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

Version: 5.0.0.0
Protocol Posting Date: June 2022
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2023
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 (cecectomy or 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, mixed adenocarcinoma and neurendocrine 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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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 5.0.0.0

- AJCC 9th Version Updates

Reporting Template

Protocol Posting Date: June 2022
Select a single response unless otherwise indicated.

CASE SUMMARY: (APPENDIX: Resection)
Standard(s): AJCC-UICC 9

SPECIMEN (Note A)

Procedure
___ Appendectomy
 # Right colectomy or cecectomy often includes appendectomy but sometimes follows appendectomy and may need staging.
___ Right colectomy#
___ Cecectomy#
___ 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
___ Neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Mixed neuroendocrine-non-neuroendocrine neoplasm
___ Medullary carcinoma
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated carcinoma
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined (explain): _____
+Histologic Type Comment: _____

Histologic Grade# (Note D)
 # The grade of the appendiceal and peritoneal tumors is concordant in most instances but can be discordant in some cases. In case of discordance of grades, the final grade should be assigned based on the peritoneal metastasis. (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 (including LAMN and HAMN)# (select all that apply)

 # Presence of acellular mucin is not considered a positive margin in the context of LAMN or HAMN but should be recorded in a comment or note. (Note H)

___ All margins negative for non-invasive tumor

___ Low-grade dysplasia present at proximal margin: _____

___ High-grade dysplasia present at proximal margin: _____

___ Low-grade appendiceal mucinous neoplasm present at margin

Margin(s) Involved by Low-grade Appendiceal Mucinous Neoplasm (select all that apply)

___ Proximal: _____

___ Mesenteric: _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

___ High-grade appendiceal mucinous neoplasm present at margin

Margin(s) Involved by High-grade Appendiceal Mucinous Neoplasm (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): _____
 # Involvement of organs such as ovary, fallopian tube or spleen underlying involved peritoneum is still considered intraperitoneal metastasis. Involvement of lung or hepatic parenchyma distinct from peritoneal involvement is considered extraperitoneal distant metastasis.
___ Ovary#: _____
___ Fallopian tube#: _____
___ Spleen#: _____
___ Other intraperitoneal metastasis, including peritoneal mucinous deposits containing tumor cells (specify): _____
___ Liver: _____
___ Lung: _____
___ Site(s) other than peritoneum (specify, if known): _____

___ Cannot be determined: _____

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 9th Version) (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 is applicable only to LAMN. High-grade appendiceal mucinous neoplasms (HAMN) are staged similar to mucinous adenocarcinoma, even though robust data on HAMN are lacking.

___ pTis (LAMN): Low-grade appendiceal mucinous neoplasm confined to 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 is 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 tumor involvement of regional lymph node(s)

pN1: Tumor involvement of one to three regional lymph nodes (tumor in lymph node measuring greater than or equal to 0.2 mm) or any number of tumor deposits is present with no tumor involvement in all identifiable lymph nodes

___ pN1a: Tumor involvement of one regional lymph node
___ pN1b: Tumor involvement of two or three regional lymph nodes
___ pN1c: No tumor involvement of regional lymph nodes, but there are tumor deposits in the subserosa or mesentery
___ pN1 (subcategory cannot be determined)
___ pN2: Tumor involvement of four or more regional lymph nodes

pM Category (required only if confirmed pathologically)#

 # 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 - pM cannot be determined from the submitted specimen(s)

pM1: Microscopic confirmation of 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: Microscopic confirmation of 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

___ Sessile serrated lesion / adenoma / polyp

___ 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. Adenomatous proliferation with an intact muscularis mucosae is considered an appendiceal adenoma. Tumors with obliteration of muscularis mucosa in which the neoplastic epithelium rests on fibrous tissue or tumors with nondestructive mural or peritoneal involvement qualify for the diagnosis of LAMN.[2] Low-grade appendiceal mucinous neoplasm (LAMN) is considered a low-grade carcinoma. Tumors with destructive invasion and desmoplasia are classified as invasive adenocarcinoma. Both LAMN and invasive carcinomas should be staged as per this protocol.[2] If the histologic features of the appendiceal primary qualify for LAMN, the histologic type in the tumor synoptic should be selected as LAMN even if there is peritoneal involvement.

High-grade appendiceal mucinous neoplasms (HAMNs) are rare tumors that resemble LAMN in lacking destructive invasion but show high-grade cytologic features.[3] This is now included in WHO 2019[1] and also in the AJCC 9th edition.[2] HAMNs are rare, and there are limited data regarding their prognosis when they are confined to the appendix. As per WHO[1] and AJCC[2], they are staged similarly to mucinous adenocarcinomas. 'HAMNs that have disseminated to the peritoneal cavity are likely to behave like other mucinous tumors that have spread to the peritoneum.'[1]

Goblet cell adenocarcinoma[1,2] has replaced goblet cell carcinoid and mixed goblet cell carcinoid/adenocarcinoma terms.[4,5]

Adenocarcinoma subtypes are included in the menu of diagnostic terms of AJCC 9th 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.[6,7,8]

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. Forthcoming AJCC Version 9 Appendix Cancer Staging System. Copyright 2022 American College of Surgeons.
3. 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.
4. Carr NJ, Sobin LH. Neuroendocrine tumors of the appendix. *Semin Diagn Pathol.* 2004;21(2):108-119.
5. 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.
6. 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.
7. 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.
8. 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.

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 2019 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 a signet-ring component. The grade of the appendiceal and peritoneal tumors is concordant in most instances, but some cases this can be discordant. In case of discordance of grades, while the grade of appendiceal tumor and the peritoneal tumor is recorded independently, the final grade of the tumor for staging is assigned based on the peritoneal metastasis (see note I).

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

Appendiceal mucinous neoplasms with only pushing borders are represented by LAMN and HAMN, which represent G1 and G2 tumors respectively. In cancer protocols, the histologic type and grade of the primary appendiceal neoplasm (LAMN or HAMN) and peritoneal metastasis should be recorded independent of each other. G1 tumors are typically represented by LAMN with or without peritoneal involvement. G2 mucinous tumors in the appendix are represented by HAMN with or without peritoneal involvement or mucinous adenocarcinomas with destructive invasion and associated desmoplasia. The G2 mucinous tumors often show 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 (>10%). With extra-appendiceal spread, G2 tumors can show invasion (with desmoplasia) in the peritoneum or a pattern of small mucin pools with numerous strips, buds, or tumor clusters. There may be perineural invasion and lymphovascular invasion. Most mucinous G2 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, and these can be either pure signet ring cell adenocarcinoma or high-grade goblet cell adenocarcinoma, which can be difficult to distinguish in some cases. Peritoneal tumors are classified as G3 when they have a signet ring cell component. When making this assessment, “pseudosignet ring cells” (degenerate tumor cells that resemble signet ring cells floating in mucin) do not qualify as G3.

The above grading schemes are not applicable to poorly differentiated neuroendocrine carcinoma and goblet cell adenocarcinoma. Tumors with no differentiation (undifferentiated carcinomas) are categorized as grade 4 in the WHO 2010 classification, but G4 is not included in the AJCC 9th edition[7].

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. Forthcoming AJCC Version 9 Appendix Cancer Staging System. Copyright 2022 American College of Surgeons.

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. Tumor deposits are not relevant for LAMN or HAMN. 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. Forthcoming AJCC Version 9 Appendix Cancer Staging System. Copyright 2022 American College of Surgeons.

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.

For staging protocols, the presence of mucin pool with cells and LAMN/HAMN at the appendiceal margin should be recorded. The presence of acellular mucin pools at the margin has not adequately studied, and at present for clinical purposes it is not considered a positive margin (AJCC,9th ed)[1] (Yantiss 2009,

Arnason T, 2015)[2]. The presence of cellular mucin or LAMN at the margin does not predict recurrence and a conservative approach is recommended (Arnason T, 2015)[3].

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.

References

1. Forthcoming AJCC Version 9 Appendix Cancer Staging System. Copyright 2022 American College of Surgeons.
2. 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):248-255.
3. Arnason T, Kamionek M, Yang M, Yantiss RK, Misdraji J. Significance of proximal margin involvement in low-grade appendiceal mucinous neoplasms. *Arch Pathol Lab Med*.2015;139(4):518-521.

I. Pathologic Stage Classification

A revised TNM staging system has been developed by the American Joint Committee on Cancer (AJCC) for the 9 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 progression to pseudomyxoma peritonei, and only designated as T3 or T4a if the neoplastic epithelium or acellular mucin extend beyond the muscularis propria. On the other hand, HAMNs are staged similarly to mucinous adenocarcinomas. The invasion in LAMN and HAMN is of a pushing nature, with epithelium herniating or dissecting through the appendix wall, with or without mucin extrusion. Acellular mucin on

the serosal surface without a stromal reaction is likely to be the result of contamination of the specimen by handling during dissection, while acellular mucin on the serosal surface with mesothelial reaction, stromal fibrosis and/or neovascularization represents involvement of the serosa by LAMN/HAMN and is relevant for staging. 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\mucin are 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] For staging purposes presence of acellular mucin pools in the lymph nodes is not considered as metastasis (i.e. N0) (AJCC, 9th ed)[1]. 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. 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] Hence the presence or absence of epithelial cells in mucin should be clearly noted in the surgical pathology report. In the peritoneum, G1 tumors may involve peritoneal surfaces or organs with a pushing front without desmoplasia, and lack infiltrative invasion. Perineural invasion and lymphovascular invasion are usually not seen. 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). If the grade of the primary appendiceal tumor and the peritoneal tumor are discordant, both should be recorded in the case; however, the grade of the peritoneal tumor will drive prognosis. 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, such as frequently occurs with the ovary. M1c designation is used for metastasis to nonperitoneal sites, such as the lung.

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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 (MSI-H).[1,2] Although data regarding use of therapies directed at MSI-H appendiceal tumors is sparse, in view of implications for identifying Lynch syndrome and potential immunotherapy, MSI and/or DNA-MMR testing is considered appropriate for all invasive carcinomas (mucinous or non-mucinous).

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