The American Society of Colon and Rectal Surgeons, Clinical Practice Guidelines for the Management of Appendiceal Neoplasms

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PREPARED ON BEHALF OF THE CLINICAL PRACTICE GUIDELINES COMMITTEE OF THE AMERICAN SOCIETY OF COLON AND RECTAL SURGEONS.

The American Society of Colon and Rectal Surgeons is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines Committee is composed of society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This Committee was created to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus. This is accompanied by the development of clinical practice guidelines based on the best available evidence. These guidelines are inclusive but not prescriptive. Their purpose is to provide information to support decision-making rather than to dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, healthcare workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines.

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It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care nor exclusive of methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all the circumstances presented by the individual patient.

STATEMENT OF THE PROBLEM

Historically, the estimated incidence of appendiceal tumors was 0.12 cases per 1,000,000 people per year; however, based on recent large database studies, the incidence may be as high as 0.97 per 100,000 population.[1–3] It is unclear whether this increase reflects an actual change in the disease occurrence or simply greater recognition and reporting. Although tumors of the appendix are rare, surgeons should be familiar with the implications of appendiceal pathology, because almost 300,000 appendectomies are performed annually in the United States, and neoplasia is found in ≈1% to 2% of these specimens.[4–6]

CLASSIFICATION BY HISTOPATHOLOGY

Given the rarity and multiple different terms used to describe appendiceal neoplasms, consistency regarding their classification not only allows for improved reporting but also for more precise management. In general terms, ap-

pendiceal neoplasms can be broadly described as epithelial, such as adenomas or adenocarcinomas, or nonepithelial (eg, neuroendocrine or lymphoma). The epithelial group is often further subdivided based on mucin production, because mucinous tumors have distinctly different biologic behavior and oncologic outcomes from nonmucinous neoplasms.[4] The World Health Organization classifies the majority of noninvasive epithelial lesions as low-grade appendiceal mucinous neoplasms (LAMNs).[7] Histologically, LAMNs are characterized by well-differentiated adenomas that can proliferate outside the appendix in a malignant fashion. Acellular or cellular extra-appendiceal mucin may be associated with LAMNs, although this is not a requirement. The LAMN terminology includes lesions that were described previously as *mucoceles* or *mucinous cystadenomas*, which are terms no longer in use. Some authors have suggested an intermediate grouping between traditional LAMNs and invasive carcinoma.[8] These LAMNs of uncertain malignant potential may exhibit gross perforation, mural fibrosis, mucin dissecting within the appendiceal wall, or acellular mucin in the periappendiceal soft tissues. High-grade appendiceal neoplasms (HAMNs) share some histologic features with LAMNs but exhibit more aggressive cytologic atypia. The distinct biological and clinical behaviors of HAMNs are poorly characterized.[9]

Appendiceal adenocarcinomas may be either mucinous or nonmucinous. Mucinous adenocarcinomas are characterized by invasive glands containing high-grade cytologic atypia and extracellular mucin in >50% of the lesion.[7] Appendiceal adenocarcinomas resemble their colorectal counterparts histologically, regularly expressing p53, CD44, and CDX2. They often demonstrate signet ring cells if poorly differentiated, are prone to lymphatic spread, and are staged according to the TNM classification. Goblet cell carcinoid tumors represent a variant of adenocarcinoma that demonstrates some features similar to traditional neuroendocrine tumors (NETs; eg, positive chromogranin A staining).[7] However, these mixed adenoneuroendocrine carcinomas are more aggressive than traditional NETs and should generally be treated in a similar manner to classic appendiceal adenocarcinomas.[10,11]

Appendiceal neoplasms may perforate and spread throughout the peritoneal cavity.[12] When this spread includes abundant mucin production, the term *pseudomyxoma peritonei* (PMP) is used. Some authors make the distinction that PMP represents a clinical finding rather than a diagnosis and should be reserved for diffuse spread of mucin throughout the abdomen as opposed to mucin deposits that are confined adjacent to the appendix.[9] Because PMP often recurs after treatment and the 10-year overall survival (OS) rate after surgery for PMP is 63%, PMP should be considered a malignant condition.[13,14] Variable degrees of cellularity within PMP can lead to vastly different patient prognoses.[11,13,15,16] To reduce confusion and improve consistency in the literature, a consensus reporting classification was published recently for both PMP and appendiceal neoplasia.[14] The authors recommended categorizing PMP based on the degree of cellularity within the mucin as follows: acellular, low-grade histologic features, high-grade histologic features, and PMP with signet ring cells (Table 1). The low-grade group includes the commonly reported term of disseminated peritoneal adenomucinosis, whereas peritoneal mucinous carcinomatosis is designated as high grade. Because the grouping is based on histology, clinical features such as omental caking or ovarian involvement may represent either low- or high-grade PMP. This classification aligns with other schemes and helps determine treatment and prognosis.[17,18]

TABLE 1. Histologic classification of PMP

Pathologic lesion	*Criteria*
Acellular mucin	• Mucin within peritoneal cavity without neoplastic epithelial cells
Low-grade mucinous carcinoma peritonei (DPAM)	• Epithelial component typically scanty • Minimal cytological atypia • Strips, gland-like structures or small cell clusters
High-grade mucinous carcinoma peritonei (PMCA)	• Relatively more cellular • Cribriform growth pattern • High-grade cytological atypia • Numerous mitoses
High-grade mucinous carcinoma peritonei with signet rings cells (PMCA-S)	• Any lesion with a signet ring cell component, that is, round cells with intracytoplasmic mucin pushing nucleus against cell membrane

Adapted from Carr et al.[9]
DPAM = disseminated peritoneal adenomucinosis; PMCA = peritoneal mucinous carcinomatosis; PMCA-S = peritoneal mucinous carcinomatosis with signet ring cells; PMP = pseudomyxoma peritonei.

Nonepithelial appendiceal neoplasms include NETs. These lesions are histologically similar to those found elsewhere in the GI tract.[7] Appendiceal NETs are frequently asymptomatic and identified incidentally after routine appendectomy. Staging remains controversial and may be based on tumor size, depth of invasion, or degree of differentiation. Other rare nonepithelial appendiceal neoplasms include GI stromal tumors, lymphomas, and neural proliferations, which are not considered in this guideline.

METHODOLOGY

Selected members of the ASCRS Clinical Practice Guidelines committee drafted de novo position statements after performing a thorough search and review of the relevant literature. With input from the authors, a professional librarian conducted a systematic literature search encompassing January 1, 1997, to April 30, 2019, inclusive, across the Ovid Medline, Embase, and Scopus medical databases. Pertinent inclusion criteria were English language article and adult human patients, and both current and archaic terminology for appendiceal neoplasms were included as follows: (*appendiceal*, *appendix*, *appendicular*)

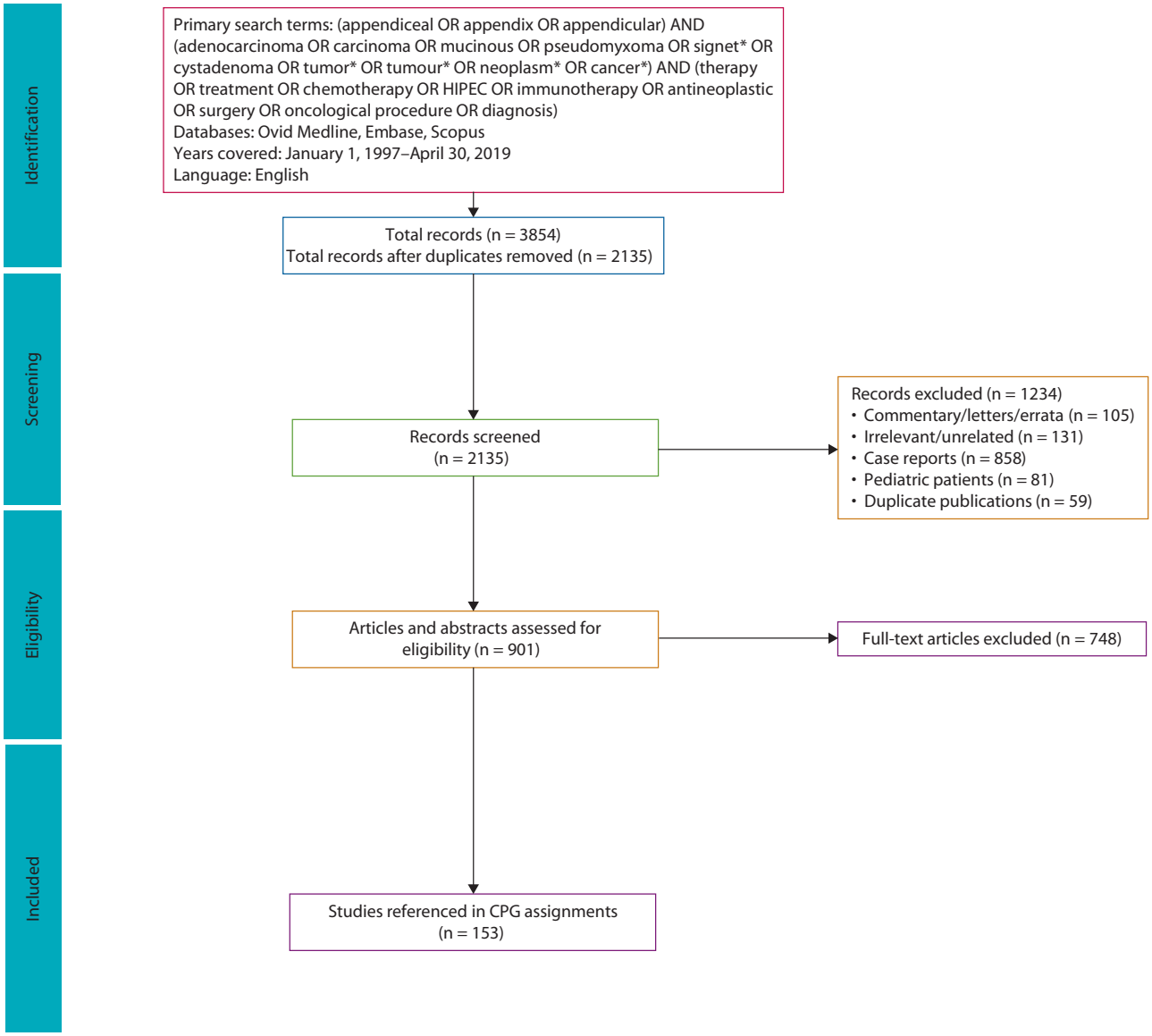

FIGURE 1. Literature search flow sheet. CPG = Clinical Practice Guidelines.

AND (*adenocarcinoma*, *carcinoma*, *mucinous*, *pseudomyxoma*, *signet**, *cystadenoma*, *tumor**, *tumour**, *neoplasm*, *cancer*). These groups were combined with various treatment modalities to include surgery and chemotherapy. Refer to Figure 1 for the full search algorithm. Directed searches of references in selected published articles yielded additional records. The initial search produced 2135 records after removal of duplicates. These were screened for relevance, yielding 901 abstracts for review as the basis for the recommendations. A directed search of references embedded in the candidate publications was performed. Emphasis was placed on prospective trials, meta-analyses, systematic reviews, and practice guidelines. Peer-reviewed observational studies and retrospective studies were included when higher-quality evidence was insufficient. The final source material used was evaluated for methodologic quality, the evidence base was examined, and a treatment guideline was formulated by the subcommittee. The final grade of recommendation and level of evidence for each statement were determined using the Grades of Recommendation, Assessment, Development, and Evaluation system (Table 2). When agreement was incomplete regarding the evidence base or treatment guideline, consensus from the committee chair, vice chair, and 2 assigned reviewers determined the outcome. Members of the American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines Committee worked in joint production of these guidelines from inception to final publication. Recommendations formulated by the subcommittee were reviewed by the entire Clinical Practice Guidelines Committee. Final recommendations were approved by the ASCRS Executive Committee. In general,

TABLE 2. The GRADE System: grading recommendations

	Description	*Benefit versus risk and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low- or very-low-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendations, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, low- or very-low-quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Adapted from Guyatt G, Gutermen D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129:174-181. Used with permission.
GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; RCT = randomized controlled trial.

each ASCRS Clinical Practice Guideline is updated every 5 years.

GENERAL CONSIDERATIONS

1. Patients with appendiceal neoplasms should undergo a complete history and physical examination. Grade: Strong recommendation based on low-quality evidence, 1C.

Neoplasms of the appendix are not often suspected before surgery and may be discovered either intraoperatively or incidentally in the pathologic specimen. Vague symptoms of fatigue, weight gain, chronic abdominal pain, and early satiety may be signs of advanced disease. Tumors can also present as appendicitis, bowel obstruction, or a pelvic mass.[19,20] A thorough history and physical examination are essential. History should include previous surgical history, particularly appendectomy, with review of the associated operative note and pathology report, because patients may not be aware of the presence of an incidental neoplasm or mucin. Pathology slides should typically be reviewed in cases of diagnostic uncertainty. Physical examination should include a pelvic and digital rectal examination to assess for pelvic masses and mobility of surrounding structures. Rare presentations of mucinous appendiceal neoplasms include findings of pseudomyxomatous material in ventral, incisional, and inguinal hernias.[21,22]

Although decision-making for performing an interval appendectomy after initial nonoperative management of presumed appendicitis is complex, the surgeon must consider that the risk for occult appendiceal neoplasm appears greater in this subgroup compared with the general population.[23–28] Modern retrospective and database studies suggest an incidence of malignancy between 2.3% and 12.0%; in particular, older age and indeterminate imaging appear to be significant risk factors for appendiceal cancer.[23,24,26,27] Periappendiceal abscess may be an even stronger predictor of occult neoplasm; the Finnish Peri-Appendicitis Acuta multicenter randomized controlled trial found an overall neoplasm incidence of 20% in these patients.[27] At a minimum, patients should be informed of this risk.

2. Colonoscopy should be performed in patients with confirmed or suspected appendiceal neoplasms. Grade: Strong recommendation based on low-quality evidence, 1C.

Patients with appendiceal neoplasms are at increased risk of harboring synchronous colonic lesions compared with

the general population, with population-based studies reporting 13% to 42% of patients with primary epithelial appendiceal lesions having concurrent colorectal neoplasia.[5,6,29,30] In a population-based study from the Netherlands from 1995 to 2005 that included 1482 patients with an appendiceal epithelial neoplasm, 193 (13%) had an incidental colonic adenoma (n = 37) or adenocarcinoma (n = 156).[5] In this study, the primary pathology of the appendiceal neoplasms was reported as mucinous cystadenoma (32%), mucocele (31%), and nonmucinous adenoma (26%), and the majority of the colonic adenocarcinomas discovered were right sided. By comparison, single-institution studies suggest that <4% of patients with colorectal cancer have synchronous appendiceal neoplasms.[31,32] In a single-surgeon series of 169 consecutive patients who underwent prophylactic appendectomy during segmental resection for colorectal cancer (including 63 right colectomies), the rate of incidental appendiceal neoplasia was 4%.[32] Although appendiceal neoplasms are rarely diagnosed at the time of colonoscopy, they may present endoscopically with an inverted or mass-like protrusion or mucous or polypoid tissue at the appendiceal orifice.[30,33]

3. Appendectomy should be performed if a grossly abnormal appendix is encountered during an unrelated abdominal operation. Grade: Strong recommendation based on low-quality evidence, 1C.

During an abdominal or pelvic operation, appendectomy is warranted for incidental findings of luminal dilation, serosal puckering or irregularity, or a mass. Care should be taken to avoid intraoperative perforation and spillage, and conversion to open surgery may be necessary in certain situations.[34–36] In a small series of 24 consecutive patients with appendiceal mucinous neoplasms, all were managed laparoscopically without intraoperative spillage. In this series, the majority required partial cecectomy (15/24; 62.5%) or ileocecectomy (8/24; 33.3%), whereas 1 patient underwent simple appendectomy.[37] The extent of resection is predominantly based on involvement of the base of the appendix. The priority is obtaining a pathologic diagnosis with a grossly negative margin. In most cases, appendectomy or partial cecectomy is sufficient when an abnormal appendix is encountered incidentally. When performing a laparoscopic approach, surgeons should consider using a specimen retrieval bag to help avoid spilling mucin.

An incidental finding of intraperitoneal mucin suggests the presence of a mucinous neoplasm of the GI or gynecologic tracts. In this setting, careful inspection of the appendix (and adnexa in a female patient) is warranted. Data from multiple retrospective, single-institution studies do not support routine appendectomy for a normal-appearing appendix in the setting of an ovarian mucinous neoplasm, because the incidence of synchronous appendiceal pathology in these cases is low.[38–40]

APPENDICEAL NETS

4. Preoperative assessment of patients with appendiceal NETs should typically include history and physical examination, colonoscopy, and CT or MRI of the chest, abdomen, and pelvis. Grade: Strong recommendation based on low-quality evidence, 1C.

Preoperative evaluation of patients with appendiceal NETs should involve a thorough history and physical examination, with a review of systems that specifically document the presence or absence of symptoms that could be associated with carcinoid syndrome, such as facial flushing, diarrhea, and dyspnea. NETs arising from the small intestine or from the colon are associated with higher rates (15%–30%) of synchronous NETs compared with appendiceal NETs, the latter having a low incidence of synchronicity often uncalculated in many series.[41] Irrespective of the risk of synchronous NETs, a preoperative colonoscopy is important because of the association of NETs with synchronous noncarcinoid neoplasms.[42] A series of 13,715 NETs from various body regions, including different segments of the alimentary tract, reported a synchronous cancer rate of 22.4% for the entire NET cohort.[43] Smaller series report similar rates of synchronous malignancies, with colorectal cancers representing between 25% and 50% of these synchronous lesions.[44,45] Because appendiceal NETs can metastasize to the liver, as well as to the lungs, and because the management of metastatic NET differs from nonmetastatic appendiceal NET, patients should typically undergo clinical staging with an intravenous, contrast-enhanced CT or MRI of the chest, abdomen, and pelvis.

5. NET-specific imaging is not required for all patients with appendiceal NETs. Grade: Weak recommendation based on moderate-quality evidence, 2B.

Because most appendiceal NETs will express somatostatin receptors, somatostatin receptor scintigraphy (SRS) can be used to identify foci of NETs.[46] Furthermore, because SRS can confirm that enhancing lesions express somatostatin receptors, this study is useful in supporting the selection of somatostatin receptor antagonists as therapy in settings of locally advanced or metastatic disease.[47] With the fine resolution of modern CT and MRI, complementary use of SRS provides the highest yield in cases of indeterminate findings for potentially metastatic disease based on CT and MRI and in patients with symptoms consistent with carcinoid syndrome (eg, flushing, diarrhea, and bronchospasm). Although ≈80% or more of NETs will express somatostatin receptors, suggesting that SRS is likely to reveal the presence of an NET,[48] there are insufficient data to support the routine use of SRS for routine surveillance.

Positron emission tomography (PET)-CT scans are an additional imaging modality for evaluating metastatic disease from appendiceal NETs. In comparison with tra-

ditional 2-[18F] fluoro-2-deoxy-D-glucose PET-CT, SRS is more sensitive for detection of well-differentiated NETs (eg, those expressing somatostatin receptors), whereas 2-[18F] fluoro-2-deoxy-D-glucose PET detects more poorly differentiated tumors.[49] More recently, (68Ga)dotatate PET-CT has been shown to be equivalent or superior to SRS for detecting gastroenteric NETs.[50] In 1 study, (68Ga)dotatate PET-CT detected occult lesions in 65.2% of NET patients with negative biochemical testing, 40% of which were not present on SRS.[51] The use of routine (68Ga)dotatate PET-CT imaging should be balanced with the high cost of these studies.

6. Biochemical testing should be performed in patients with localized or metastatic appendiceal NETs to establish baseline measures for future surveillance and disease monitoring. Grade: Weak recommendation based on moderate-quality evidence, 2B.

Appendiceal NETs are not commonly biochemically active unless there is a significant burden of hepatic metastatic disease. The most common metabolites produced by appendiceal NETs include chromogranin A and 5-hydroxyindoleacetic acid, the former evaluated with serum and the latter with a 24-hour urine collection. Elevated levels of either of these metabolites have been associated with poor prognosis.[52,53] Importantly, these markers are not reliable for the purposes of diagnosing the presence of an NET or for guiding therapeutic decisions.[54,55]

7. Extent of surgical resection of appendiceal NETs is determined by tumor size and histologic features. Grade: Strong recommendation based on low-quality evidence, 1C.

For nonmetastatic NETs confined to the appendix, treatment is generally based on the size of the primary tumor. Lesions <1 cm in diameter and without unfavorable features are adequately treated with appendectomy taking care to remove the entire mesoappendix. Long-term disease-free survival in these patients is 100%.[56–58] Tumors >2 cm are best treated with formal right hemicolectomy, because the reported risk of nodal metastases may be as high as 40%.[56,59–61] Appendiceal NETs between 1 and 2 cm in size have an intermediate risk of nodal metastases in most series.[56,57,62] However, the largest clinical series found no nodal disease in primary tumors <2 cm, and some authors recommend appendectomy alone for all lesions under this threshold.[63,64] In addition to size, histologic features influence surgical decision-making. Findings on histology that may be unfavorable include mesoappendiceal invasion >3 mm, advanced grade consisting of elevated mitotic index (>2 mitoses per high-power field) or Ki-67 index (>3%) and lymphatic or vascular invasion.[60,65] Decision-making for right hemicolectomy in small- and intermediate-sized appendiceal NETs should be made on a case-by-case basis, with consideration given to histologic features and patient comorbidities and preferences.[60] Although the majority of appendiceal NETs occur in the tip of the appendix, patients with tumor present at the base of the appendix or those resected with a positive margin may need to undergo more extensive resection to obtain negative surgical margins.[63]

8. Surveillance after resection of appendiceal NETs with curative intent should involve physical examination, serial biochemical testing, and imaging of the chest, abdomen, and pelvis using either CT or MRI. Grade: Weak recommendation based on low-quality evidence, 2C.

For patients who have undergone surgical resection with curative intent, it is recommended that surveillance for disease recurrence be performed in patients deemed to be candidates for further treatment should a recurrence be detected. Surveillance involves clinical, biochemical, and radiographic components. Although the interval between surveillance evaluations and the duration of surveillance is not standardized because of the rarity and often indolent nature of NETs, the interval between surveillance examinations typically ranges from 6 to 12 months, depending on the histologic grade of NET, and it is generally recommended that the duration of surveillance extends for 10 years after curative resection.[66,67] Serum chromogranin A levels and urine 5-hydroxyindoleacetic acid levels can correlate both with response to therapy and recurrence, but because of the nonspecific nature of these biomarkers, correlation with imaging studies is required.[68] Currently, there are insufficient data to support routine use of SRS or other NET-specific imaging modalities for routine surveillance, although they may be beneficial in confirming recurrent disease discovered on CT or MRI, as well as assessing somatostatin receptor expression for potential therapeutic consideration.[69,70]

APPENDICEAL MUCINOUS NEOPLASMS AND ADENOCARCINOMA

9. Tumor markers typically should be assessed on diagnosis of appendiceal epithelial neoplasms and routinely followed after resection. Grade: Weak recommendation based on low-quality evidence, 2C.

The serum tumor markers CEA, CA19-9, and CA125 are frequently obtained on diagnosis of appendiceal mucinous neoplasms and routinely monitored to assess disease remission or progression.[71] Although their individual predictability of disease recurrence has not been well characterized, most high-volume institutions routinely combine tumor markers with imaging at baseline, during chemotherapy, and after surgery, if applicable. In the setting of muci-

nous adenocarcinoma of the appendix, a normal baseline CA-125 has been shown to correlate with the likelihood of achieving complete cytoreduction.[72] Elevated baseline CA19-9 has also been described as an independent predictor of worse progression-free survival (PFS) and can be useful to diagnose disease recurrence after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[72,73] CEA has been reported to normalize after complete cytoreduction, as compared with CA 19-9 and CA-125, which may remain elevated.[74] Taflampas et al[75] showed a significantly longer disease-specific survival in treated patients with normal preoperative markers, and they suggested that tumor marker elevation may help tailor the need for perioperative systemic chemotherapy. However, surveillance imaging seems more sensitive for detecting peritoneal disease recurrence than tumor markers alone.[76]

With regard to the use of other markers to distinguish low-grade versus HAMNs, many have proposed molecular profiling, including cyclooxygenase 2 expression and KRAS, TP53, and SMAD4 gene mutations, without conclusive evidence on their impact on diagnosis or management.[77–81] Although some generalizations may be extrapolated from colorectal cancer, the rarity of appendiceal adenocarcinoma limits the ability to make conclusions regarding specific genetic defects.

10. Cross-sectional imaging with CT or MRI should be performed on diagnosis of appendiceal epithelial neoplasms and routinely followed after resection. Grade: Strong recommendation based on low-quality evidence, 1C.

CT of the chest, abdomen, and pelvis is the most common imaging modality used to evaluate the primary tumor and assess for metastatic disease. The addition of a PET scan has not been shown to improve staging or significantly change management.[82] MRI can detect extraluminal mucin and has also been shown to be superior to CT in the detection of peritoneal disease using a combination of diffusion-weighted imaging and delayed postgadolinium sequences.[83] In small noncomparison studies, MRI has proven useful to predict the peritoneal cancer index (PCI) before surgery, and it is often used in postoperative surveillance after CRS and HIPEC.[76,83] Unfortunately, accurate preoperative diagnosis can be challenging because of a wide range of clinical presentations and overlapping imaging appearances of appendiceal neoplasms. Although some have proposed using the 2010 World Health Organization pathologic classification as a framework to report imaging findings in patients with appendiceal neoplasms, no structured imaging reporting systems are routinely used in this patient population.[84]

Although there are no formal surveillance guidelines for appendiceal neoplasms after appendectomy, patients with low-grade localized tumors of the appendix who undergo appendectomy alone rarely develop PMP; therefore, frequent postoperative imaging for extended intervals is typically of minimal benefit.[6,85,86] Postoperative surveillance must be individualized in these situations according to tumor and patient characteristics. One approach for localized and completely resected LAMN is to obtain MRI with tumor markers every 6 months for 2 years because most early recurrences occur within that timeframe.[85] Patients with high-grade tumors or who undergo right hemicolectomy because of a locally advanced or perforated tumor, questionable surgical margins, or who had lymphatic or peritoneal disease should typically undergo CT or MRI every 4 to 6 months for the first 2 years and yearly thereafter for ≥5 years. In patients with acellular or low-grade peritoneal disease who have undergone CRS and HIPEC, CT or MRI of the abdomen and pelvis is recommended at 2 months postoperatively (baseline), then annually for ≥5 years.[86,87] In patients with high-grade peritoneal disease, additional imaging of the chest and more frequent surveillance every 6 months for the first 6 years postoperatively may help detect recurrent disease earlier.[88] Although peritoneal recurrences beyond 10 years may occur and some institution-specific surveillance protocols may extend to 15 years, there is no clear evidence supporting prolonged surveillance.[89]

11. Peritoneal cytology has minimal impact on the management of patients with appendiceal tumors and is not recommended as routine practice. Grade: Weak recommendation based on low-quality evidence, 2C.

Although positive peritoneal cytology is useful to various degrees in patients with pancreatic, gastric, or ovarian malignancy, the use of cytology in patients with appendiceal neoplasms remains unknown.[90–92] Some insight may be gained from extrapolation of studies on colorectal cancer with peritoneal spread. Positive peritoneal cytology occurs in 23.5% of treated patients and correlates with OS (19 vs 44 mo for negative peritoneal cytology; $p = 0.01$).[93] Yonemura et al[94] also showed that positive cytology was independently associated with worse PFS in 205 patients with colorectal cancer undergoing complete CRS and HIPEC. Neither of these studies performed subgroup analysis for patients with appendiceal malignancies or evaluated its role in the decision to perform HIPEC. In patients with appendiceal neoplasms, there is no evidence to support the routine evaluation of peritoneal cytology, because its impact on management and prognosis remains unclear.

12. Patients with LAMNs with negative margins and no evidence of perforation or peritoneal involvement are safely treated with appendectomy alone. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

In modern observational studies, oncologic outcomes after appendectomy, including the entire mesoappendix for

LAMN without perforation or peritoneal involvement, have shown very low recurrence rates, consistent with the indolent behavior of these neoplasms.[95–97] Appropriate initial surgical management is critical because iatrogenic rupture of the appendix can convert the situation from localized to disseminated; therefore, if an unruptured LAMN cannot be safely resected laparoscopically, conversion to an open operation is recommended. Limited published data suggest that a microscopically positive resection margin after appendectomy for nonperforated LAMN does not predict disease recurrence and therefore does not warrant formal right colectomy.[98] Guaglio et al[85] prospectively examined 41 patients with LAMN treated by appendectomy (n = 31) or right colectomy (n = 5) with close radiographic and biochemical surveillance. Appendiceal rupture was present in 21 patients (51%). At a median follow-up of 58 months, 5-year recurrence-free survival was 95%, with only 2 patients experiencing peritoneal recurrences at 18 and 22 months postappendectomy.

Rarely, a primary appendiceal mucinous neoplasm will harbor high-grade cytology yet lack infiltrative invasion associated with adenocarcinoma. These lesions are best classified as HAMNs.[14] Although appendectomy alone is typically sufficient for treating HAMNs, care should be taken to exclude the presence of associated invasive adenocarcinoma, including comprehensive histologic evaluation of the entire surgical specimen.

13. Patients with nonmetastatic adenocarcinoma of the appendix should undergo right hemicolectomy. However, in the setting of peritoneal spread, colectomy may not confer a survival benefit. Grade: Strong recommendation based on low-quality evidence, 1C.

In patients with appendiceal adenocarcinoma, the rate of metastatic disease to regional lymph nodes ranges from 20% to 67%, with positive nodes more likely in the nonmucinous (intestinal) subtype.[99–103] Because of this substantial risk, adenocarcinoma confined to the appendix should be treated with right hemicolectomy, because formal resection of the nodal basin allows for more complete staging and may have a therapeutic benefit.[102] The recommendation for formal colectomy also includes appendiceal goblet cell carcinoids, tumors characterized by a mixture of histologic features of both neuroendocrine and epithelial adenocarcinoma.[104] The natural history of patients with goblet cell carcinoid of the appendix closely resembles high-grade appendiceal tumors, and it should be treated in a similar manner.[103,105–107]

In the setting of peritoneal metastases, routine right hemicolectomy to remove clinically normal lymph nodes is not recommended. Several single-institution and retrospective observational studies have failed to demonstrate a survival benefit to right colectomy versus appendectomy alone in patients undergoing CRS and HIPEC.[100,102,108,109] Turaga et al[102] examined population-based data using Surveillance, Epidemiology, and End Results and found that right colectomy did not improve survival after adjusting for age, sex, T stage, metastatic disease, and grade. Interestingly, no benefit to colectomy was seen in node-positive patients without peritoneal metastases either, suggesting that nodal positivity reflects a more aggressive biology that is not impacted by surgical resection. Despite these reservations, it should be noted that right colectomy is sometimes necessary to achieve a complete cytoreduction of peritoneal disease originating from the appendix.

14. CRS is indicated in selected patients with appendiceal neoplasms and evidence of peritoneal involvement. Grade: Strong recommendation based on moderate-quality evidence, 1B.

Surgical resection remains the benchmark therapy for patients with appendiceal neoplasms with peritoneal metastases. The goal of CRS is eradication of gross disease; when this goal is achieved, CRS is often combined with intraperitoneal chemotherapy, such as HIPEC (see subsequent recommendation). Typically, CRS entails selective peritonectomies, especially over the diaphragms and within the pelvis, excision or destruction of tumor implants on the surfaces of the small intestine and colon, supracolic omentectomy, and other resections as indicated by involvement (eg, splenectomy).[110–112] Individualized decisions regarding CRS with or without HIPEC should be undertaken by a multidisciplinary team, preferably at experienced centers.[109,113] Proper patient selection is crucial in treating patients with peritoneal involvement from appendiceal neoplasms.[114] Findings on cross-sectional imaging may help determine resectability and guide selection of suitable candidates for cytoreduction.[115,116] Diagnostic laparoscopy may also be used to estimate the likelihood of complete cytoreduction or to obtain tissue if other techniques such as CT-guided biopsy are not feasible. Peritoneal involvement may be quantified using Sugarbaker's Peritoneal Carcinomatosis Index (PCI) or the Peritoneal Surface Disease Severity Score.[117–119] PCI is an intraoperative determination based on the size of tumor deposits in 13 regions within the abdomen and ranges from 0 to 39. The Peritoneal Surface Disease Severity Score incorporates clinical symptoms, PCI, and tumor histology to produce a maximum score of 22; stage IV is considered >10. Although useful for objectively measuring disease, such scoring systems may not correlate with survival in appendiceal neoplasms treated with complete cytoreduction.[110] However, successful cytoreduction is less likely in patients with biliary or ureteral obstruction, multifocal bowel obstruction, or extensive small bowel involvement. In almost every analysis of clinical and pathologic factors, completeness of cytoreduction is consistently an independent predictor of outcome.[13,15,110,114,120–126]

Women with peritoneal spread often experience ovarian involvement. Metastatic ovarian tumors may grow rapidly and typically are resistant to systemic chemotherapy. Mehta et al[127] retrospectively evaluated 258 female patients with ≥1 remaining ovary who underwent CRS and HIPEC for colorectal and appendiceal tumors. Overall, 141 of 258 patients (55%) had ovarian tumor involvement. Of 40 patients with 1 macroscopic ovarian metastasis, microscopic involvement of the contralateral ovary was found in 18 (45%) of 40. Of 141 patients in whom both ovaries were macroscopically normal, 24 (17%) of 141 had microscopic ovarian involvement. Given the risk of occult ovarian metastases in this patient population, bilateral salpingo-oophorectomy should be strongly considered, and patients should be appropriately counseled preoperatively.[128]

The management of patients with limited peritoneal involvement of acellular mucin in the setting of LAMN remains controversial, particularly when it is isolated to the right lower quadrant.[6,86,129] Appendectomy with cytoreduction of the periappendiceal peritoneum in these cases has been associated with reasonably low peritoneal recurrence rates between 3% and 7%. Conversely, LAMNs associated with cellular mucin deposits are associated with a higher risk of subsequent peritoneal involvement (33%–78%); these patients should be considered for HIPEC.[130,131]

15. In selected patients with appendiceal epithelial neoplasms, intraperitoneal chemotherapy may offer additional benefit for reducing peritoneal disease recurrence compared with CRS alone. Grade: Strong recommendation based on moderate-quality evidence, 1B.

After complete resection of all gross peritoneal disease, patients with appendiceal neoplasms may be treated with intraperitoneal chemotherapy. Most commonly, this is performed concurrently with CRS through the delivery of HIPEC. Interest in CRS and HIPEC for appendiceal neoplasms increased after a large randomized, controlled trial for carcinomatosis from colorectal and appendiceal cancers demonstrated a doubling of survival for CRS/HIPEC compared with systemic chemotherapy alone (22.3- vs 12.6-mo median OS).[120] Additional long-term follow-up demonstrated a median OS of 48 months and a 5-year survival of 45% for those patients for whom a complete cytoreduction could be achieved.[132] Multiple large retrospective and prospective phase II studies including patients with both low-grade and high-grade peritoneal disease have demonstrated improved long-term patient survival, decreased tumor recurrence, longer time to disease progression, and less frequent repeat operative interventions in patients who undergo CRS plus HIPEC compared with debulking procedures alone or palliative systemic chemotherapy.[13,15,124,133–141] A 2012 observational study by Chua et al[13] including 2298 patients reported superior PFS associated with HIPEC after CRS (HR = 0.65; $p = 0.03$) for metastatic appendiceal mucinous neoplasm, but there was no OS difference in their multivariate analysis.[142] Median OS was 16.3 years, and median PFS was 8.2 years. Mitomycin or platinum-based chemotherapeutics are the most common drugs used during HIPEC.

Aside from HIPEC, other methods for delivering intraperitoneal chemotherapy include the early postoperative intraperitoneal chemotherapy (EPIC) or delayed postoperative approaches.[16,126,143–149] Generally, similar results are obtained among the various approaches, and few head-to-head comparisons exist; a retrospective study in Norway of 93 patients compared EPIC and HIPEC after complete cytoreduction and showed no difference in 10-year OS and DFS.[16] An ongoing randomized, controlled trial of HIPEC versus EPIC may provide additional answers about which treatment is superior.[142]

16. Systemic chemotherapy may improve survival in patients with metastatic HAMNs. Benefit from systemic chemotherapy for low-grade lesions with peritoneal spread is questionable. Grade: Strong recommendation based on low-quality evidence, 1C.

The role of systemic chemotherapy and the optimal chemotherapeutic drug regimen for treatment of metastatic appendiceal malignancies continues to be investigated. Although lacking level I evidence, 5-fluorouracil–based systemic chemotherapy (similar to that used for colorectal adenocarcinoma) is typically recommended for patients with high-grade peritoneal disease or nodal metastases. Blackham et al[150] reported improved PFS with perioperative systemic chemotherapy in patients with high-grade PMP undergoing CRS plus HIPEC, especially in patients who underwent suboptimal cytoreduction and those with signet ring cell histology. Systemic chemotherapy showed no benefit in patients with low-grade disease. Bijelic et al[151] reported a 30% partial or complete tumor response in patients with high-grade PMP who received preoperative systemic chemotherapy and then underwent CRS plus HIPEC. This subgroup of patients demonstrated significantly longer OS when compared with patients with no tumor response (median not reached versus 29.5 mo in those without response; $p = 0.03$). Targeted therapy and preoperative noncytotoxic agents based on immunohistochemistry for cyclooxygenase 2 expression and KRAS mutational status have shown no significant impact on survival.[78] Conversely, systemic chemotherapy combined with bevacizumab has shown improved OS and PFS for unresectable high-grade appendiceal adenocarcinoma, and currently there is a prospective phase II trial evaluating the impact of adjuvant 5-fluorouracil–based chemotherapy with bevacizumab (clinicaltrials.gov NCT02420509).[152] Although the timing of perioperative

systemic chemotherapy has shown conflicting results, as with other malignancies, there are several potential advantages of preoperative chemotherapy, including the ability to assess disease response and patient tolerance, administer upfront systemic therapy that would likely be indicated postoperatively in the majority of patients, and allow for as-yet-undeclared distant metastatic disease to appear on imaging and possibly preclude CRS of questionable benefit.[153]

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