National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Appendiceal Neoplasms and Cancers

Version 1.2026 — October 30, 2025

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Appendiceal Neoplasms and Cancers

NCCN Guidelines Index
Table of Contents
Discussion

Al B. Benson III, MD/Chair †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Alan P. Venook, MD/Vice-Chair † ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Stacey A. Cohen, MD/Lead †
Fred Hutchinson Cancer Center

Mohamed Adam, MD/Co-Lead ¶
UCSF Helen Diller Family Comprehensive Cancer Center

Manju Ambelil, MD ≠
Fox Chase Cancer Center

George J. Chang, MD, MS, MHCM ¶
The University of Texas MD Anderson Cancer Center

Kristen K. Ciombor, MD †
Vanderbilt-Ingram Cancer Center

Madison Conces, MD ‡ †
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Dustin Deming, MD †
University of Wisconsin Carbone Cancer Center

Ignacio Garrido-Laguna, MD, PhD †
Huntsman Cancer Institute at the University of Utah

Jean L. Grem, MD †
Fred & Pamela Buffett Cancer Center

Carla Harmath, MD ϕ
The UChicago Medicine Comprehensive Cancer Center

Paul Haste, MD ϕ
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

J. Randolph Hecht, MD †
UCLA Jonsson Comprehensive Cancer Center

J. Kevin Hicks, PharmD, PhD Σ
Moffitt Cancer Center

Sarah Hoffe, MD §
Moffitt Cancer Center

Steven Hunt, MD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Hisham Hussan, MD ¤
UC Davis Comprehensive Cancer Center

Kimberly L. Johung, MD, PhD §
Yale Cancer Center/Smilow Cancer Hospital

Nora Joseph, MD ≠
University of Michigan Rogel Cancer Center

Natalie Kirilcuk, MD ¶
Stanford Cancer Institute

Midhun Malla, MD, MS †
O'Neal Comprehensive Cancer Center at UAB

Rifat Mannan, MD ≠
City of Hope National Medical Center

Jennifer K. Maratt, MD, MS ¤
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Wells A. Messersmith, MD †
University of Colorado Cancer Center

Jeffrey Meyer, MD, MS §
Johns Hopkins Kimmel Cancer Center

Jeffrey Meyerhardt, MD, MPH †
Dana-Farber Brigham and Women's Cancer Center

Eric D. Miller, MD, PhD §
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Mary F. Mulcahy, MD ‡ †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Steven Nurkin, MD, MS, MBA ¶
Roswell Park Comprehensive Cancer Center

Hitendra Patel, MD †
UC San Diego Moores Cancer Center

Katrina Pedersen, MD, MS †
Mayo Clinic Comprehensive Cancer Center

Leonard Saltz, MD † ‡ Þ
Memorial Sloan Kettering Cancer Center

Charles Schneider, MD †
Abramson Cancer Center at the University of Pennsylvania

David Shibata, MD ¶
St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

Benjamin Shogan, MD ¶
The UChicago Medicine Comprehensive Cancer Center

Laurie Singer ¥
DoubleLL Productions

Constantinos T. Sofocleous, MD, PhD ϕ
Memorial Sloan Kettering Cancer Center

Anna Tavakkoli, MD, MSc ¤
UT Southwestern Simmons Comprehensive Cancer Center

Christopher G. Willett, MD §
Duke Cancer Institute

Christina Wu, MD †
Mayo Clinic Comprehensive Cancer Center

NCCN
Faviolla Baez-Cruz, PhD
Lisa Gurski, PhD
Frankie Jones

ϕ Diagnostic/Interventional radiology
¤ Gastroenterology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
Σ Pharmacology/ Pharmacy
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

[NCCN Guidelines Panel Disclosures]

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Appendiceal Neoplasms and Cancers

NCCN Guidelines Index
Table of Contents
Discussion

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

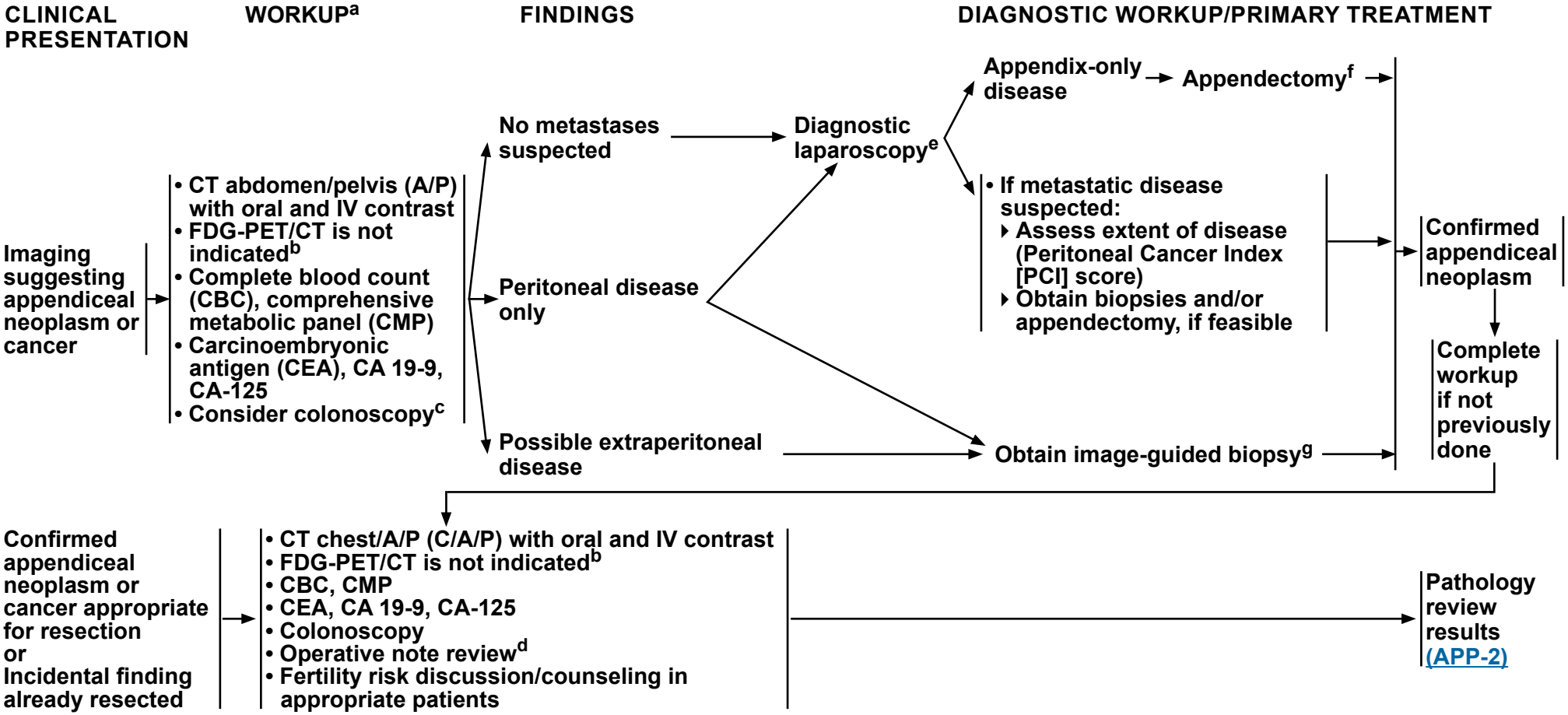
NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Appendiceal Neoplasms and Cancers

NCCN Guidelines Index
Table of Contents
Discussion



[a] FDA added a Black Box warning to the capecitabine label, recommending to test patients for genetic variants of *DPYD* prior to initiating capecitabine unless immediate treatment is necessary. For information on *DPYD* testing and fluoropyrimidine-associated toxicity, see the NCCN Guidelines for Colon Cancer.

[b] Use of FDG-PET/CT is only considered in rare circumstances where CT findings are indeterminate or when CT with contrast is not possible. See Principles of Imaging (APP-A).

[c] Colonoscopy is needed for a confirmed appendiceal neoplasm to rule out other primary lesions. This could be done concurrently with the other diagnostic studies, but should not delay treatment.

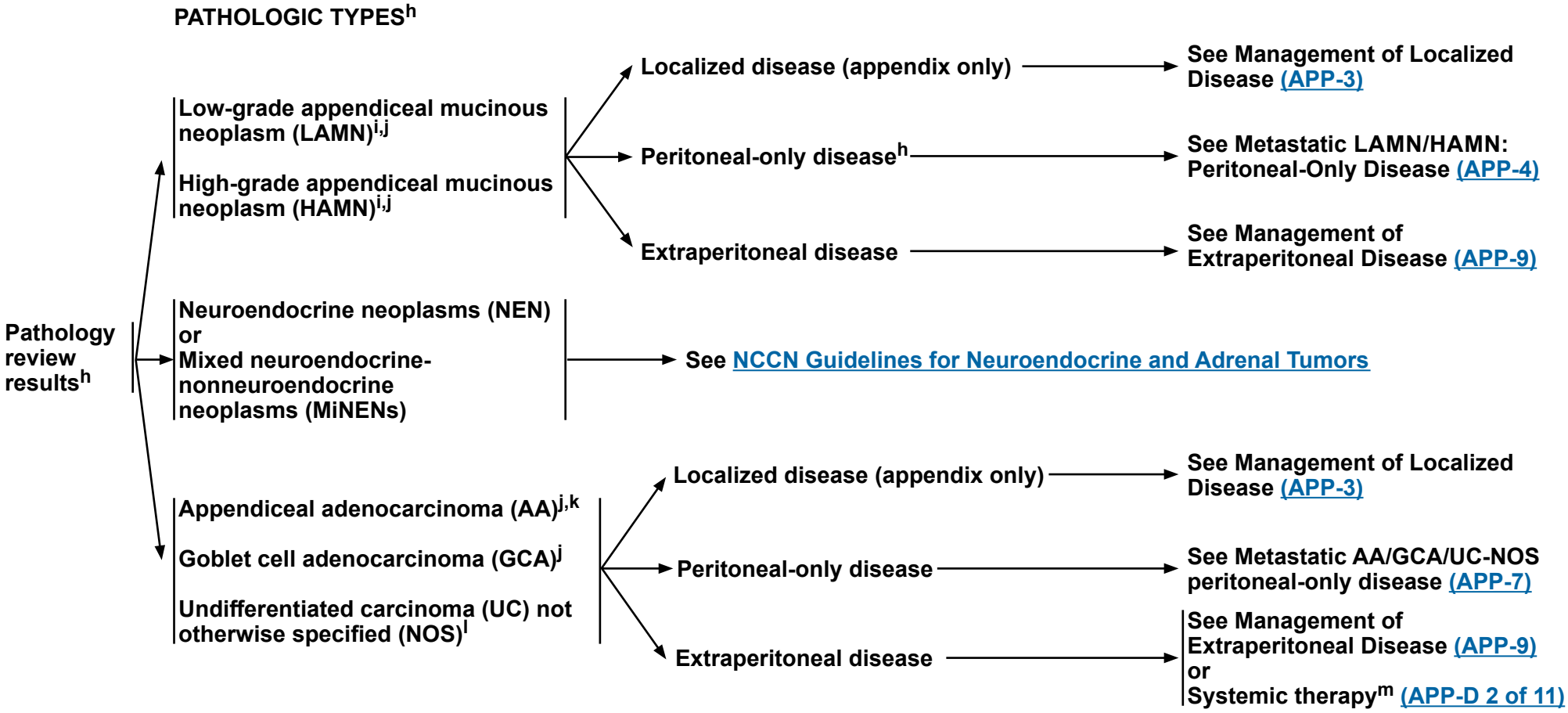
[d] Thorough review of operative notes is encouraged upon confirmation of appendiceal neoplasm in order to rule out more aggressive disease (eg, perforation, ascites present, signs of mucin).

[e] Diagnostic laparoscopy should be performed by a surgeon with experience in this disease process.

[f] See Principles of Surgery and CRS/IPCT (APP-C) for circumstances where a right hemicolectomy may be recommended.

[g] For peritoneal-only disease, image-guided biopsy is preferred for lesions that are safely accessible percutaneously when a non-surgical approach is preferred to confirm the diagnosis (eg, due to comorbidities or extraperitoneal disease). If inaccessible, surgical biopsy may be needed for diagnostic confirmation.

Note: All recommendations are category 2A unless otherwise indicated.



[h] Primary and metastatic disease are evaluated separately. See Principles of Pathology and Molecular Review (APP-B).

[i] Lesions with extra-appendiceal acellular mucin are considered low risk for dissemination. Lesions with extra-appendiceal mucin-containing neoplastic epithelium are considered high risk for recurrence or peritoneal dissemination and the peritoneal-only disease pathway would be followed.

[j] Lesions containing ≤50% signet-ring cells are classified as mucinous adenocarcinomas with signet-ring cells. Tumors containing >50% signet-ring cells are classified as signet-ring cell carcinomas. Signet-ring cell carcinomas are associated with a high level of metastasis and worse prognosis.

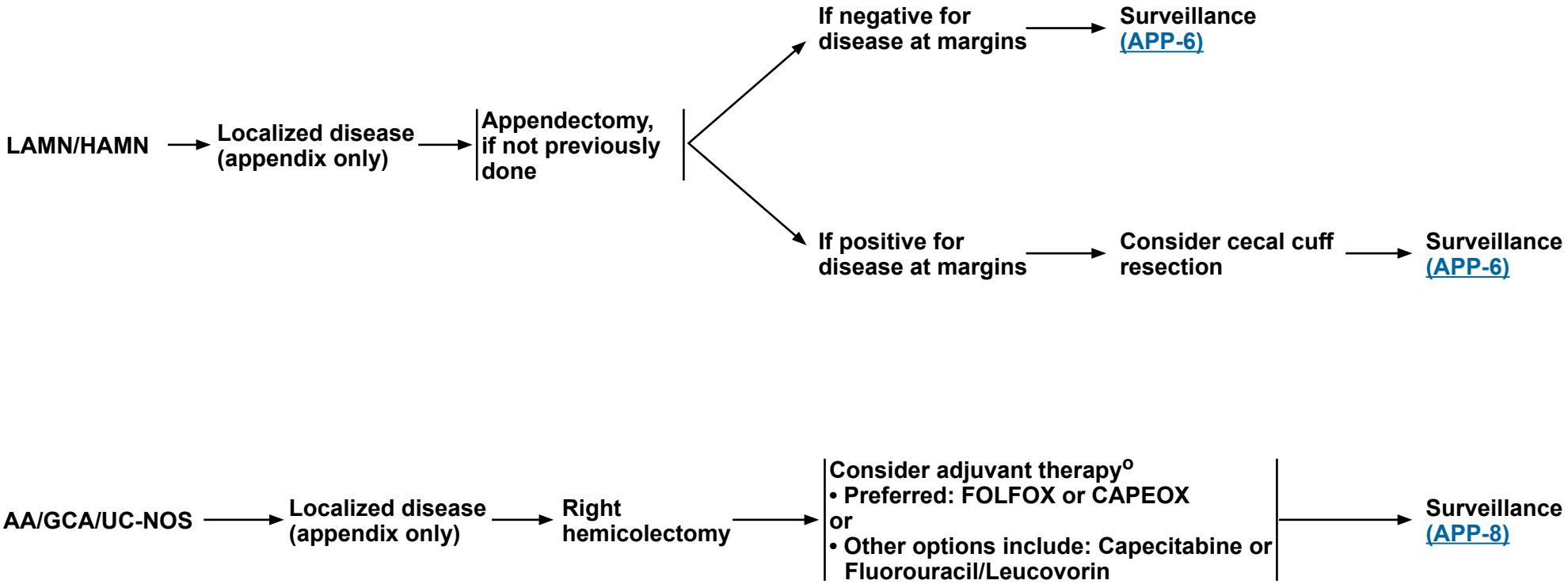
[k] Lesions containing ≤50% of mucin are classified as non-mucinous adenocarcinomas. Tumors containing >50% mucin are considered mucinous adenocarcinomas.

[l] UCs only show epithelial marker expression if there is no histologic, immunohistochemical, or molecular indicators of the tissue of origin. Nagtegaal ID, et al. Histopathology 2020;76:182-188.

[m] Biomarker testing is recommended, although there may be a higher rate of assay failure if specimen has low cellularity. See Principles of Pathology and Molecular Review (APP-B).

Note: All recommendations are category 2A unless otherwise indicated.

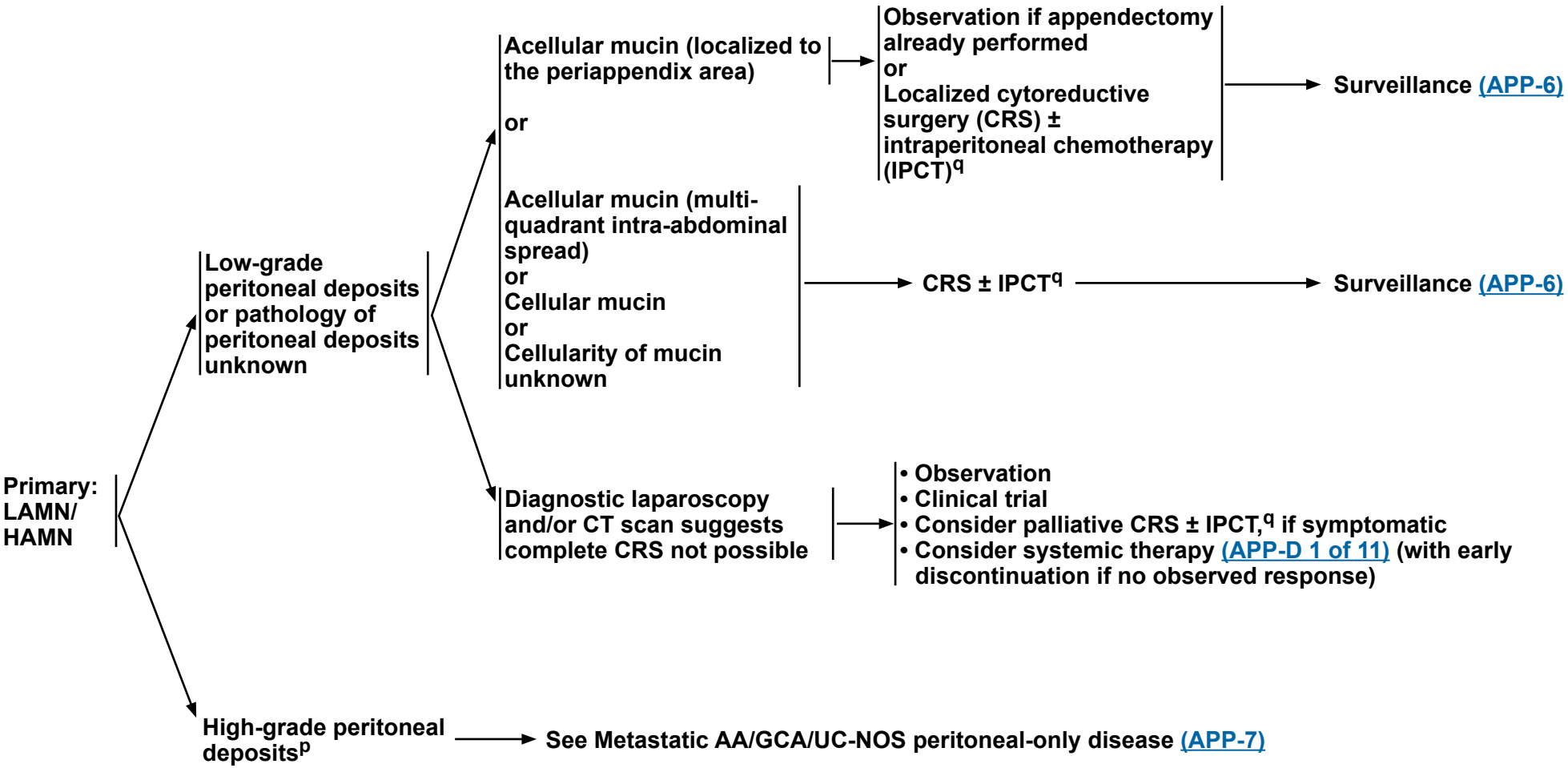
MANAGEMENT OF LOCALIZED DISEASE[n]



[n] Multidisciplinary team evaluation, including formal surgical evaluation.
[o] Strongly consider adjuvant chemotherapy for patients with nodal disease or perforation noted at the time of surgery. May be considered in other instances depending on high-risk features (extrapolating from colon cancer, these features may be: poorly differentiated/undifferentiated histology; lymphatic/vascular invasion; bowel obstruction; <12 lymph nodes examined; perineural invasion [PNI]; localized perforation; close, indeterminate, positive margins; or high-tier tumor budding). Circulating tumor (ctDNA) is prognostic, but not predictive.

Note: All recommendations are category 2A unless otherwise indicated.

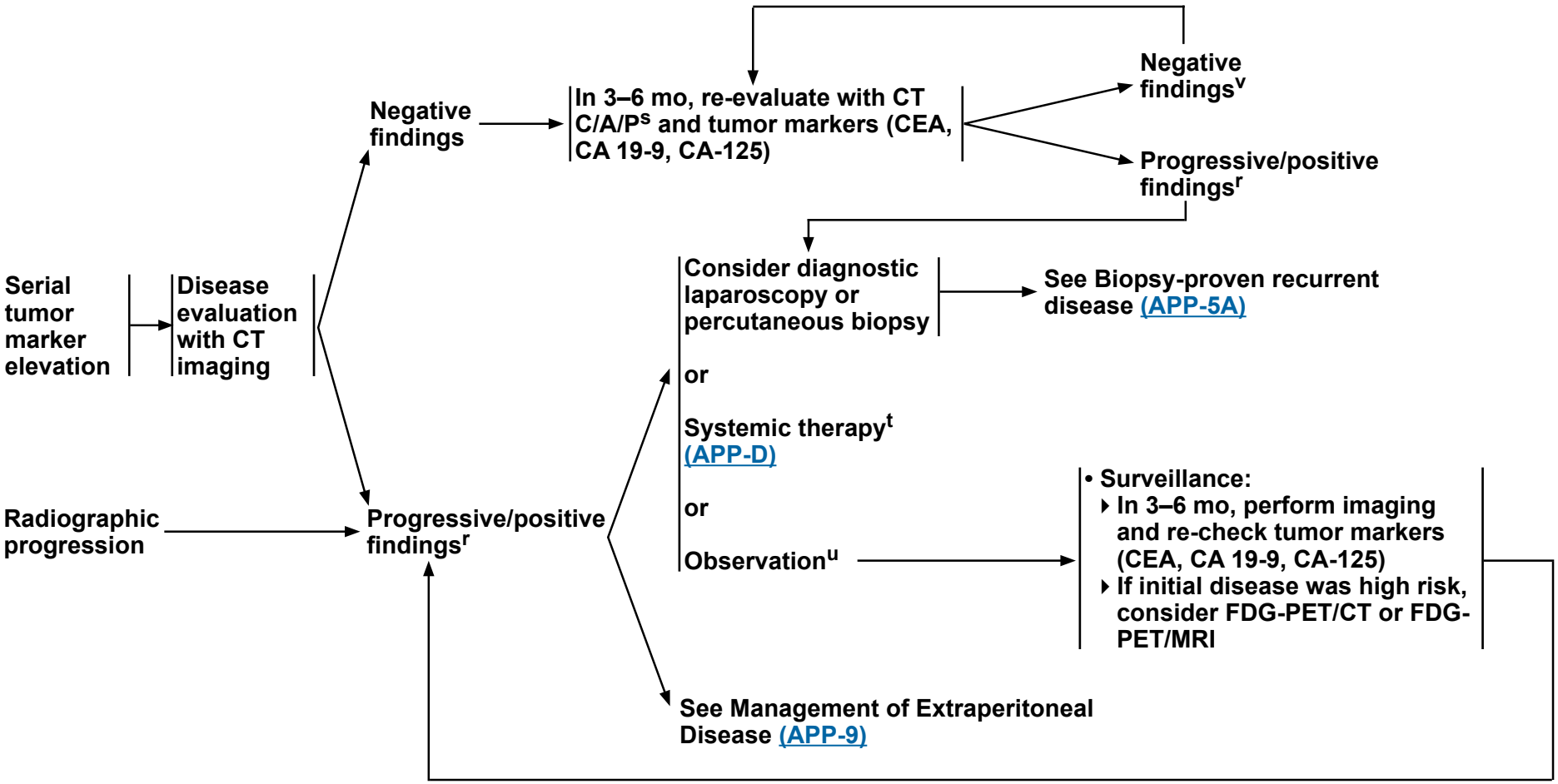
METASTATIC LAMN/HAMN: PERITONEAL-ONLY DISEASE[n]



[n] Multidisciplinary team evaluation, including formal surgical evaluation.
[p] High-grade peritoneal deposits behave clinically like high-risk disease and should follow those treatment pathways, even if the primary is low grade.
[q] Principles of Surgery and CRS/IPCT (APP-C).

Note: All recommendations are category 2A unless otherwise indicated.

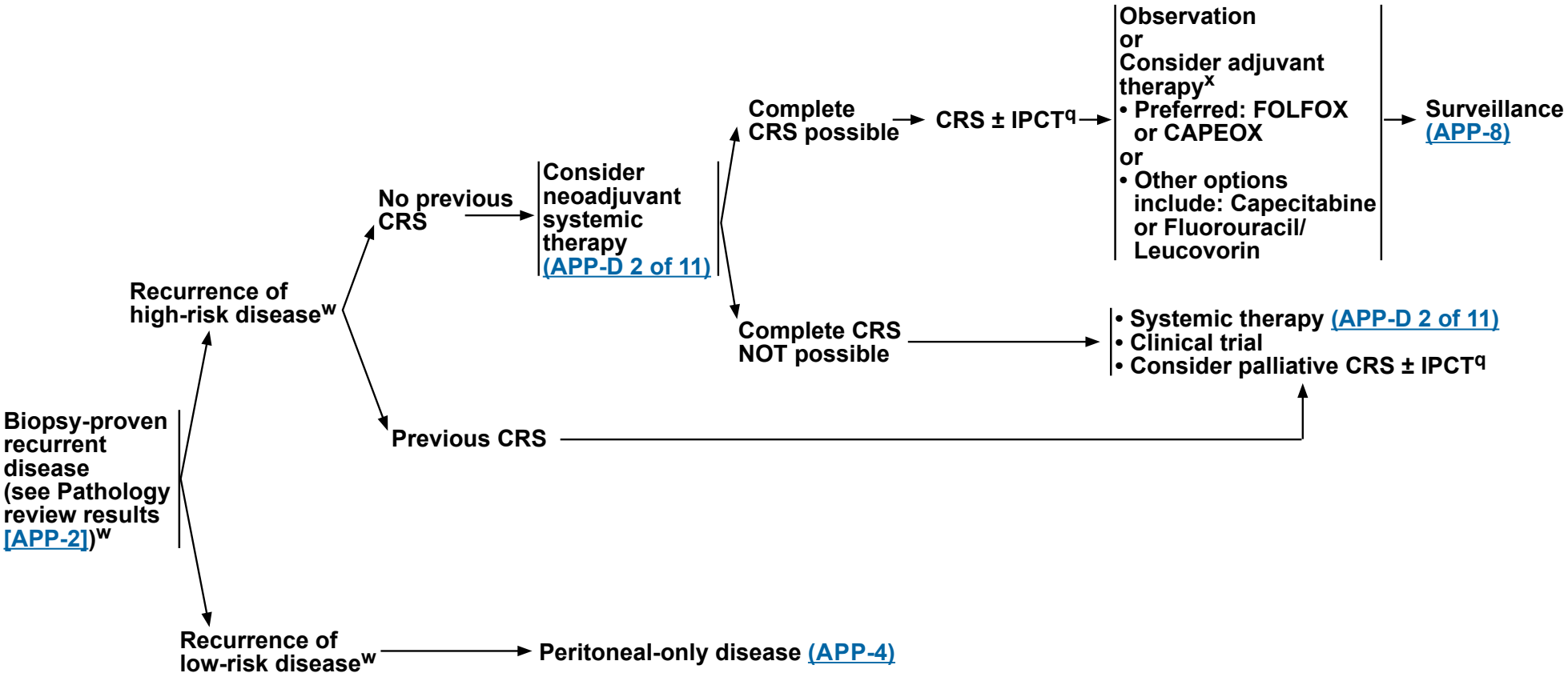
WORKUP FOR RECURRENCE[n]



[n] Multidisciplinary team evaluation, including formal surgical evaluation.
[r] ctDNA assays are not recommended in this setting. These assays have a lower sensitivity for peritoneal disease and false negatives are common.
[s] If CT is normal and disease is considered high risk at initial diagnosis, consider FDG-PET/CT or FDG-PET/MRI.
[t] For progressive disease in a patient who is not a surgical candidate, systemic therapy may be considered without a biopsy. Follow the systemic therapy pathway according to the risk level of histology.
[u] In select cases per clinical judgment. For low-risk disease and indolent changes, observation with continued disease assessment may be considered.
[v] If consistently negative findings on multiple rounds of re-evaluation, interval may be lengthened to every 6–12 months.

Note: All recommendations are category 2A unless otherwise indicated.

BIOPSY-PROVEN RECURRENCE[n]



[n] Multidisciplinary team evaluation, including formal surgical evaluation.
[q] Principles of Surgery and CRS/IPCT (APP-C).
[w] Risk status should be according to pathology of metastatic disease; subsequent treatment should be based on the highest risk pathology found (thus, a low-risk primary with high-risk metastatic disease should be treated as per high-risk pathways).
[x] This recommendation has been extrapolated from colon cancer; duration of perioperative therapy should be limited to no more than 6 months.

Note: All recommendations are category 2A unless otherwise indicated.

SURVEILLANCE: LAMN/HAMN AND NO HIGH-GRADE PERITONEAL DEPOSIT

Resected localized disease[y] →
- History and physical examination every 6–12 mo for 2 y, then annually for up to 10 y
- CEA, CA 19-9, CA-125 every 6–12 mo for 2 y, then annually for up to 10 y[z]
- A/P CT or MRI every 6–12 mo from date of surgery for 2 years then every 12–24 mo for up to 10 y
- FDG-PET/CT is not indicated
- Colonoscopy, if no preoperative colonoscopy was done
- Principles of Survivorship (APP-E)

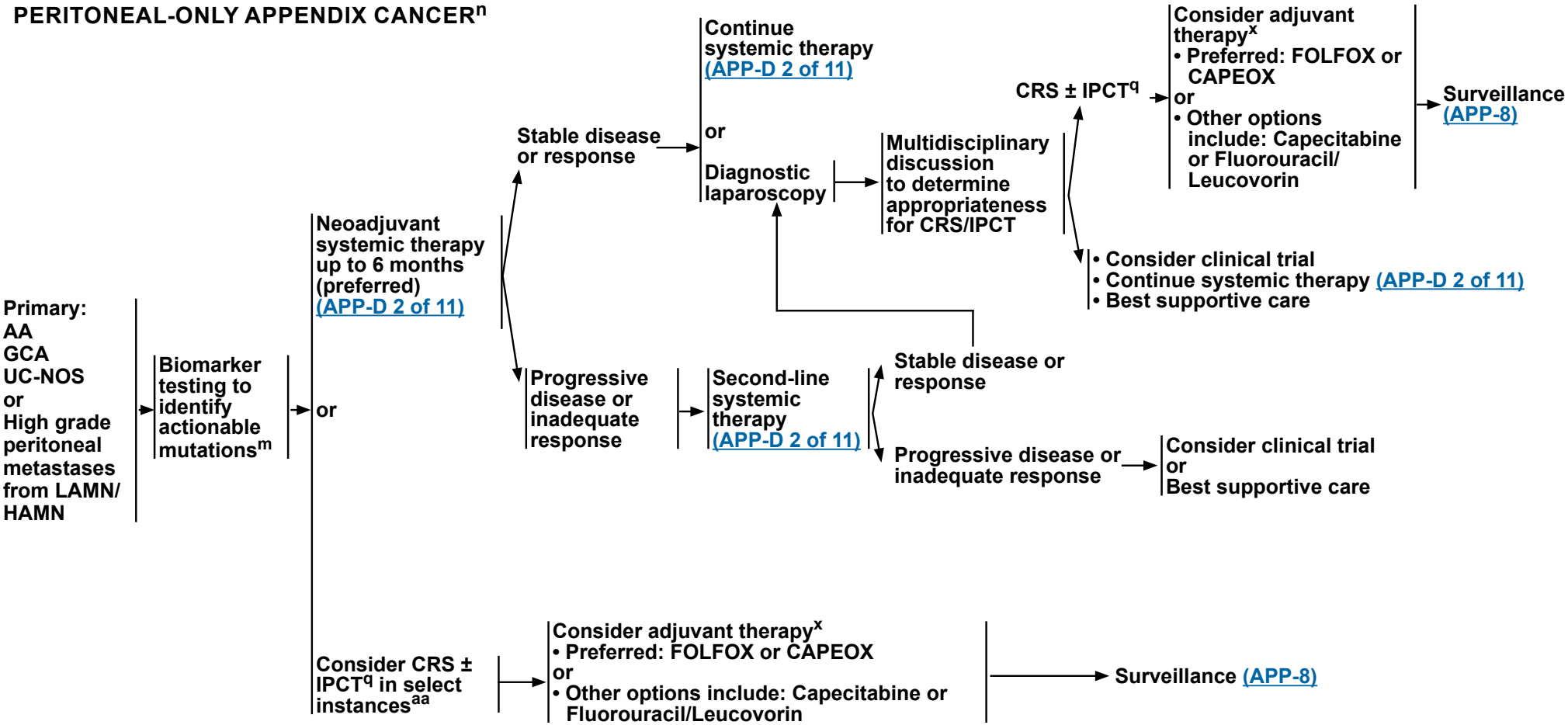
Resected metastatic disease →
- History and physical examination every 6 mo for 2 y, then annually for up to 10 y
- CEA, CA 19-9, CA-125 every 6–12 mo for 2 y, then annually for up to 10 y[z]
- C/A/P CT or MRI every 6 mo from date of surgery for 2 years then every 12 mo for up to 10 y
- FDG-PET/CT is not indicated
- Colonoscopy, if no preoperative colonoscopy was done
- Principles of Survivorship (APP-E)

→ **Rising tumor markers, unexplained abdominal symptoms, documented recurrence, or radiographic progression** → **See Recurrence (APP-5)**

[y] For completely resected LAMN confined to the appendix without high-risk features (eg, extra-appendiceal cellular mucin, presence of signet ring cells), surveillance may not be needed.
[z] It may not be necessary to measure all tumor markers at all surveillance timepoints as guided by prior marker elevations for the specific patient.

Note: All recommendations are category 2A unless otherwise indicated.

METASTATIC AA/GCA/UC-NOS PERITONEAL-ONLY APPENDIX CANCER[n]



[m] Biomarker testing is recommended, although there may be a higher rate of assay failure if specimen has low cellularity. See Principles of Pathology and Molecular Review (APP-B).
[n] Multidisciplinary team evaluation, including formal surgical evaluation.
[q] Principles of Surgery and CRS/IPCT (APP-C).
[x] This recommendation has been extrapolated from colon cancer; duration of perioperative therapy should be limited to no more than 6 months.
[aa] Select instances including low disease burden and/or well-differentiated adenocarcinoma.

Note: All recommendations are category 2A unless otherwise indicated.

SURVEILLANCE: AA/GCA/UC-NOS

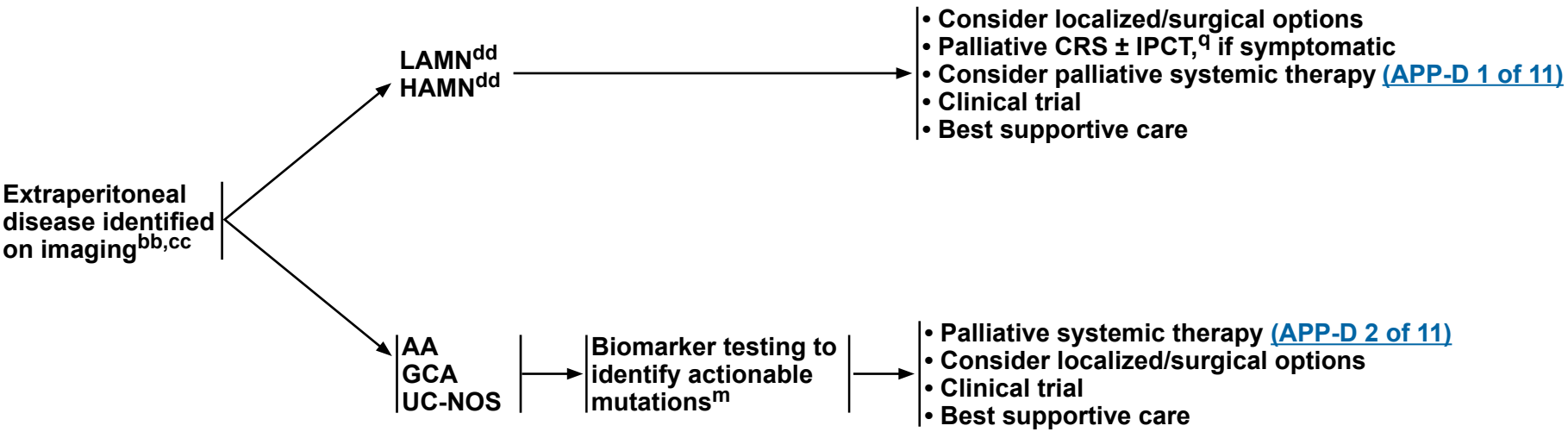
Resected localized disease →
- History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA, CA 19-9, CA-125 every 3–6 mo for 2 y, then 6–12 mo for a total of 5 y
- C/A/P CT every 6–12 mo from date of surgery for a total of 5 y
- FDG-PET/CT is not indicated
- Colonoscopy, if no preoperative colonoscopy was done
- Principles of Survivorship (APP-E)

Resected metastatic disease, including resected LAMN/HAMN primary with high-grade metastatic disease →
- History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA, CA 19-9, CA-125 every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- C/A/P CT every 3–6 mo for 2 years then every 6–12 mo for a total of 5 y
- FDG-PET/CT is not indicated
- Colonoscopy, if no preoperative colonoscopy was done
- Principles of Survivorship (APP-E)

→ **Rising tumor markers, unexplained abdominal symptoms, or documented recurrence** → **See Recurrence (APP-5)**

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF EXTRAPERITONEAL DISEASE[n]



[m] Biomarker testing is recommended, although there may be a higher rate of assay failure if specimen has low cellularity. See Principles of Pathology and Molecular Review (APP-B).
[n] Multidisciplinary team evaluation, including formal surgical evaluation.
[q] Principles of Surgery and CRS/IPCT (APP-C).
[bb] If CT is not feasible, consider MRI of abdomen to differentiate between liver and extrahepatic disease.
[cc] Specify whether the metastases is within the liver parenchyma (extraperitoneal metastasis) or scalloping along the liver edge (still intraperitoneal metastasis).
[dd] It would be extremely unusual for low-risk disease to have extraperitoneal spread; therefore, pathologic confirmation is recommended to rule out high-risk disease.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF IMAGING[1-5]

- It is important to note that imaging may be negative in the setting of peritoneal metastases, or that it may underestimate the peritoneal disease volume. Direct visualization (laparoscopic evaluation when feasible) should be performed for confirmation in the staging setting and when recurrence is suspected clinically and imaging findings are negative.
- The mainstay of staging imaging should consist of a CT of the C/A/P OR non-contrast CT of the chest with MRI of the A/P.
  - Evaluate local extent of tumor, presence of associated inflammation and/or perforation, and infiltration of adjacent structures and regional metastases.
  - Evaluate for distant metastases (ie, lymph nodes, lung, liver, peritoneum, other organs)
  - CT exam should be performed with oral and IV iodinated contrast, unless contraindicated.
  - If IV iodinated contrast is contraindicated due to severe allergy, then CT of the chest without contrast and MRI of the A/P with IV gadolinium-based contrast agent (GBCA) can be obtained instead.
  - In patients with chronic renal failure (estimated glomerular filtration rate [eGFR] <30 mL/min) who are not on dialysis, IV contrast material is also contraindicated, and IV GBCA such as gadofosveset trisodium, gadoxetate disodium, gadobenate dimeglumine, or gadoteridol may be used.
  - If both IV iodinated contrast and IV GBCA are contraindicated, CT of the chest without contrast and MRI of the A/P without contrast should be considered. PET/CT may also be considered as an alternate.
  - Consider MRI of the liver in cases where better resolution of indeterminate liver lesions is needed and/or MRI of select cases of hepatic metastases when planning metastasectomy or liver-directed therapies. In these cases, utilization of hepatocyte-specific GBCA is preferred for precise localization and quantification of metastases.

- FDG-PET/CT
  - FDG-PET/CT is usually not indicated. In select cases (ie, neuroendocrine neoplasm), DOTATATE PET/CT should be considered.
    - ◊ FDG-PET does not supplant a contrast-enhanced diagnostic CT or MRI and can be used to evaluate an equivocal finding on a contrast-enhanced CT or MRI, but should not be the preferred imaging study.
  - FDG-PET may under-appreciate disease burden, especially for mucinous tumors.

- Monitoring
  - For treatment response monitoring, typically a CT of the A/P (in cases of resected localized disease), or CT of the C/A/P (in cases of resected metastatic disease) with oral and IV contrast, or non-contrast CT of the chest with MRI of the A/P should be used.
    - ◊ For patients who have had liver-directed therapy (ablation-based, ie, radiofrequency ablation [RFA], microwave ablation [MWA]; radiation-based, ie, radioembolization, stereotactic body radiation therapy [SBRT]), MRI of the liver is preferred over CT for the assessment of treatment response.
    - ◊ In select cases FDG-PET may be indicated to assess residual tumor viability if curative liver resection is contemplated, but should be done in partnership with a contrasted CT or MRI.
    - ◊ For mucinous tumors, MRI of the A/P may be preferred over CT as mucinous implants may be easier to distinguish from adjacent structures due to their T2 signal.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF IMAGING
REFERENCES

[1] Chicago Consensus Working Group. The Chicago Consensus on peritoneal surface malignancies: Standards. Cancer 2020;126:2516-2524.
[2] Chicago Consensus Working Group. The Chicago Consensus on peritoneal surface malignancies: Management of appendiceal neoplasms. Cancer 2020;126:2525-2533.
[3] Expert Panel on Gastrointestinal Imaging; Korngold EK, Moreno C, Kim DH, et al. ACR Appropriateness Criteria® Staging of Colorectal Cancer: 2021 Update. J Am Coll Radiol 2022;19:S208-S222.
[4] Govaerts K, Chandrakumaran K, Carr NJ, et al. Single centre guidelines for radiological follow-up based on 775 patients treated by cytoreductive surgery and HIPEC for appendiceal pseudomyxoma peritonei. Eur J Surg Oncol 2018;44:1371-1377.
[5] Leonards LM, Pahwa A, Patel MK, et al. Neoplasms of the appendix: Pictorial review with clinical and pathologic correlation. Radiographics 2017;37:1059-1083.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY AND MOLECULAR REVIEW

Appendiceal Cancer Appropriate for Resection

- Primary appendiceal neoplasms are rare and most often found incidentally during an appendectomy following clinical presentation of acute appendicitis.
- Individual management and treatment of primary appendiceal cancers are dependent on classification, grading, and staging.
- According to the most recent WHO classification of tumors, appendiceal epithelial neoplasms are categorized as follows[1]:
  - Serrated lesions and polyps
  - Mucinous neoplasm
  - Adenocarcinoma
  - GCA
  - Neuroendocrine neoplasms

Background: Appendiceal Mucinous Neoplasms

- There is much ongoing debate over terminology and classification of mucinous neoplasms due to the fact that even low-grade neoplasms can result in pseudomyxomatous peritonei and lack of consensus criteria for invasion into the appendix.
- Current terminology includes low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), low-grade mucinous carcinoma peritonei, high-grade mucinous carcinoma peritonei, and high-grade mucinous carcinoma peritonei with signet ring cells.
- Older terminology that is no longer recommended includes: mucinous tumor of uncertain malignant potential, mucinous cystadenoma of the appendix, borderline tumor of the appendix, mucinous cystadenocarcinoma of the appendix, disseminated peritoneal adenomucinosis, and peritoneal mucinous carcinomatosis with or without signet ring cells.[1,2,3]
- However, some pathologists prefer to use the term "mucinous cystadenoma" to refer to entirely submitted mucinous tumors with no mural or extra-appendiceal mucin. If mural changes are present, such as disruption or atrophy of the muscularis mucosa, these lesions are best classified as LAMN.[4,5]
  - Low-grade appendiceal mucinous neoplasm (LAMN):
    - ◊ LAMNs are characterized by tall mucinous epithelial cells in villous or flat arrangement, which invade with a distinct pushing border in contrast to infiltrative glands associated with desmoplasia.
    - ◊ LAMNs are most often associated with atrophy of the appendiceal wall, loss of lymphoid tissue, and effacement of the muscularis mucosa, which can be helpful in differentiating other entities on the histologic differential diagnosis such as ruptured diverticula.[4,5]
    - ◊ Mucin pools are common and can extend into the serosa and beyond.
    - ◊ According to the 9th version of the AJCC, LAMNs confined to the muscularis propria, including acellular mucin or mucinous epithelium, are staged as carcinoma in situ (pTis). pT1 and pT2 are not applicable in LAMN.
    - ◊ Acellular mucin or mucinous epithelium that extends into the subserosa or serosa is classified as pT3 or pT4a, respectively.[6]
    - ◊ LAMNs are almost always microsatellite stable (MSS), *BRAF* V600E negative, and frequently harbor *KRAS* mutations.[2]

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY AND MOLECULAR REVIEW

- **High-grade appendiceal mucinous neoplasm (HAMN):**
  - ◊ **HAMNs retain some similar findings as LAMN but show progression to a more aggressive lesion with the acquisition of high-grade cytologic features and complex architecture.**
  - ◊ **As such, HAMNs are staged as mucinous adenocarcinomas, although HAMNs are rare and robust data are limited.[2]**
- **Mucinous carcinoma peritonei:**
  - ◊ **Extra-appendiceal mucin is characterized as acellular or with neoplastic cells that can be low grade, high grade, or high grade with signet ring cells.**
  - ◊ **The presence or absence of neoplastic cells and the degree of cytologic atypia have prognostic implications in that acellular mucin confined to the right lower quadrant has a low risk of progression whereas mucin with high-grade neoplastic epithelium with signet ring cells is associated with a much worse prognosis.[2,7]**
- **Appendiceal adenocarcinoma (AA):**
  - ◊ **Outside of LAMN and pseudomyxoma peritonei, other primary AAs are rare and can arise from several distinct precursor lesions such as mucinous neoplasms, intestinal-type adenomas, and GCAs.**
  - ◊ **These adenocarcinomas often demonstrate abundant extracellular mucin but are distinguished from mucinous neoplasms by a few key differences.**
  - ◊ **These tumors are highly cellular, have high-grade nuclear features, and show an infiltrative growth pattern with desmoplastic response.[8,9]**
  - ◊ **Primary mucinous adenocarcinomas are rarely microsatellite unstable (microsatellite instability-high [MSI-H]). However, non-mucinous subtypes have been shown to be MSI-H.[10]**
  - ◊ **Mucinous subtypes are associated with better outcomes than non-mucinous subtypes. However, higher histologic grade in mucinous subtypes is associated with lower overall 5-year survival rates.[11]**
- **Appendiceal goblet cell adenocarcinoma (GCA):**
  - ◊ **These tumors have been historically classified as NETs but are now recognized as a distinct clinicopathologic entity with biologic potential more similar to adenocarcinomas than NETs.[9]**
  - ◊ **Older terminology includes goblet cell carcinoid, goblet cell type adenocarcinoid, mucinous carcinoid, and crypt cell carcinoma.**
  - ◊ **Microscopically, GCAs are characterized by deep mucosal and submucosal circumferential infiltration without associated surface epithelial dysplasia.**
  - ◊ **Extension into the muscularis propria and serosa is commonly observed.**
  - ◊ **GCAs are defined by the presence of a low-grade component comprised of small nests, clusters, and cords of goblet cells. Paneth cells and neuroendocrine cells may be present but are not required for a diagnosis of GCA.**
  - ◊ **The presence of infiltrating single or small clusters of mucinous or non-mucinous cells, complex cribriform glands, or solid sheets of cells or signet ring cells are evidence of a high-grade component.**

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY AND MOLECULAR REVIEW

- **Appendiceal goblet cell adenocarcinoma (GCA) (continued):**
  - ◊ **Recognizing low- and high-grade patterns is critical, as grading GCA depends on the percentages of each component.**
    - **– Grade 1 and 2 tumors demonstrate >75% and 50%–75% of tubular or clustered growth, respectively.**
    - **– Grade 3 tumors reveal <50% low-grade pattern and >50% of any combination of the high-grade pattern.[12,13]**
  - ◊ **As GCAs are often deeply invasive, patients with low-grade histology may present with evidence of metastasis.**
  - ◊ **Interestingly, GCAs have different molecular profiles from other AAs and neuroendocrine neoplasms in that lower rates of *KRAS* and *APC* mutations are consistently reported. However, microsatellite instability (MSI) and high tumor mutational burden (TMB-H) are also rare in these tumors.[14,15]**
- **Appendiceal neuroendocrine neoplasms:**
  - ◊ **Neuroendocrine neoplasms arising in the appendix include well-differentiated NETs, poorly differentiated neuroendocrine carcinomas (NECs), and MiNENs.[16]**
  - ◊ **Please see NCCN Guidelines for Neuroendocrine and Adrenal Tumors.**

Biomarker Testing

- **Biomarker testing, including:**
  - **_RAS_ and _BRAF_ V600E mutations; HER2 status; mismatch repair (MMR) or MSI status (if not previously done)**
  - **Testing should be conducted as part of multigene panel testing (MGPT), which would identify rare and actionable mutations and fusions such as _POLE/POLD1, RET,_ and _NTRK 1/2/3_.**
  - **For more information on biomarker testing, see the Principles of Pathologic and Molecular Review in the NCCN Guidelines for Colon Cancer.**

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY AND MOLECULAR REVIEW
REFERENCES

[1] Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-188.
[2] Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology 2017;71:847-858.
[3] Carr NJ, Cecil TD, Mohamed F, et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: The results for the Peritoneal Surface Oncology Group International (PSOGI) modified Delphi process. Am J Surg Pathol 2016;40:14-26.
[4] Pai RK, Beck AH, Norton JA, et al. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. Am J Surg Pathol 2009;33:1425-1439.
[5] Misdraji J, Yantiss RK, Graeme-Cook FM, et al. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol 2003;27:1089-1103.
[6] Overman MJ. AJCC Cancer Staging System: Appendix. 9th Version. American College of Surgeons; 2022.
[7] Baratti D, Kusamura S, Milione M, et al. Validation of the recent PSOGI pathologic classification of pseudomyxomatous peritonei in a single-center series of 265 patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2018;25:404-413.
[8] Misdraji J, Young RH. Primary epithelial neoplasms and other epithelial lesions of the appendix (excluding carcinoid tumors). Semin Diagn Pathol 2004;21:120-133.
[9] Yantiss RK. Advances in Surgical Pathology: Colorectal Carcinoma and Tumors of the Vermiform Appendix (ed 1). Philadelphia: Lippincott Williams & Wilkins (LWW); 2013:301-312.
[10] Taggart MW, Galbincea J, Mansfield PF, et al. High-level of microsatellite instability in appendiceal carcinomas. Am J Surg Pathol 2013;37:1192-1200.
[11] 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;122:213-221.
[12] Taggart MW, Abraham SC, Overman MJ, et al. Goblet cell carcinoid tumor, mixed goblet cell carcinoid-adenocarcinoma, and adenocarcinoma of the appendix: comparison of clinicopathologic features and prognosis. Arch Pathol Lab Med 2015;139:782-790.
[13] Yozu M, Johncilla ME, Srivastava A, et al. Histologic and outcome study supports reclassifying appendiceal goblet cell carcinoids as goblet cell adenocarcinomas, and grading and staging similarly to colonic adenocarcinomas. Am J Surg Pathol 2018;42:898-910.
[14] Arai H, Baca Y, Battaglin F, et al. Molecular characterization of appendiceal goblet cell carcinoid. Mol Cancer Ther 2020;19:2634-2640.
[15] Wen KW, Grenert JP, Joseph NM, et al. Genomic profile of appendiceal goblet cell carcinoid is distinct compared to appendiceal neuroendocrine tumor and conventional adenocarcinoma. Hum Pathol 2018;77:166-174.
[16] Volante M, Daniele L, Asioli S, et al. Tumor staging but not grading is associated with adverse clinical outcome in neuroendocrine tumors of the appendix: a retrospective clinical pathologic analysis of 138 cases. Am J Surg Pathol 2013;37:606-612.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGERY AND CRS/IPCT

- **Localized Disease:**
  - **Appendiceal tumors are heterogenous groups of tumors. Knowledge about the different pathologic types is key to appropriate surgical management.**
  - **Appendiceal tumors are rare but they are more common among patients with complicated appendicitis.**
  - **Histologies at lower risk of hematogenous spread, including LAMN and HAMN:**
    - ◊ **Negative margin appendectomy is largely considered to be sufficient. Ileocecectomy may be considered when appendectomy or extended appendectomy is not feasible.**
    - ◊ **Management of HAMN is controversial with some advocating for right colectomy.**
    - ◊ **Presence of perforation is a risk factor for peritoneal recurrence and warrants closer surveillance.**
  - **Histologies at higher risk of hematogenous spread, including adenocarcinoma:**
    - ◊ **Right hemicolectomy with adequate lymphadenectomy is recommended.**
  - **There is no clear role for routine second look laparoscopy in the absence of other suggestive risk factors for recurrent disease.**

- **Peritoneal Disease:**
  - **In cases of incidental peritoneal mucinous or non-mucinous disease during appendectomy or surgical exploration, the focus should be on obtaining a diagnosis rather than extensive resection. Diagnosis can be confirmed by appendectomy and/or biopsy of the most solid-appearing peritoneal implants.**
  - **Preoperative imaging may underestimate the extent of disease in the peritoneal cavity.**
  - **Staging laparoscopic exploration may be helpful in estimating the extent of peritoneal disease (PCI) and extent of surgery that will be required.**
  - **Patients deemed possible surgical candidates should be evaluated and treated by an experienced peritoneal surface malignancy surgeon for candidacy for CRS/IPCT. Expertise in peritoneal resections, multivisceral resections, and organ preservation techniques is key.**
    - ◊ **Candidacy for CRS/IPCT is determined through a multidisciplinary evaluation of the patient's overall health, disease biology and extent, and tumor resectability.**
  - **The extent of CRS should be individualized with the focus on optimal cytoreduction with organ preservation.**
  - **For surgical candidates, optimal cytoreduction (not debulking) with completeness of cytoreduction (CC) score of 0 or 1 is recommended.**
  - **Mitomycin C is the most commonly used agent for IPCT. Oxaliplatin is another option, but is less preferred, especially in patients who have received or will be receiving IV oxaliplatin.[1,2]**
  - **Repeat CRS/IPCT may be considered for patients with a history of previous CRS, particularly those with low-grade peritoneal tumors and/or limited peritoneal spread. For high-grade disease, the time since prior surgery should be taken into consideration.**
  - **In cases where disease is incompletely cytoreduced or resected or CRS is aborted, consider clinical trial, systemic therapy, or best supportive care.**

[1] Levine EA, Votanopoulos KI, Shen P, et al. A Multicenter Randomized Trial to Evaluate Hematologic Toxicities after Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin or Mitomycin in Patients with Appendiceal Tumors. J Am Coll Surg 2018;226:434-443.
[2] Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:256-266.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGERY AND CRS/IPCT

- **No Extraperitoneal Metastasis:**
  - **LAMN/HAMN Primary:**
    - ◊ **The majority of mucinous appendiceal (non-adenocarcinoma) neoplasms are less likely to respond to systemic therapy.**
    - ◊ **CRS/IPCT is recommended for low-grade (and select high-grade) mucinous tumors.**
    - ◊ **Optimal cytoreduction should be pursued when possible.**
    - ◊ **Palliative CRS/IPCT may be considered for unresectable disease in patients who are otherwise surgical candidates.**
  - **AA/GCA/UC-NOS:**
    - ◊ **Surgical candidates are suggested to receive perioperative systemic therapy for up to 6 months.**
    - ◊ **Regular multidisciplinary review is recommended to assess surgical candidacy and optimal timing of surgery, recognizing that patients may have poor response to systemic therapy but still have disease that is amenable to CRS.**
    - ◊ **Additional systemic therapy may be considered for patients who are not resectable at initial diagnosis with the possibility of converting to resectable disease.**
    - ◊ **The PCI score and CC score should be reported for cytoreductive surgery.**
    - ◊ **Surgery is discouraged for high PCI.**
    - ◊ **If a patient is not a candidate for surgery, treatment should follow metastatic colon cancer guidelines.**
- **Extraperitoneal Disease:**
  - **Liver surface metastasis (scalloping) is not considered extraperitoneal disease.**
  - **Management should follow systemic therapy guidelines with palliative measures used as needed for refractory symptoms.**
  - **Palliative debulking surgery can be considered for disease not responding or poorly responding to systemic therapy, but may be of limited benefit.**

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY FOR LAMN OR HAMN[*,a,b,c]

INITIAL THERAPY
• Capecitabine ± Bevacizumab • Fluorouracil/Leucovorin ± Bevacizumab • FOLFIRI (Leucovorin/Fluorouracil/Irinotecan)[d] ± Bevacizumab • FOLFOX (Leucovorin/Fluorouracil/Oxaliplatin)[e] ± Bevacizumab

For AA/GCA/UC-NOS, see APP-D 2 of 11
Footnotes APP-D 3 of 11

[*] Prolonged chemotherapy exposure is not recommended for patients who are not demonstrating a clinical response.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY FOR AA/GCA/UC-NOS[a,b,c,f]

INITIAL THERAPY

Intensive Therapy Recommended

- CAPEOX (Capecitabine/Oxaliplatin)[e] ± Bevacizumab
- FOLFIRI[d] ± Bevacizumab
- FOLFIRINOX (Leucovorin/Fluorouracil/Irinotecan/Oxaliplatin)[e,g] ± Bevacizumab
- FOLFOX[e] ± Bevacizumab
- *BRAF* V600E mutation positive:
  - FOLFOX[e]/Encorafenib + (Cetuximab or Panitumumab)

Intensive Therapy NOT Recommended

- Capecitabine ± Bevacizumab
- Fluorouracil/Leucovorin ± Bevacizumab

FOR ANY LINE OF THERAPY (if dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])[h,i,j]

- Cemiplimab-rwlc
- Dostarlimab-gxly
- Ipilimumab + Nivolumab[k]
- Nivolumab[k]
- Pembrolizumab[l]
- Penpulimab-kcqx
- Retifanlimab-dlwr
- Tislelizumab-jsgr
- Toripalimab-tpzi

SECOND-LINE AND SUBSEQUENT THERAPY (if not previously given)

- (FOLFIRI or Irinotecan)[d] ± Bevacizumab
- FOLFIRINOX[e,g] ± Bevacizumab
- (CAPEOX or FOLFOX)[e] ± Bevacizumab
- IROX (Irinotecan[d]/Oxaliplatin[e]) ± Bevacizumab
- For disease that has progressed through all available regimens:
  - Fruquintinib
  - Regorafenib
  - Trifluridine and Tipiracil ± Bevacizumab (Bevacizumab combo preferred)
- Best supportive care (NCCN Guidelines for Palliative Care)

Biomarker-directed therapy

- *BRAF* V600E mutation positive
  - Encorafenib + (Cetuximab or Panitumumab)
- *KRAS* G12C mutation positive
  - (Adagrasib or Sotorasib)[m] + (Cetuximab or Panitumumab)
- HER2-positive and *RAS* and *BRAF* WT
  - (Pertuzumab or Tucatinib)[n] + Trastuzumab[n]
- HER2-positive (IHC 3+)
  - Fam-trastuzumab deruxtecan-nxki[o]
- *NTRK 1/2/3* gene fusion-positive
  - Entrectinib
  - Larotrectinib
  - Repotrectinib[p]
- *RET* gene fusion-positive
  - Selpercatinib
- If *KRAS/NRAS/BRAF* WT[q]:
  - CAPEOX[e] + (Cetuximab or Panitumumab)
  - (Cetuximab or Panitumumab)[r] ± Irinotecan[d]
  - FOLFIRI[d] + (Cetuximab or Panitumumab)[r]
  - FOLFOX[e] + (Cetuximab or Panitumumab)

Footnotes APP-D 3 of 11

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY
FOOTNOTES

[a] For systemic therapy references, see Regimens and Dosing (APP-D 4 of 11).
[b] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[d] Irinotecan should be used with caution in patients with Gilbert syndrome or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
[e] Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.
[f] There is no clear evidence for anti-EGFR therapy, even among *RAS/RAF* WT cancers.
[g] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[h] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] If disease response, consider discontinuing checkpoint inhibitor after 2 years of treatment.
[j] If no previous treatment with a checkpoint inhibitor. Nivolumab + ipilimumab may be considered as subsequent therapy if checkpoint inhibitor monotherapy was previously received.
[k] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[l] Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.
[m] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.
[n] If no previous treatment with HER2 inhibitor.
[o] Some activity was seen after a previous HER2-targeted regimen. May not be indicated in patients with underlying lung issues due to lung toxicity (3.5% report of drug-related deaths from interstitial lung disease on the DESTINY-CRC01 trial).
[p] On the TRIDENT-1 trial, repotrectinib showed activity in both NTRK TKI-naïve and NTRK TKI-pretreated patients.
[q] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[r] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REGIMENS AND DOSING[c]

Modified FOLFOX6[1,2,3]
Oxaliplatin 85 mg/m² IV Day 1[s]
Leucovorin 400 mg/m² IV Day 1[t]
Fluorouracil 400 mg/m² IV bolus Day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

Modified FOLFOX7[4]
Oxaliplatin 85 mg/m² IV Day 1[s]
Leucovorin 400 mg/m² IV Day 1[t]
Fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

FOLFOX + Bevacizumab[5,u]
Bevacizumab 5 mg/kg IV Day 1
Repeat every 2 weeks

FOLFOX + Panitumumab[6] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, Day 1
Repeat every 2 weeks

FOLFOX + Cetuximab[7] (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly or Cetuximab 500 mg/m² IV over 2 hours, Day 1, every 2 weeks (preferred for every 2 weeks)

CAPEOX[8]
Oxaliplatin 130 mg/m² IV Day 1[s]
Capecitabine 1000[v] mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CAPEOX + Bevacizumab[8,u]
Oxaliplatin 130 mg/m² IV Day 1[s]
Capecitabine 1000[v] mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV Day 1
Repeat every 3 weeks

CAPEOX + Cetuximab[9-11] (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly or Cetuximab 500 mg/m² IV over 2 hours, Day 1, every 2 weeks (preferred for every 2 weeks)

CAPEOX + Panitumumab[9-11] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, Day 1
Repeat every 2 weeks

FOLFIRI[12,13]
Irinotecan 180 mg/m² IV over 30–90 minutes, Day 1
Leucovorin[t] 400 mg/m² IV infusion to match duration of Irinotecan infusion, Day 1
Fluorouracil 400 mg/m² IV bolus Day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

FOLFIRI + Bevacizumab[14,u]
Bevacizumab 5 mg/kg IV Day 1
Repeat every 2 weeks

References

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[s] Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[t] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[u] Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
[v] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REGIMENS AND DOSING[c]

FOLFIRI + Cetuximab (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly[15]
or Cetuximab 500 mg/m² IV over 2 hours, Day 1, every 2 weeks[16] (preferred for every 2 weeks)

FOLFIRI + Panitumumab[17](*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, Day 1
Repeat every 2 weeks

FOLFIRINOX[18,g]
Oxaliplatin 85 mg/m² IV Day 1,[s] Leucovorin 400 mg/m² IV over 2 hours on Day 1, Irinotecan 165–180 mg/m² IV over 30–90 minutes on Day 1, Fluorouracil 400 mg/m² IV Push Day 1, Fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion.
Repeat every 2 weeks

Modified FOLFIRINOX[19,20,g]
Oxaliplatin 85 mg/m² IV on Day 1,[s] Leucovorin 400 mg/m² IV over 2 hours on Day 1, Irinotecan 150 mg/m² IV over 30–90 minutes on Day 1, Fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks

FOLFIRINOX or Modified FOLFIRINOX + Bevacizumab[21,u]
Bevacizumab 5 mg/kg IV Day 1
Repeat every 2 weeks

IROX[22]
Oxaliplatin 85 mg/m² IV,[s]
followed by Irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

IROX + Bevacizumab[u]
Bevacizumab 7.5 mg/kg IV Day 1
Repeat every 3 weeks

Bolus or infusional Fluorouracil/Leucovorin
Roswell Park regimen[23]
Leucovorin 500 mg/m² IV over 2 hours, Days 1, 8, 15, 22, 29, and 36
Fluorouracil 500 mg/m² IV bolus 1 hour after start of Leucovorin, Days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

References

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[g] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[s] Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[u] Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REGIMENS AND DOSING[c]

Simplified biweekly infusional Fluorouracil/Leucovorin (sLV5FU2)[12]
Leucovorin[t] 400 mg/m² IV over 2 hours on Day 1,
followed by Fluorouracil bolus 400 mg/m² followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks
Weekly
Leucovorin 20 mg/m² IV over 2 hours on Day 1, Fluorouracil 500 mg/m² IV bolus injection 1 hour after the start of Leucovorin. Repeat weekly[24]
or
Fluorouracil 2600 mg/m² by 24-hour infusion plus Leucovorin 500 mg/m²
Repeat every week[24]

Bolus or infusional Fluorouracil + Bevacizumab[u]
Bevacizumab 5 mg/kg IV on Day 1
Repeat every 2 weeks

Capecitabine[25,v]
Capecitabine 850–1250 mg/m² PO twice daily for 14 days
Repeat every 3 weeks

Capecitabine + Bevacizumab[26,u]
Bevacizumab 7.5 mg/kg IV Day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, Days 1 and 8
Repeat every 3 weeks[27,28]
or Irinotecan 180 mg/m² IV over 30–90 minutes, Day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m² IV over 30–90 minutes, Day 1
Repeat every 3 weeks

Irinotecan + Bevacizumab[31,u]
Irinotecan 180 mg/m² IV Day 1
Bevacizumab 5 mg/kg IV Day 1
Repeat every 2 weeks
or
Irinotecan 300–350 mg/m² IV Day 1
Bevacizumab 7.5 mg/kg IV Day 1
Repeat every 3 weeks

Irinotecan + Cetuximab (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² first infusion, followed by 250 mg/m² IV weekly[29]
or Cetuximab 500 mg/m² IV over 2 hours, Day 1, every 2 weeks[16]
(preferred for every 2 weeks)

Irinotecan + Panitumumab[17,30] (*KRAS*/*NRAS*/*BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Cetuximab (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² first infusion, followed by 250 mg/m² IV weekly[29]
or Cetuximab 500 mg/m² IV over 2 hours, Day 1, every 2 weeks[16]
(preferred for every 2 weeks)

Panitumumab[32] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on Days 1–21[33]
or
First cycle: Regorafenib 80 mg PO daily on Days 1–7, followed by 120 mg PO daily on Days 8–14, followed by 160 mg PO daily on Days 15–21[34]
Subsequent cycles: Regorafenib 160 mg PO daily on Days 1–21
Repeat every 28 days

References

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[t] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[u] Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
[v] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REGIMENS AND DOSING[c]

Trifluridine and Tipiracil ± Bevacizumab[35,36]
Trifluridine and Tipiracil 35 mg/m^2 up to a maximum dose of 80 mg per dose (based on the Trifluridine component)
PO twice daily Days 1–5 and 8–12
Bevacizumab 5 mg/kg on Days 1 and 15
Repeat every 28 days

Pembrolizumab[37] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
Pembrolizumab 2 mg/kg IV every 3 weeks
or Pembrolizumab 200 mg IV every 3 weeks
or Pembrolizumab 400 mg IV every 6 weeks
or Pembrolizumab 4 mg/kg IV every 6 weeks

Nivolumab[38] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks
or Nivolumab 6 mg/kg IV every 4 weeks

Ipilimumab[39] + Nivolumab (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
Nivolumab 3 mg/kg (30-minute IV infusion) and Ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for 4 doses, followed by Nivolumab 3 mg/kg IV or Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks

Dostarlimab-gxly[40] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks

Cemiplimab-rwlc[41,42] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
350 mg IV on Day 1
Repeat every 3 weeks

Retifanlimab-dlwr[43,44] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
500 mg IV on Day 1
Repeat every 4 weeks

Tislelizumab-jsgr[45-48] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
200 mg IV on Day 1
Repeat every 3 weeks

Toripalimab-tpzi[49] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
3 mg/kg IV on Day 1
Repeat every 2 weeks

Penpulimab-kcqx[50] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb])
200 mg IV on Day 1
Repeat every 2 weeks

Pertuzumab[51] + Trastuzumab
(HER2-positive and *RAS* and *BRAF* WT)
Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Pertuzumab 840 mg IV loading dose on Day 1 of cycle 1, followed by 420 mg IV every 21 days

Tucatinib[52] + Trastuzumab
(HER2-positive and *RAS* and *BRAF* WT),
Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Tucatinib 300 mg PO twice daily

Fam-trastuzumab deruxtecan-nxki[53] (HER2-positive, IHC 3+)
Fam-trastuzumab deruxtecan-nxki 5.4 mg/kg IV on Day 1
Repeat every 21 days

References

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REGIMENS AND DOSING[c]

Encorafenib + Cetuximab[54-56] (*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 400 mg/m^2 IV followed by 250 mg/m^2 IV weekly
or Cetuximab 500 mg/m^2 IV every 2 weeks

Encorafenib + Panitumumab[54-56](*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

FOLFOX/Encorafenib + Cetuximab[57] (*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 500 mg/m^2 IV Day 1
Oxaliplatin 85 mg/m^2 IV Day 1
Leucovorin 400 mg/m^2 IV Day 1
Fluorouracil 400 mg/m^2 IV bolus on Day 1, followed by 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

FOLFOX/Encorafenib + Panitumumab[57] (*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6mg/kg IV every Day 1
Oxaliplatin 85 mg/m^2 IV Day 1
Leucovorin 400 mg/m^2 IV Day 1
Fluorouracil 400 mg/m^2 IV bolus on Day 1, followed by 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

Larotrectinib[58] (*NTRK 1/2/3* gene fusion-positive)
100 mg PO twice daily

Entrectinib[59] (*NTRK 1/2/3* gene fusion-positive)
600 mg PO once daily

Repotrectinib[60] (*NTRK 1/2/3* gene fusion-positive)
160 mg PO daily for first 14 days,
Then increase to 160 mg PO twice daily

Selpercatinib[61] (*RET* gene fusion-positive)
Patients ≥50 kg: 160 mg PO twice daily
Patients <50 kg: 120 mg PO twice daily

Adagrasib + Cetuximab[62] (*KRAS* G12C mutation positive)
Adagrasib 600 mg PO BID
Cetuximab 500 mg/m^2 IV every 2 weeks

Adagrasib + Panitumumab (*KRAS* G12C mutation positive)
Adagrasib 600 mg PO BID
Panitumumab 6 mg/kg IV every 2 weeks

Sotorasib + Cetuximab (*KRAS* G12C mutation positive)
Sotorasib 960 mg PO daily
Cetuximab 500 mg/m^2 IV every 2 weeks

Sotorasib + Panitumumab[63] (*KRAS* G12C mutation positive)
Sotorasib 960 mg PO daily
Panitumumab 6 mg/kg IV every 2 weeks

Fruquintinib[64]
5 mg PO daily on Days 1–21
Repeat every 28 days

References

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REFERENCES

[1] deGramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-2947.
[2] Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399.
[3] Maindrault-Goebel F, de Gramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Ann Oncol 2000;11:1477-1483.
[4] Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. Ann Oncol 2014;25:1172-1178.
[5] Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. BMC Cancer 2007;7:91.
[6] Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-4705.
[7] Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: A randomized clinical trial. JAMA 2017;317:2392-2401.
[8] Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019.
[9] Iwamoto S, Maeda H, Hazama S, et al. Efficacy of CapeOX plus cetuximab treatment as a first-line therapy for patients with extended RAS/BRAF/PIK3CA wild-type advanced or metastatic colorectal cancer. J Cancer 2018;9:4092-4098.
[10] Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2020;21:398-411.
[11] Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377:2103-2114.
[12] Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer 1999;35:1343-1347.
[13] Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786.
[14] Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-1075.
[15] Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.
[16] Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-458.
[17] Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-4713.
[18] Conroy T, Bosset J-F, Etienne P-L, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:702-715.
[19] Bennouna J, Andre T, Campion L, et al. Rationale and design of the IROCAS study: multicenter, international, randomized phase 3 trial comparing adjuvant modified (m) FOLFIRINOX to mFOLFOX6 in patients with high-risk stage III (pT4 and/or N2) colon cancer-A UNICANCER GI-PRODIGE Trial. Clin Colorectal Cancer 2019;18:e69-e73.
[20] Ychou M, Rivoire M, Thezenas S, et al. A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP Trial. Ann Surg Oncol 2013;20:4289-4297.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REFERENCES

[21] Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16:1306-1315.
[22] Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. J Clin Oncol 2008;26:4544-4550.
[23] Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Protocol C-03. J Clin Oncol 1993;11:1879-1887.
[24] Jäger E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. J Clin Oncol 1996;14:2274-2279.
[25] Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097-4106.
[26] Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1077-1085.
[27] Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413-1418.
[28] Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 2003;21:807-814.
[29] Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Intrapatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. J Clin Oncol 2012;30:2861-2868.
[30] Andre T, Blons H, Mabro M, et al. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. Ann Oncol 2013;24:412-419.
[31] Yildiz R, Buyukberber S, Uner A, et al. Bevacizumab plus irinotecan-based therapy in metastatic colorectal cancer patients previously treated with oxaliplatin-based regimens. Cancer Invest 2010;28:33-37.
[32] Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664.
[33] Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-312.
[34] Bekaii-Saab TS, Ou F-S, Ahn DH, et al. Regorafenib-dose optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncol 2019;20:1070-1082.
[35] Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-1919.
[36] Prager GW, Taieb J, Fakih M, et al. Trifluridine–tipiracil and bevacizumab in refractory metastatic colorectal cancer. N Engl J Med 2023;388:1657-1667.
[37] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520.
[38] Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability-high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-1191.
[39] Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. J Clin Oncol 2018;36:773-779.
[40] André T, Berton D, Curigliano G, et al. Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: A nonrandomized controlled trial. JAMA Netw Open 2023;6:e2341165.
[41] Paccaly AJ, Migden MR, Papadopoulos KP, et al. Fixed dose of cemiplimab in patients with advanced malignancies based on population pharmacokinetic analysis. Adv Ther 2021;38:2365-2378.
[42] Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol 2020;21:294-305.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PALLIATIVE SYSTEMIC THERAPY – REFERENCES

[43] Berton D, Pautier P, Lorusso D, et al. Antitumor activity and safety of the PD-1 inhibitor retifanlimab in patients with recurrent microsatellite instability-high or deficient mismatch repair endometrial cancer: Final safety and efficacy results from cohort H of the POD1UM-101 phase I study. Gynecol Oncol 2024;186:191-198.
[44] Lakhani N, Cosman R, Banerji U, et al. A first-in-human phase I study of the PD-1 inhibitor, retifanlimab (INCMGA00012), in patients with advanced solid tumors (POD1UM-101). ESMO Open 2024;9:102254.
[45] Li J, Xu Y, Zang A, et al. Tislelizumab in previously treated, locally advanced unresectable/metastatic microsatellite instability-high/mismatch repairdeficient solid tumors. Chin J Cancer Res 2024;36:257-269.
[46] Pang K, Yang Y, Tian D, et al. Long-course chemoradiation plus concurrent/sequential PD-1 blockade as neoadjuvant treatment for MMR-status-unscreened locally advanced rectal cancer: protocol of a multicentre, phase 2, randomised controlled trial (the POLAR-STAR trial). BMJ Open 2023;13:e069499.
[47] Yang Z, Zhang X, Zhang J, et al. Rationale and design of a prospective, multicenter, phase II clinical trial of safety and efficacy evaluation of long course neoadjuvant chemoradiotherapy plus tislelizumab followed by total mesorectal excision for locally advanced rectal cancer (NCRT-PD1-LARC trial). BMC Cancer 2022;22:462.
[48] Zhang L, Geng Z, Hao B, et al. Tislelizumab: A modified anti-tumor programmed death receptor 1 antibody. Cancer Control 2022;29:10732748221111296.
[49] Hu H, Kang PL, Zhang J, et al. Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 2022;7:38-48.
[50] Chen X, Wang W, Zou Q, et al. Penpulimab, an anti-PD-1 antibody, for heavily pretreated metastatic nasopharyngeal carcinoma: a single-arm phase II study. Signal Transduct Target Ther 2024;9:148.
[51] Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2019;20:518-530.
[52] Strickler JH, Cercek A, Siena S, et al. Additional analyses of MOUNTAINEER: A phase II study of tucatinib and trastuzumab for HER2-positive mCRC [abstract]. Ann Oncol 2022;33:S808-S869.
[53] Raghav KPS, Siena S, Takashima A, et al. Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): Primary results from the multicenter, randomized, phase 2 DESTINY-CRC02 study [abstract]. J Clin Oncol 2023;41(Suppl):Abstract 3501.
[54] Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with *BRAF* V600E-mutant metastatic colorectal cancer: Safety lead-in results from the phase III BEACON colorectal cancer study. J Clin Oncol 2019;37:1460-1469.
[55] Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. N Engl J Med 2019;381:1632-1643.
[56] Kopetz S, Grothey A, Van Cutsem E, et al. Quality of life with encorafenib plus cetuximab with or without binimetinib treatment in patients with BRAF V600E-mutant metastatic colorectal cancer: patient-reported outcomes from BEACON CRC. ESMO Open 2022;7:100477.
[57] Kopetz S, Yoshino T, Cutsem EV, et al. Encorafenib, cetuximab and chemotherapy in BRAF-mutant colorectal cancer: a randomized phase 3 trial. Nat Med 2025;31:901-908.
[58] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.
[59] Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
[60] Solomon BJ, Drilon A, Lin JJ, et al. 1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial [abstract]. Ann Oncol 2023;34:S787-S788.
[61] Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol 2022;23:1261-1273.
[62] Yaeger R, Weiss J, Pelster M, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. N Engl J Med 2023;388:44-54.
[63] Kuboki Y, Yaeger R, Fakih MG, et al. 45MO Sotorasib in combination with panitumumab in refractory KRAS G12C-mutated colorectal cancer: Safety and efficacy for phase Ib full expansion cohort [abstract]. Ann Oncol 2022;33:S136-S196.
[64] Dasari A , Lonardi S, Garcia-Carbonero R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet 2023;402:41-53.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURVIVORSHIP

Surveillance

- Surveillance recommendations can be found on APP-6 and APP-8.
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years for high-risk disease. For low-risk disease, routine CEA monitoring and routine CT scanning are not recommended beyond 10 years.

Survivorship Care Planning

The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient.[1]

- Develop survivorship care plan that includes:
  - Overall summary of treatment, including all surgeries, radiation treatments, and systemic therapy received.
  - Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
  - Surveillance recommendations.
  - Delineation of appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.
  - Health behavior recommendations.
  - Fertility counseling.

Management of Late/Long-Term Sequelae of Disease or Treatment[2-6]

- For issues related to distress, pain, neuropathy, fatigue, or sexual dysfunction, see NCCN Guidelines for Survivorship.
- For chronic diarrhea or incontinence:
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.
- Management of an ostomy:
  - Consider participation in an ostomy support group or coordination of care with a health care provider specializing in ostomy care (ie, ostomy nurse).
  - Screen for distress around body changes (NCCN Guidelines for Distress Management) and precautions around involvement with physical activity (see page SPA-C in the NCCN Guidelines for Survivorship).
- For oxaliplatin-induced neuropathy:
  - Consider duloxetine for painful neuropathy only, not effective for numbness, tingling, or cold sensitivity.[7]
  - Consider non-pharmacologic therapies such as heat or acupuncture.
  - Pregabalin or gabapentin are not recommended.

Counseling Regarding Healthy Lifestyle and Wellness[8] (NCCN Guidelines for Survivorship)

- Undergo all age- and gender-appropriate cancer and preventive health screenings as per national guidelines.
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources. Diet recommendations may be modified based on severity of bowel dysfunction.
- Drink alcohol sparingly, if at all.
- Receive smoking cessation counseling as appropriate (NCCN Guidelines for Smoking Cessation).

Additional health monitoring and immunizations should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURVIVORSHIP – REFERENCES

[1] Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press; 2006.
[2] Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer: patient-reported symptoms 4 years after diagnosis. Cancer 2007;110:2075-2082.
[3] Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369.
[4] Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994.
[5] DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer 2006;15:244-251.
[6] McGough C, Baldwin C, Frost C, et al. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-2287.
[7] Lavoie Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. JAMA 2013;309:1359-1367.
[8] Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2006;56:254-281.

Note: All recommendations are category 2A unless otherwise indicated.

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 assessed
N0	No tumor involvement of regional lymph node(s)
N1	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
N1a	Tumor involvement of one regional lymph node
N1b	Tumor involvement of two or three regional lymph nodes
N1c	No tumor involvement of regional lymph nodes, but there are tumor deposits in the subserosa or mesentery
N2	Tumor involvement of four or more regional lymph nodes

M	**Distant Metastasis**
cM0	No distant metastasis
cM1	Distant metastasis
cM1c	Metastasis to sites other than peritoneum
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

Note: 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.

American Joint Committee on Cancer (AJCC)
TNM Staging System for Appendix Cancer 9th ed., 2022

Table 2. **Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage 0	Tis(LAMN)		
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1	M0
Stage IIIB	T3-T4	N1	M0
Stage IIIC	Any T	N2	M0
Stage IVA	Any T	Any N	M1a-M1b
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

ABBREVIATIONS

A/P	abdomen/pelvis
AA	appendiceal adenocarcinoma
C/A/P	chest/abdomen/pelvis
CBC	complete blood count
CC	completeness of cytoreduction
CEA	carcinoembryonic antigen
CMP	comprehensive metabolic panel
CRS	cytokine release syndrome
ctDNA	circulating tumor DNA
dMMR	mismatch repair deficient
FDG	fluorodeoxyglucose
GBCA	gadolinium-based contrast agent
GCA	goblet-cell adenocarcinoma
HAMN	high-grade appendiceal mucinous neoplasm
IHC	immunohistochemistry
IPCT	intraperitoneal chemotherapy
LAMN	low-grade appendiceal mucinous neoplasm
MGPT	multigene panel testing
MiNEN	mixed neuroendocrine-nonneuroendocrine neoplasm
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MWA	microwave ablation
mut/Mb	mutations/megabase
NET	neuroendocrine tumor
NOS	not otherwise specified
PCI	Peritoneal Cancer Index
PNI	perineural invasion
RFA	radiofrequency ablation
SBRT	stereotactic body radiation therapy
TMB	tumor mutational burden
UC	undifferentiated carcinoma
WT	wild-type

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Appendiceal Neoplasms and Cancers