[1] 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.

T Category Considerations

When confined to muscularis propria, LAMN is classified as Tis (LAMN) as there is no significant risk of extra- appendiceal spread and designated as T3 or T4a if it extends beyond muscularis propria. Tumors (including acellular mucin) that involve the serosal surface (visceral peritoneum) or directly invade adjacent organs or structures are assigned to the T4 category. T4a tumors are characterized by localized involvement of the serosal surface (visceral peritoneum) in the area of the primary tumor by acellular mucin or cellular tumor. Serosal involvement of the appendix by acellular mucin may demonstrate an excellent outcome with only localized surgical resection.[2,3] In view of the small risk of recurrence, this localized involvement is categorized as T4a along with tumors with cellular mucinous involvement of appendiceal serosa. Tumors with perforation in which tumor cells or acellular/cellular mucin is continuous with the serosal surface through inflammation also are considered T4a. Acellular mucin involving the serosal surface is considered as T4a, due to a small risk of peritoneal recurrence. In some instances, acellular mucin may be seen on the serosal surface due to "carryover" related to specimen handling or sectioning artifact. In these instances, mucin dissection into the stroma and tissue reaction such as inflammation, mesothelial hyperplasia and neovascularization can help in this distinction.

Tumors that directly invade other organs or structures are categorized as T4b. However, luminal or mural spread into adjacent parts of the bowel (e.g., appendiceal tumor extending into the cecum through the lumen or wall) is not considered T4b and should be categorized by the deepest area of invasion. Direct invasion of other segments of the colorectum via the serosa (e.g., invasion of adherent ileum) is considered T4b. A tumor grossly adherent to other organs or structures is classified as cT4b; however, if

no tumor is identified on pathological examination of the adhesion, the T category is assigned based on the depth of wall invasion observed on microscopic examination (typically pT1–3).

N Category Considerations

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[4] but is an adverse prognostic finding.[5] Among patients with high-stage disease (peritoneal spread of appendiceal carcinoma), lymph node status appears to have less impact on overall survival.[6,7]

M Category Considerations

Seeding of peritoneum or abdominal organs is considered distant metastasis. Extensive sampling should be performed before using the designation of M1a. Peritoneal mucinous deposits containing tumor cells should be staged as M1b and are grouped based on tumor grade as stage IVA (mucinous G1 tumors) or stage IVB (nonmucinous G1 and all G2/G3/G4 tumors). The highest grade is used in case if there is a discordance in tumor between the appendix and peritoneum. Peritoneal implants involving abdominopelvic organs, such as the serosa of the small or large bowel and the surfaces of the ovary, spleen, or liver, should be classified as M1b, even if the implants demonstrate infiltration of underlying tissue. M1c designation is used for metastasis to nonperitoneal sites.

References

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J. Additional Findings

Appendiceal perforation may be an adverse prognostic factor, but its adverse significance as an independent prognostic is not well established.[1,2,3]

Diverticula are a common finding in the appendix and may represent a route of egress for mucin in cases of LAMN.[4] Ruptured diverticula can show extraappendiceal mucin with or without epithelium and should not be mistaken for LAMN.[5]

Appendiceal adenocarcinomas have been reported in the setting of inflammatory bowel disease, although causation has not been established.[6]

Well-differentiated neuroendocrine tumors (typical carcinoid tumor) of any size should be reported using the CAP protocol for neuroendocrine tumors of the appendix.[7]

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K. Ancillary Studies

A minority of appendiceal carcinomas show high levels of microsatellite instability, but MSI testing is not currently recommended as standard of care for these tumors.[1,2]

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