APPENDICEAL ADENOCARCINOMA

GENERAL OVERVIEW

- Rare malignancy (~0.4% of gastrointestinal cancers); incidence is increasing, including among younger adults.
- Appendiceal adenocarcinoma is biologically distinct from CRC. Histology, grade, pattern of spread should drive management.
- Presentation is often acute appendicitis or an incidental finding after appendectomy.

Pathologic classification — confirm before treatment

Entity	Clinical relevance
LAMN	Low-grade cytology with pushing/non-infiltrative growth; may disseminate mucin/cells and cause pseudomyxoma peritonei (PMP).
HAMN	High-grade cytology but no infiltrative-type invasion. Rarer and biologically higher risk than LAMN; expert pathology review and careful assessment for perforation/extra-appendiceal disease are important.
Mucinous adenocarcinoma	Often KRAS/GNAS altered; grade and peritoneal disease biology are major determinants of treatment.
Non-mucinous adenocarcinoma	More CRC-like pattern of spread; nodal staging is important.
Goblet cell adenocarcinoma	Distinct aggressive entity; manage as appendiceal adenocarcinoma, not as a neuroendocrine tumor.
Signet-ring cell component	Adverse prognostic feature; expert pathology review is recommended.

Molecular profile / biomarkers

- KRAS is the most frequent driver; GNAS is enriched in mucinous tumors, whereas TP53 alterations are associated with higher-grade/aggressive biology.
- For advanced disease: test RAS/BRAF, MMR/MSI and HER2; broad NGS is preferred when available. Consider NTRK/RET fusions and POLE/POLD1 in appropriate cases.

UZA PRACTICE POINT

- Request expert GI pathology review when histology or grade is uncertain.
- Distinguish LAMN from HAMN and both from mucinous adenocarcinoma: LAMN = low-grade cytology; HAMN = high-grade cytology; adenocarcinoma requires infiltrative-type invasion.

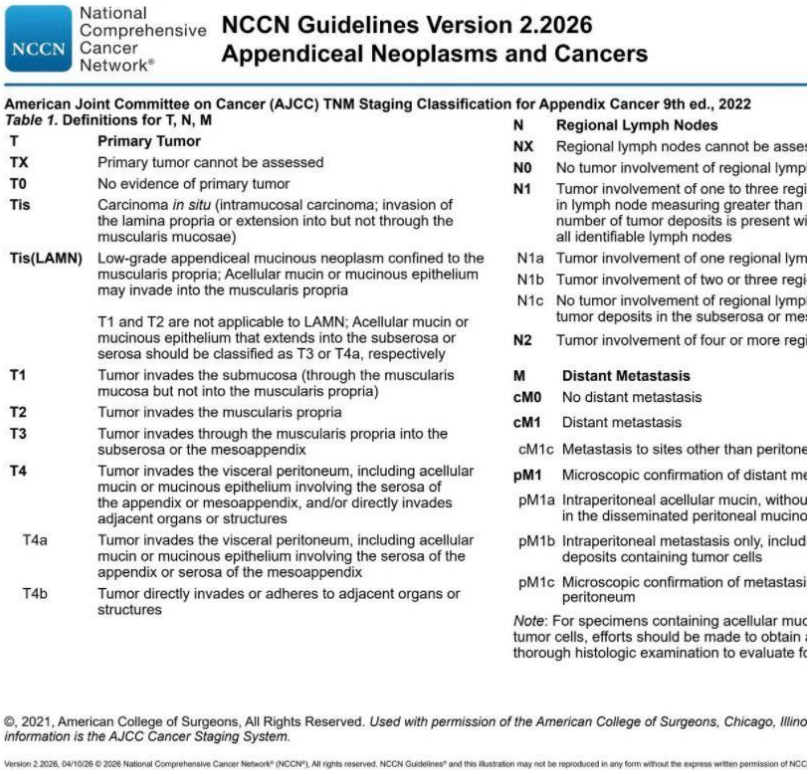
Initial work-up

Required	Selected / not routine
CT chest + abdomen/pelvis with IV contrast; colonoscopy.	MRI for indeterminate liver/peritoneal findings; diagnostic laparoscopy when occult peritoneal disease would alter resectability/planning.
Review operative/pathology report: perforation, margin, grade, LVI/PNI, nodes and extra-appendiceal mucin/cells.	FDG-PET/CT is not routinely indicated, particularly for low-grade mucinous disease.

APPENDICEAL ADENOCARCINOMA

STAGING AND LOCALIZED DISEASE

AJCC 9th edition — appendix carcinoma



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Appendiceal Neoplasms and Cancers

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Appendix Cancer 9th ed., 2022
***Table 1.* Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(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
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4	Tumor invades the visceral peritoneum, including acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Tumor invades the visceral peritoneum, including acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be asse
N0	No tumor involvement of regional lymp
N1	Tumor involvement of one to three regi in lymph node measuring greater than number of tumor deposits is present wi all identifiable lymph nodes
N1a	Tumor involvement of one regional lym
N1b	Tumor involvement of two or three regi
N1c	No tumor involvement of regional lymp tumor deposits in the subserosa or me
N2	Tumor involvement of four or more regi

M	Distant Metastasis
cM0	No distant metastasis
cM1	Distant metastasis
cM1c	Metastasis to sites other than peritone
pM1	Microscopic confirmation of distant me
pM1a	Intraperitoneal acellular mucin, withou in the disseminated peritoneal mucino
pM1b	Intraperitoneal metastasis only, includ deposits containing tumor cells
pM1c	Microscopic confirmation of metastasi peritoneum

Note: For specimens containing acellular muc tumor cells, efforts should be made to obtain thorough histologic examination to evaluate fo

Localized disease — surgery

- LAMN confined to the appendix, completely excised and without perforation or extra-appendiceal mucin/cells: appendectomy is sufficient; additional colectomy is not indicated solely for LAMN.
- HAMN confined to the appendix and completely excised: appendectomy is generally sufficient, but because of high-grade cytology, expert pathology review, complete staging and closer surveillance/MDT discussion are appropriate; perforation or extra-appendiceal mucin/cells changes management.
- Invasive appendiceal adenocarcinoma without peritoneal disease: right hemicolectomy with adequate nodal staging is generally recommended when oncologically appropriate.
- Goblet cell adenocarcinoma: right hemicolectomy is generally recommended for localized invasive disease.

Adjuvant systemic therapy

Clinical setting	Practical approach
Node-positive adenocarcinoma	Recommend adjuvant FOLFOX or CAPOX, extrapolating from colon cancer and appendiceal consensus data.
Node-negative, high-risk invasive adenocarcinoma	Consider individually for T4/perforation, poor differentiation or signet-ring features, LVI/PNI, positive/close margin, inadequate nodal staging, obstruction or other adverse features.
Stage II without high-risk features	Observation is reasonable; a survival benefit from adjuvant chemotherapy has not been established.
Low-grade/well-differentiated mucinous adenocarcinoma	Routine systemic chemotherapy is not supported in the absence of higher-risk invasive disease.

APPENDICEAL ADENOCARCINOMA

PERITONEAL AND METASTATIC DISEASE

Peritoneal-only disease — resectability assessment

- Discuss potentially operable patients in a dedicated peritoneal-surface malignancy MDT. Assess histology/grade, PCI, distribution, small-bowel involvement, performance status and likelihood of complete cytoreduction.
- For low-grade peritoneal disease, evaluation for cytoreductive surgery (CRS) is central; systemic chemotherapy should not automatically precede surgery.
- For selected high-grade disease, CRS ± HIPEC can be considered when complete cytoreduction appears achievable; systemic therapy may be appropriate before surgery depending on biology and burden.

Systemic therapy by biology

Disease biology	Preferred strategy
LAMN / grade 1 PMP or low-grade mucinous peritoneal disease, resectable	CRS ± intraperitoneal chemotherapy/HIPEC at an expert center when peritoneal disease is present. Routine perioperative systemic chemotherapy is not supported for low-grade disease.
Low-grade mucinous peritoneal disease, unresectable	Observation can be appropriate if indolent/asymptomatic. Cytotoxic chemotherapy has low activity and has not shown a clear survival benefit.
HAMN / high-grade mucinous / non-mucinous / goblet cell adenocarcinoma	Evaluate for CRS ± HIPEC when complete cytoreduction appears feasible. For invasive/high-grade disease, CRC-type systemic regimens may be used, with timing individualized to biology and burden.
Actionable biomarker	Use biomarker-directed treatment according to evidence/access: MSI-H/dMMR immunotherapy; BRAF/HER2/NTRK and other targets according to the mCRC framework and Belgian access.

KEY CHANGE FROM PREVIOUS VERSION

- “Neoadjuvant systemic therapy for up to 6 months” is not a universal preferred strategy for peritoneal-only appendiceal cancer. In particular, low-grade mucinous disease is relatively chemotherapy-resistant.

Extraperitoneal metastatic disease

- Systemic therapy generally follows metastatic colorectal cancer principles, but expected benefit varies substantially by appendiceal histology and grade; clinical trial participation is encouraged.

Surveillance after curative-intent treatment

- Physical and CEA, every 3–6 months for 2 years, then every 6–12 months to 5 years; tailor intensity to grade and recurrence risk.
- CT chest/abdomen/pelvis every 6–12 months; colonoscopy according to findings and CRC surveillance principles.

APPENDICEAL ADENOCARCINOMA

CLINICAL PEARLS AND SELECTED REFERENCES

Clinical pearls

- Histology and grade are treatment-defining. LAMN and HAMN are distinct: LAMN has low-grade cytology, HAMN high-grade cytology; neither has infiltrative-type invasion. Infiltrative invasion defines appendiceal adenocarcinoma.
- Peritoneal dissemination is the dominant metastatic pattern for mucinous tumors; nodal and hematogenous spread are more relevant in non-mucinous/high-grade disease.
- Low-grade mucinous appendiceal adenocarcinoma is poorly responsive to conventional systemic chemotherapy; CRS-based management is preferred when technically feasible.
- Evidence is limited by rarity and heterogeneity; referral to an experienced appendiceal/peritoneal malignancy team and clinical trials should be considered early.

SELECTED REFERENCES

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