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CONSENSUS STATEMENT

Consensus guideline for the management of patients with appendiceal tumors, part 1: Appendiceal tumors without peritoneal involvement

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ABSTRACT

Background: Appendiceal tumors comprise a heterogeneous group of tumors that may be localized or disseminated throughout the peritoneum. Limited high-quality

The collaborators for the Peritoneal Surface Malignancies Consortium Group for this article are listed in the Supporting Materials. These expert leaders had critical input into this article and approve its publication.

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clinical data exist, and many practices have been extrapolated from colorectal cancer without validation in appendiceal cohorts. There are many controversies regarding the treatment of appendiceal tumors, and practices vary widely between centers and care settings. A national consensus update of best management practices for appendiceal malignancies was performed to better standardize care.

Methods: The 2018 Chicago Consensus guideline was updated through a modified Delphi consensus performed over two rounds using nationally circulated surveys. Supporting evidence was evaluated using rapid systematic reviews. Key systemic therapy concepts were summarized by content experts.

Results: Most supporting literature consists of observational studies, but high-quality studies increasingly are becoming available to drive management. Two consensus-based pathways were generated for localized appendiceal tumors: one for epithelial mucinous neoplasms and another for appendiceal adenocarcinoma. Of 138 participants responding in the first round, 133 (96%) engaged in the second round. Greater than 90% consensus was achieved for all pathway blocks. Key points include minimizing intervention invasiveness when permitted by pathologic classification and margin status and determining which margin and pathologic findings are indications for consideration of cytoreduction with or without intraperitoneal chemotherapy. Surveillance and systemic therapy recommendations are also presented.

Conclusions: With growing but still primarily observational evidence currently dictating care, these consensus recommendations provide expert guidance in the treatment of appendiceal tumors without peritoneal involvement.

KEYWORDS
appendiceal malignancies, cytoreductive surgical procedures, guidelines, peritoneal neoplasms, peritoneal surface malignancies

INTRODUCTION

Appendiceal tumors comprise a diverse group of pathologies of the vermiform appendix. Their incidence has been markedly increasing, doubling in the years 2004–2017 alone; recent estimates report 0.97 cases per 100,000 individuals.[1–3] Although still a rare disease, it is critical for general surgeons to be familiar with appendix tumors because of the substantially higher incidence of 1%–3% in those undergoing appendectomy and for primary and emergency care generalists to avoid missed diagnoses.[4–7] Complicated appendicitis, including perforation or abscess, is associated with greater risk of a neoplastic diagnosis, with rates ranging from 5% to 29%.[5,8–12]

Mucinous neoplasms represent over one half of appendix tumors; the rest are predominantly epithelial (65%–70%), followed by neuroendocrine (approximately 20%).[13] The most common epithelial malignancies are mucinous adenocarcinoma (35%–40%), followed by colonic/intestinal type (7%–27%), goblet cell (about 20%), and signet ring adenocarcinoma (estimates usually <10%).[1,14,15] Approximately 40%–50% of appendix tumors present with distant disease at diagnosis, usually peritoneal.[3,14,16–19]

Prognosis varies widely across disease histology and stage. Low-grade neuroendocrine tumors, not addressed by this guideline, have the best prognosis; of nonmetastatic epithelial tumors, the most recent studies report 5-year overall survival rates of 63%–75% for well differentiated and moderately differentiated mucinous disease and 60%–70% for nonmucinous tumors.[1,3,14,17,18,20–23] Data on nonmetastatic, higher grade tumors are scant because these tumors often present at more advanced stages.

Given the rarity of appendiceal tumors, prospective studies are challenging, and randomized studies are rare; thus data to guide their management are low-quality, and there are no well established standards of care.[24,25] To fill this need, the multidisciplinary Chicago Consensus Working Group was formed in 2018 to generate consensus recommendations for peritoneal malignancies, including appendix tumors.[26] Herein, these recommendations are updated by expert consensus for the clinical management of patients with localized appendiceal mucinous neoplasms (AMNs) and localized

appendiceal adenocarcinoma, supported with recent evidence synthesized through rapid systematic reviews.

Conceptual overview and changes from the 2018 Chicago Consensus

All pathways feature a more comprehensive, multidisciplinary initial evaluation recommendation.[26] Pathways have been streamlined to emphasize preferred treatment options. Surveillance recommendations have been unified across pathways. Finally, systemic chemotherapy tables have been developed to describe prevailing trends in systemic treatment.

Peritoneal disease has been removed from the pathology-defined, localized pathways and reorganized as a unified treatment pathway, which will be addressed in a separate document. However, tumor pathology remains an important component of directing management, and a review of key issues in pathologic classification and their impact on clinical management is presented alongside that document.

MATERIALS AND METHODS

The methods for the 2024 consensus update of the 2018 Chicago Consensus guidelines have been described in detail in a separate article available in an open-access repository and are provided in Supporting Information S4.[27] Major components are presented below.

Consensus group structure

The Appendiceal Tumor Working Group included 14 multidisciplinary specialists whose area of clinical practice and academic interest includes the care of appendiceal tumors and a physician scientist with demonstrated expertise in conducting systematic reviews, representing eight National Comprehensive Cancer Network centers and three other institutions. Two core members of the steering committee coordinated and revised the pathways (F.M., E.G.). Sixteen trainees (medical students, residents, and fellows) conducted the rapid reviews.

Modified Delphi process

The original Chicago Consensus guidelines were reviewed by the Appendiceal Tumor Working Group and consortium leadership to align with evidence published since the last consensus. Recommendations were revised using two rounds of modified Delphi consensus across the consortium by soliciting degrees of agreement with each recommendation on a five-point Likert scale using Qualtrics survey. A threshold of 75% was set for inclusion of a guideline, and revision was required below and was considered above 90% consensus to improve agreement.

Rapid review of the literature

Rapid systematic reviews were performed of PubMed indexed literature in Medline in three key areas, which were developed in conjunction with a medical librarian specialist. The search period ranged up to August 2023. The search strategies and study protocol were registered with the international Prospective Register of Systematic Reviews and the search strategy may be reviewed in Supporting Information S4 (see Table S1).

The following key review question is addressed in this document:

1. In patients with moderate to poorly differentiated appendiceal adenocarcinoma undergoing cytoreductive surgery, which systemic therapy sequences and regimens are associated with superior survival and safety outcomes (total neoadjuvant, perioperative, adjuvant alone)? (Prospective Register of Systematic Reviews CRD42023463216)

The other two key questions will be discussed in part 2 of the appendiceal tumor guidelines with the accompanying peritoneal disease pathway.

Reviews were conducted and data extracted according to the consortium review methodology, which is publicly available and included in Supporting Information S4. Further criteria emerging from screening may be reviewed in Supporting Information S4 (see Table S2). Because no randomized trials were eligible for inclusion, quality analysis used the Newcastle–Ottawa framework, which allots up to nine stars for methodologic quality, with six or higher considered good quality.[28,29] Abstract and full-text screening was performed in duplicate, and extraction and quality analysis were performed individually with secondary verification.

The systemic chemotherapy table presented herein was drafted collaboratively by the Appendiceal Tumor Working Group, with directed guidance from medical oncologist contributors. It was then circulated for feedback from the consortium group alongside the Delphi round 2 consensus survey.

RESULTS

Pathways

Of 138 specialists who voted on the clinical pathways for AMNs and appendiceal adenocarcinoma in the first round, 133 (96%) participated in the second round. The group comprised 96 (70%) surgical oncologists, 20 (14%) medical oncologists, 15 (11%) pathologists, and 7 (5%) specialists from other disciplines and patient advocates. This pathway was divided into eleven main blocks. After two Delphi rounds, the blocks are summarized below with supporting literature

incorporated where appropriate; agreement tables may be found in Tables S4 and S5.

Rapid review

In total, 1179 abstracts were screened; of these, 247 were included for full-text review, and a total of 34 were selected for inclusion in the review because they reported outcomes specific to patients with peritoneal metastases of moderately differentiated and poorly differentiated appendiceal origin who underwent cytoreductive surgery and received systemic chemotherapy. Exclusions are quantified in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1) and are further described in Table S2. Outcomes were overall survival, disease-free survival, and adverse events. Seventeen studies reported on preoperative or neoadjuvant chemotherapy,[30–46] five reported on postoperative or adjuvant chemotherapy,[47–51] ten reported on both,[52–60,63] and two reported on other or unspecified regimens, as summarized in Table 1.[61,62] These studies addressed qualitatively (see Principles of Systemic Therapy, below), and applied in blocks 3 and 6 of the appendiceal adenocarcinoma pathway (see Appendiceal Adenocarcinoma, below). Quality-assessment data are provided in Table S3.

PRINCIPLES OF SYSTEMIC THERAPY

One of the key current issues in appendix tumors involves the role, regimen, and timing of systemic chemotherapy, which is currently influenced by a combination of the few small, single, prospective or retrospective studies in appendix tumors and by larger

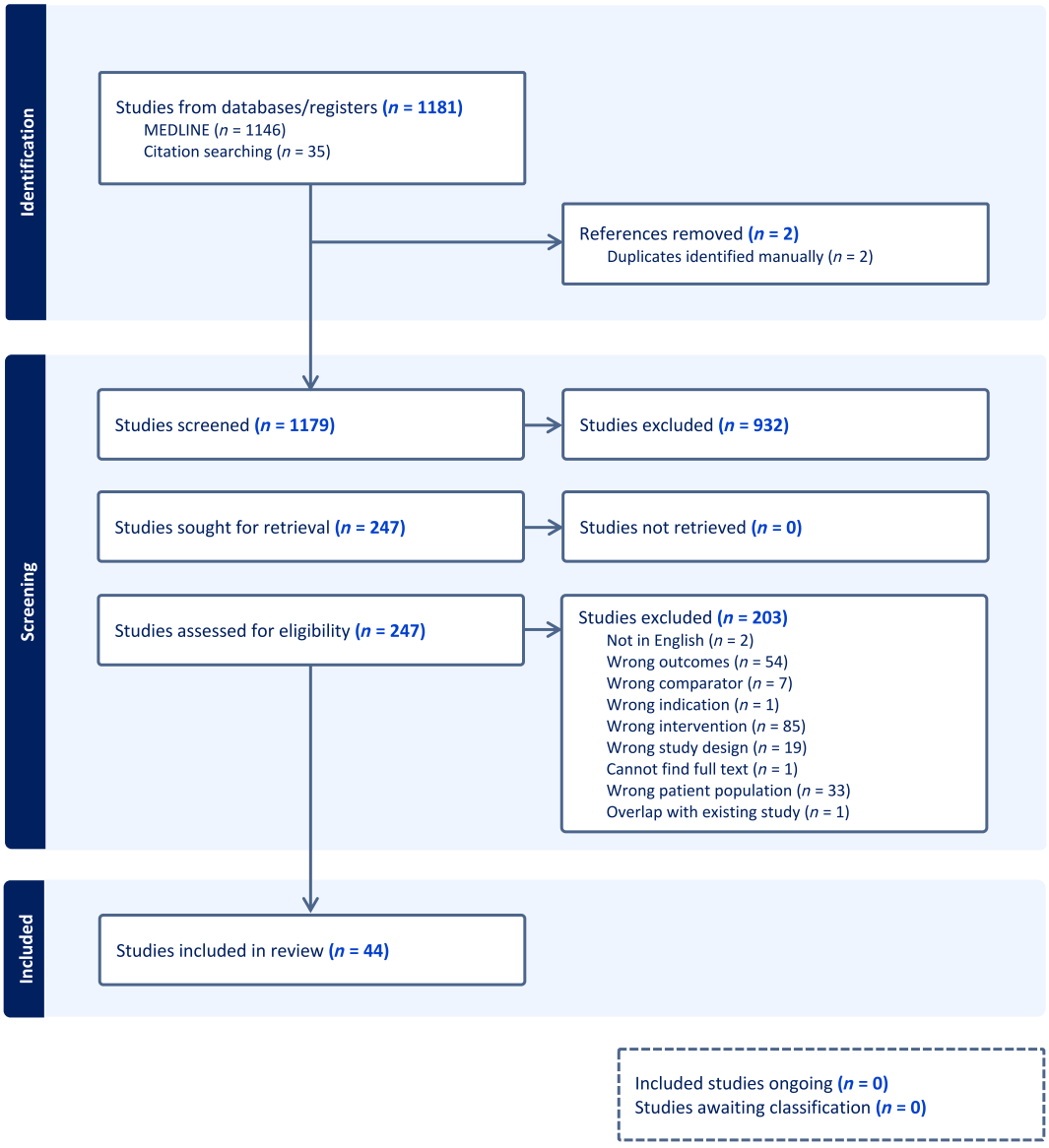

FIGURE 1 Covidence PRISMA diagram for key question 1: Systemic chemotherapy regimens and timing relative to cytoreduction in peritoneal appendiceal malignancy. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1 Key question 1: Systemic chemotherapy regimens and timing relative to cytoreduction in peritoneal appendiceal malignancy—summary of included studies.

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
Barrak 2021[31]	United States	Retrospective cohort, 1994–2020	Patients undergoing CRS ± IPCT for peritoneal appendiceal disease with mixed neuroendocrine features	6/44 Tang A, 25/44 Tang B, 13/44 Tang C	NACT, 32/47; no NACT, 12/47	All comers • Median OS, 48.5 months • 5-year OS, 34.88% • 10-year OS, 8.72% (no overall significant difference in the HR for NACT) NACT complete responders, 5/32 • Median OS, 65 months	NR
Sugarbaker and Chang 2021[30]	United States	Retrospective cohort, 1996–2011	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease, including total gastrectomy and temporary high-diverting jejunostomy	27/58 DPAM, 25/58 PMCA, 6/58 PMCA-S	NACT, 10/58; no NACT, 48/58	• Median OS, 12 years • 5-year OS, 76% • 10-year OS, 58% • 20-year OS, 37%	20/58 (34.5%) G3/G4; 2/58 (3.4%) postoperative deaths
Sugarbaker 2010[32]	United States	Retrospective cohort, January 2005 to July 2009	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal disease	34 PMCA, 9/34 PMCA-S, 7/34 with neuroendocrine component	NACT: 3 months of FOLFOX/XELOX ± 3 months of additional NACT	Disease stability after NACT • 24/34 clinical • 22/34 imaging • 17/34 intra-operative (17 with/progression) Disease response • 7/34 with pathologic partial response • 3/24 with pathologic complete response	NR
Sugarbaker and Chang 2022[33]	United States	Retrospective cohort, 1989–2020	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease	6/39 MACA-intermediate 6/39 MACA G1 17/39 MACA G2 1/39 MACA G3 (nonsignet ring) 9/39 MACA-S	NACT, 25/39	NACT • Median OS, 5 years • 7/39 patients with major response to NACT No NACT • Median OS, 7.0 years (nonsignificant difference) • HR for OS of partial/no response/no preop chemo vs. NACT, 4.8	15/39 (38%) had one or more reoperation; 4/39 (11%) had a class 4 adverse event

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
Bijelic 2012[34]	United States	Retrospective cohort, January 2005 to July 2009	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease	NACT • 9/34 PMCA-S • 25/34 PMCA/ adenocarcinoid No NACT • 4/24 PMCA-S • 20/24 PMCA/ adenocarcinoid	NACT: Six (12/34) or 12 (22/34) cycles of FOLFOX (30/34)/XELOX (4/34)	NACT • Median OS, 37.2 months (29.5 months if no histologic response) No NACT • Median OS, 50.5 months ($p = .56$)	NACT • 26/34 G3/G4 No NACT • 14/24 G3/ G4 ($p = .16$)
Ihemelandu and Sugarbaker 2016[35]	United States	Retrospective cohort, 1989–2012	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal disease	NACT • 152/225 PMCA • 38/225 PMCA-S • 35/225 PMCA-A No NACT • 209/269 PMCA • 42/269 PMCA-S • 18/269 PMCA-A	NACT: Three or four cycles of FOLFOX/XELOX	• Median OS: 45.4 months for PMCA, 18.9 months for PMCA-S, 26.8 months for PMCA-A ($p < .0001$) • HR for OS with no NACT, 0.7 ($p = .171$)	NR
Sugarbaker 2023[36]	United States	Retrospective cohort, 1985–2020	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease	37/196 MACA-intermediate 65/196 MACA-1 57/196 MACA-2 6/196 MACA-3 31/196 MACA-S	NACT: 50/196 • Response to NACT, 25/196 No NACT: 146/196	NACT • Median OS 6 months No NACT • Median OS 14 months • HR for OS of NACT, 1.6 ($p = .0268$) • HR for OS of response to NACT, 1.16 ($p = .6216$)	NR
Mangieri 2022[44]	United States	Retrospective cohort	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease discovered to be high-grade on postoperative pathology	NACT, 24/73 signet ring No NACT, 12/53 signet ring	NACT: 73/136 • 65/73 FOLFOX • 4/73 5-FU + leucovorin • 3/73 capecitabine • 1/73 unknown No NACT: 53/136	NACT Median OS, 2.1 year No NACT • Median OS, 3.3 years OR for 5-year OS for no NACT, 0.164 ($p = .017$) vs. NACT OR for 5-year DFS failure for no NACT, 0.263 ($p = .048$)	NACT: 13.7% G3 or higher No NACT: 13.2% ($p = .937$)
Votanopoulos 2015[52]	United States	Retrospective cohort, 1991–2013	Patients undergoing CRS ± IPCT for peritoneal epithelial appendiceal disease	317/430 low grade 93/430 high grade	NACT, ACT, neither, or both (no details or numbers provided)	High-grade disease NACT • Median OS, 17 vs. 30 months for no NACT ($p = .02$) • HR of NACT for OS, 2.5 ($p = .006$)	HR of no NACT for perioperative minor morbidity, 0.52 (95% CI, 0.28–0.94) Major morbidity, 0.79 (95% CI, 0.41–1.53)

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
						ACT • Median OS, 32 vs. 6 months for no ACT • HR of ACT for OS, not significant Low-grade disease • HR of NACT for OS, 2.2 ($p = .04$) • HR of ACT for OS, not significant	
Blackham 2014[53]	United States	Retrospective cohort, 1997–2011	Patients undergoing CRS IPCT for peritoneal mucinous appendiceal disease	284/393 MCP-L 109/393 MCP-H (signet ring in 31 with SC and 12 without SC)	NACT • 13/284 MCP-L (median, 4.5 months) • 37/109 MCP-H (median, 4.0 months) ACT • 9/284 MCP-L (median, 4.0 months) • 22/109 MCP-H (median, 6.0 months) NACT and ACT • 11/109 MCP-H Known regimens: 5-FU (MCP-L > MCP-H), FOLFOX, FOLFIRI, anti-EGFR or anti-VEGF	High-grade disease Any SCT • Median OS, 22.1 vs. 19.6 months for no SCT ($p = .74$) ACT • Median OS for ACT, 36.4 vs. 16.0 months for NACT ($p = .07$) vs. 19.6 months for no SCT ($p = .14$) • Median PFS for ACT, 13.6 vs. 6.8 months for NACT ($p < .01$) vs. 7.0 months for no SCT ($p = .03$) Low-grade disease Any SCT • Median OS, 107 vs. 72 months for matched cohort with no SCT ($p = .46$)	NR
Cummins 2016[54]	United States	Retrospective cohort, 1991–2015	Patients undergoing CRS ± IPCT for high-grade peritoneal surface malignancy of appendiceal or colonic origin	110/165 high-grade appendiceal 55/165 colonic 54/159 high-grade adenocarcinoma 66/159 adenocarcinoid or goblet cell 39/159 signet ring cells	NACT (within 3 months of CRS), 55.8% ACT, 64.7%	NACT • Median OS, 14.4 vs. 20.4 months for no NACT ($p = .01$) ACT • Median OS, 34.8 vs. 4.8 months for no ACT ($p < .0001$)	NR by chemo group
Munoz-Zuluaga 2019[55]	United States	Retrospective cohort, 1998–2017	Patients undergoing complete CRS ±	86/151 HGMCP 65/151 HGMCP-S	NACT • 34/86 HGCMP	NACT • Adjusted HR for OS vs. no	NR by chemo group

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
			IPCT for non–low-grade peritoneal mucinous appendiceal disease		• 40/65 HGCMP-S ACT • 34/83 HGCMP • 38/61 HGMCP-S	NACT, 1.32 (p = .28) • Adjusted HR for PFS failure vs. no NACT, 1.4 (p = .24)	
Baron 2023[37]	United States	Retrospective cohort, 1999–2020	Patients undergoing complete CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal adenocarcinoma	74/180 nonsignet/nongoblet 71/180 signet ring cell 35/180 goblet cell	ACT • 27/77 non-signet/goblet • 40/77 signet ring cell • 10/77 goblet cell No ACT • 47/103 non-signet/goblet • 31/103 signet ring cell • 25/103 goblet cell	ACT • Median OS, 53 months • Median PFS, 26 months No ACT • Median OS, 77 months (p = .566) • Median PFS, 43 months (p = .245) Unadjusted HR for OS vs. no ACT, 1.14 (95% CI 0.73-1.78) • Unadjusted HR for PFS failure vs. no ACT, 1.27 (95% CI, 0.85–1.89)	ACT • 10/77 G3 or higher No ACT • 22/103 G3 or higher
Milovanov 2015[37]	United States	Retrospective cohort, 1998–2014	Patients undergoing first time CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal disease	Prior SC • 24/30 high grade • 18/30 signet ring • ACT, 82% (does not divide evenly) No prior SC • 21/42 high grade • 10/42 signet ring • ACT, 77% (does not divide evenly)	Preoperative FOLFOX, FOLFIRI, CAPEOX	1-year, 2-year, and 3-year OS *Prior SC* • 93%, 68%, and 51%, respectively *No prior SC* • 82%, 64%, and 60%, respectively (p = .74) 1-year, 2-year, and 3-year PFS *Prior SC* • 78%, 49%, and 36%, respectively *No prior SC* • 67, 53%, and 53%, respectively (p = .46)	NR by chemo group
Munoz-Zuluaga 2019[46]	United States	Retrospective cohort, 1998–2017	Patients undergoing first-time CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal disease, excluding prior debulking or two or more lines of systemic therapy	Prior SC (pSC) • 36/64 HGMCP-S • 49/59 mod-poor diff • ACT, 33/59 No prior SC • 25/76 HGMCP-S • 36/71 mod-poor diff • ACT, 37/75	Median, four cycles of preoperative FOLFOX, FOLFIRI, 5-FU/folinic acid, ± anti-VEGF	• Median OS, 40.3 months with pSC vs. 86.4 months without (p = .006) • Median PFS, 19 months with pSC vs. 43 months without (p = .007)	Prior SC, 11% G3 or higher No prior SC, 17% G3 or higher

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
						HGMCP vs. HGMCP-S • No significant differences in relationship between pSC and survival by grade • HR for OS by pSC not significant	
Morgan 2023[38]	United States	Retrospective cohort, 2013–2020	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal disease	Doublet • 8/24 mod diff • 9/24 poor diff • 13/24 signet ring Triplet • 3/18 mod diff • 9/18 poor diff • 14/18 signet ring	24/42 doublet (FOLFOX, CAPEOX, FOLFIRI); 11/24 plus bevacizumab 18/42 triplet (FOLFIRINOX, FOLFOXIRI); 12/18 with bevacizumab	Median doublet OS, 32.2 vs. 23.5 months for triplet ($p = .38$) Median doublet RFS, 9.3 vs. 11.2 months for triplet ($p = .66$) Propensity matched • Median doublet OS, 32.3 vs. 24.6 months for triplet ($p = .64$)	Discontinued for chemotoxicity: 29% (7/24) doublet vs. 39% (7/18) triplet ($p = .68$)
Kolla 2020[48]	United States	Retrospective cohort, 2006–2015	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease; chemo only evaluated after complete CRS	(Complete CRS only) • 6/68 LAMN • 27/68 well diff MACA • 9/68 mod diff MACA • 3/68 poorly diff MACA • 2/68 unknown MACA • 6/68 MACA with signet ring • 10/68 signet ring adenocarcinoma • 4/68 mod diff non-MACA • 1/68 poor diff non-MACA	26/68 receiving ACT (CAPE, CAPEOX, FOLFOX) 11/33 low grade/well diff 15/35 non–low grade/well diff	Non-low grade • Median OS, 9.03 years for ACT vs. 2.88 years for no ACT ($p = .02$) • Median RFS, 2.60 years for ACT vs. 1.16 years for no ACT ($p = .09$) Low grade • Median OS not different • Median RFS, 4.45 years for ACT vs. 2.16 years for no ACT ($p = .72$)	NR
Chen 2020[39]	United States	Retrospective cohort, 2000–2017	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal adenocarcinoma	NACT • 49/225 well diff • 38/225 mod diff • 49/225 poor diff • 44/225 signet ring • ACT, 55/225 No NACT • 274/578 well diff • 100/578 mod diff • 65/578 poor diff • 69/578 signet ring • ACT, 85/578	144/225 FOLFOX 43/225 FOLFIRI 9/225 CAPE 7/225 CAPEOX 7/225 5-FU + leucovorin 18/225 other	• Median OS, 19 months for NACT vs. 29 months for no NACT ($p < .001$) • Adjusted HR of NACT for OS, not significant • Median RFS, 12 months for NACT vs. 20 months for no NACT ($p < .001$) • Adjusted HR of NACT for RFS failure, 2.03 ($p = .001$)	43% G3 or higher with NACT vs. 33% without NACT ($p < .001$) No difference in matched analysis

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
						Propensity matched • Median OS not different; adjusted HR of NACT for OS, 1.81 (p = .04) • Median RFS 14 vs 22 months for no NACT (p = .007) • Adjusted HR of NACT for RFS failure, 1.93 (p = .003)	
Flood 2023[56]	United States	Retrospective cohort, 2009–2020	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal adenocarcinoma	NACT • 5/25 MACA • 5/25 intestinal-type adenocarcinoma • 15/25 goblet or signet ring cell adenocarcinoma No NACT • 32/61 MACA • 5/61 intestinal-type adenocarcinoma • 24/61 goblet or signet ring cell adenocarcinoma	NACT • Six to 12 cycles of 5-FU plus oxaliplatin and/or irinotecan, with or without bevacizumab or cetuximab • 12/25 received ACT, not specified No NACT • 24/61 received ACT	NACT • 8/25 with some degree of response on imaging • 2/25 with complete pathologic response • OS at 1, 2, and 3 years, 87.5%, 71%, and 47.3%, respectively • Univariate HR for OS, 1.49 (p = .388) • Univariate HR for DFS failure, 1.52 (p = .309) No NACT • OS at 1, 2, and 3 years, 89.7%, 83.8%, and 75.8%, respectively ACT • Univariate HR for OS, 1.25 (p = .665) • Univariate HR for DFS failure, 2.29 (p = .035) • HR for OS and DFS not significant in multivariable analysis	16.3% G3 or higher overall
Turner 2013[57]	United States	Retrospective cohort, 2005–2011	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal adenocarcinoma	16/45 signet ring 33/45 mucinous adenocarcinoma 2/45 adenocarcinoid 5/45 well diff 10/45 mod diff 16/45 poor diff	NACT • 26/45 at least 3 months of primarily 5-FU with oxaliplatin or irinotecan, with or without bevacizumab	NACT • 15/26 with response • 9/26 with stable disease • 2/26 with progression (median OS, 22 months)	NACT, 40% major No NACT, 30% major

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
					ACT • 29/45 not otherwise specified	No NACT • Median OS not reached, not statistically different ($p = .1191$)	
Hanna 2023[61]	United States	Retrospective cohort, 2011–2019	Patients undergoing CRS ± IPCT for non–low-grade peritoneal appendiceal adenocarcinoma	TNT • 12/25 high grade • 13/25 intermediate grade • 10/25 signet ring SAND • 4/14 high grade • 10/14 intermediate grade • 5/14 signet ring	TNT: 12 cycles preop SAND: Six cycles preop, up to six cycles postop 5-FU with oxaliplatin or irinotecan ± bevacizumab	TNT • Median OS, 62.7 months • Median RFS, 35.4 months • Recurrence rate, 36% • Adjusted HR for OS, 0.41 ($p = .03$) • Adjusted HR for RFS, 0.34 ($p = .007$) SAND • 9/14 completed adjuvant regimen • Median OS, 45.1 months ($p = .01$ vs. TNT) • Median RFS, 12.3 months ($p = .03$ vs. TNT) • Recurrence rate, 71.4% ($p = .03$ vs. TNT)	NR
Spiliotis 2017[62]	Greece	Retrospective cohort, 2005–2014	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal neoplasm	14/52 DPAM 8/52 PMCA-I 30/52 PMCA 25/52 low grade 27/52 high grade 21/52 signet ring cell	Perioperative SCT: 20/52 (5-FU or capecitabine with oxaliplatin)	Perioperative SCT • Mean OS, 24 vs. 14 months without ($p = .048$) • Median DFS, 19 vs. 10 months without ($p = .034$) • Mixed median and mean values across all histologic subgroups, with benefit displayed in chemo groups	NR
Benhaim 2019[40]	France	Retrospective cohort, 1992–2014	Patients undergoing complete CRS ± IPCT for peritoneal mucinous appendiceal disease	Nonextensive • 123/184 DPAM • 31/184 hybrid • 26/184 PMCA • 4/184 unknown • 38/184 NACT Extensive PMP • 17/61 DPAM • 26/61 hybrid • 16/61 PMCA • 2/61 unknown • 40/61 NACT	NACT: 38/184 nonextensive, 40/61 extensive	NACT • Univariate HR for OS, 2.81 vs. no NACT ($p = .00026$) • Univariate HR for DFS failure, 3.34 vs. no NACT ($p < .001$) • Neither significant in multivariable analysis	NR

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
Mercier 2019[58]	France	Retrospective cohort, 1993–2015	Patients undergoing complete CRS ± IPCT for peritoneal mucinous appendiceal disease	62/199 WHO low grade 137/199 WHO high grade	NACT, 95/257 ACT, 36/258	NACT • 6/95 no recurrence • 81/95 early recurrence • 8/95 late recurrence No NACT • 27/164 no recurrence • 115/164 early recurrence • 22/164 late recurrence • Preoperative chemo more common among early recurrence (41.5%) vs. late recurrence (28%; $p = .02$)	NR
Masckauchan 2019[45]	Canada	Retrospective cohort, 2004–2015	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease	35/109 DPAM 55/109 PMCA-I 19/109 PMCA	SCT, 34/109 in all with high-grade tumors and high tumor load; 3–6 months of 5-FU–based regimen	SCT • Univariate HR for OS, 3.939 ($p < .001$) • Adjusted HR for OS, 3.507 ($p = .002$)	26.1% G3 or higher overall
Acs 2023[41]	Germany	Retrospective cohort, 2011–2021	Patients undergoing CRS ± IPCT for peritoneal appendiceal adenocarcinoma, primary or recurrent	43/84 MACA (17 G1, 19 G2, 7 G3, 4 with signet ring, 6/84 unknown) • 9/84 signet ring cell adenocarcinoma • 19/84 intestinal-type adenocarcinoma (2 G1, 10 G2, 7 G3) • 8/84 goblet cell • 1/84 mixed adenoneurocrine	Prior SCT, 21/55; 5-FU with oxaliplatin or irinotecan with or without bevacizumab or cetuximab	Prior SCT • Univariate HR for OS, 1.220 ($p = .571$; not significant on multivariable analysis)	20.3% G3 or higher overall
Kusamura 2021[42]	International	Retrospective cohort, 1993–2017	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease	CRS alone • 197/376 low grade • 179/376 high grade (NACT, 198/376) CRS + HIPEC • 1056/1548 low grade • 492/1548 high grade (NACT, 529/1548)	Prior SCT • 198/376 CRS alone • 529/1548 CRS + HIPEC	Prior SCT • Multivariable HR for OS, 1.58 ($p < .001$)	18.6% G3 or higher overall
Baratti 2008[43]	Italy	Prospective cohort, 1996–2007	Patients undergoing CRS IPCT for any mucinous	99/104 appendiceal Of 41 reviewed • 32/41 LAMN • 6/41 MACA	Prior SCT, 23/95	Prior SCT • Multivariable HR for OS, 2.72 ($p = .0339$)	18.7% G3 or higher overall

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
			peritoneal disease, excluding: aged >75 years, ECOG performance status >2, bowel obstruction, and tumor deposits >0.5 cm on surface of small bowel on imaging	• 3/41 no tumor • 1/104 colon • 2/104 ovarian/teratoma • 2/104 unknown origin		• Multivariable HR for PFS failure, 2.04 (p = .0453)	
Schomas 2009[49]	United States	Retrospective cohort, 1985–2000	Patients undergoing CRS ± IPCT for peritoneal carcinomatosis of appendiceal origin	82/115 adenocarcinoma 33/115 cystadenocarcinoma 112/115 low grade 3/115 high grade	ACT, 22/115 (5-FU–based regimens)	ACT • OS at 5, 10, and 15 years, 48%, 14%, and 14%, respectively (p = .01 vs. no ACT) • DFS at 5, 10, and 15 years, 16%, 11%, and 11% respectively (p = .03 vs. no ACT) No ACT • OS at 5, 10, and 15 years, 72%, 47%, and 31%, respectively • DFS at 5, 10, and 15 years, 42%, 29%, and 22%, respectively	NR
Arjona-Sanchez 2013[50]	Spain	Retrospective analysis of prospective cohort, 1998–2012	Patients undergoing CRS ± IPCT for non–low-grade peritoneal mucinous appendiceal disease	11/38 PMCA-I (NACT, 6); 27/38 PMCA (NACT, 11); ACT, all	NACT, 17/36; mean, five cycles of 5-FU or capecitabine and oxaliplatin for those with unfavorable histology or high disease burden	NACT • Progression on NACT excluded from consideration • Median OS, 47 months • OS at 1, 3, and 5 years, 74%, 54%, and 43%, respectively (p = .068 vs. no NACT) • DFS at 1 and 3 years for non-CC2 patients, 60% and 29%, respectively (p = .34 vs. no NACT) No NACT • Median OS, 53 months • OS at 1, 3, and 5 years, 100%, 100%, and 75%, respectively	18.4% G3 or higher overall

(Continues)

TABLE 1 (Continued)

Reference	Country	Study design	Population	Tumor grade and type: No./total no.	Chemotherapy regimen	Survival/other outcomes	Adverse events, grade 3/4
						• DFS at 1 and 3 years for non-CC2 patients, 68% and 46%, respectively	
Ung 2014[59]	Australia	Retrospective cohort, 1996–2013	Patients undergoing CRS ± IPCT for peritoneal mucinous appendiceal disease	146/257 low-grade tumors (133/146 DPAM, 13/146 hybrid tumors) • NACT, 139/146 • ACT, 123/146 111/257 high-grade tumors (85/111 PMCA, 26/111 nonmucinous adenocarcinoma) • NACT, 67/111 • ACT, 28/111	NACT, 205/257 ACT, 98/250	DPAM/hybrid: *NACT* • Univariate HR for OS, 2.08 (p = .29) *ACT* • Univariate HR for OS, 1.90 (p = .059) PMCA: *NACT* • Univariate HR for OS, no difference *ACT* • Univariate HR for overall mortality (i.e., inverse of usual; protective), 2.70 (p = .001)	46.8% G3 or higher in PMCA, 47.3% G3 or higher in DPAM
Baumgartner 2015[63]	United States	Retrospective cohort, 2007–2013	Patients undergoing CRS ± IPCT for high-grade peritoneal surface malignancy of appendiceal or colonic origin	9/70 mod diff 41/70 poor diff 20/70 NR 41/70 mucinous 14/70 signet ring cells	NACT, 59/70 (median, 12 cycles; range, 0–54) ACT, 34/46 known	No associations between NACT, ACT, and OS or PFS	21.4% G3 or higher overall
Grotz 2017[60]	United States	Retrospective analysis of prospective cohort, 2004–2014	Patients evaluated for CRS ± IPCT for non–low-grade peritoneal appendiceal adenocarcinoma	Cohort undergoing CRS • 78/116 mucinous • 38/116 nonmucinous • 54/116 mod diff • 62/116 poor diff • 42/116 signet ring cells	NACT, 85/116 (four to six cycles FOLFOX with or without bevacizumab); ACT, 23/265	No significant differences in outcomes	18.1% G3 or higher overall at 90 days
Pallas 2017[51]	Greece	Retrospective cohort, 2006–2016	Patients undergoing CRS ± IPCT for high-grade peritoneal surface malignancy of appendiceal or colonic origin	15/100 appendiceal origin 85/100 colonic origin 58/100 signet ring cells	ACT, 72 of 100 patients 1 month after surgery	ACT: Does not reach significance on multivariable analysis for overall survival; for RFS failure (HR, 9.181; p = .002)	26% G3 or higher overall

Abbreviations: ±, with or without; 5-FU, 5-fluorouracil; ACT, adjuvant or postoperative chemotherapy; chemo, chemotherapy; CC2, a complete cytoreduction score of 2 (nodules 2.5 mm to 2.5 cm in greatest dimension); CRS, cytoreduction; DFS, disease-free survival; DPAM, diffuse peritoneal adenomucosis; ECOG, Eastern Cooperative Oncology Group; folinic acid, fluorouracil, and oxaliplatin; G1–G4, grade 1 through 4 complications, respectively; HGMCP, high-grade mucinous carcinoma peritonei; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; IPCT, intraperitoneal chemotherapy (hyperthermic intraperitoneal chemotherapy, early postoperative intraperitoneal chemotherapy, or another regimen); MACA, mucinous adenocarcinoma of the appendix; MCP-H, high-grade mucinous carcinoma peritonei; MCP-L, low-grade mucinous carcinoma peritonei; mod diff, moderately differentiated; NACT, neoadjuvant or preoperative chemotherapy; NR, not reported; OS, overall survival; PFS, progression-free survival; PMCA, peritoneal mucinous carcinomatosis; PMCA-A, peritoneal mucinous carcinomatosis with adenocarcinoid features (only where used in the original publication); poor diff, poorly differentiated; PMP, pseudomyxoma peritonei; postop, postoperatively; preop, preoperatively; pSC, prior systemic chemotherapy, otherwise unspecified; RFS, recurrence-free/relapse-free survival; -S, signet ring cell component; SAND, sandwich chemotherapy; SC, systemic chemotherapy, timing otherwise unspecified; well diff, well differentiated; WHO, World Health Organization; TNT, total neoadjuvant therapy; XELOX, oxaliplatin and capecitabine.

trials in colorectal cancer, despite increasing evidence that appendix cancer has a distinct biology from colorectal cancer.[64–68] In addition to the lack of high-quality evidence, low-grade lesions are also likely resistant to systemic chemotherapy, confounding the results of prior studies and limiting the applicability of their conclusions.[69] Table 2 summarizes the current state of practice for cytotoxic chemotherapy in appendiceal malignancy.

Cytotoxic chemotherapy for localized appendix tumors

Localized appendix tumors may include World Health Organization grade 1 primaries (either low-grade appendiceal mucinous lesions or well differentiated adenocarcinoma). High-grade AMNs most likely should be treated similarly. Because currently available studies

TABLE 2 Systemic chemotherapy for appendiceal tumors.

Tumor type and spread	Stage of therapy	Initial therapy	Subsequent therapy
Tumors without peritoneal spread			
Low-grade or high-grade appendiceal mucinous neoplasm	—	No evidence supports systemic therapy in this population at this time.	
Low-grade/well differentiated appendiceal adenocarcinoma		No evidence supports systemic therapy in this population at this time.	
Appendiceal adenocarcinoma with nodal involvement or high-risk features (described above)	Neoadjuvant/conversion	Not recommended	
	Adjuvant (after right hemicolectomy)	Consider • FOLFOX doublet chemotherapy • FOLFOXIRI or FOLFIRINOX triplet chemotherapy[a]	Regimens as described at left not previously attempted
Tumors with peritoneal spread			
Low-grade appendiceal tumor (low-grade or high-grade appendiceal mucinous neoplasm or low-grade/well differentiated appendiceal adenocarcinoma) with resectable, low-grade peritoneal involvement	—	No evidence supports systemic therapy in this population at this time.	
Low-grade appendiceal tumor (low-grade or high-grade appendiceal mucinous neoplasm or low-grade/well differentiated appendiceal adenocarcinoma) with unresectable peritoneal involvement that is also low-grade	—	Limited evidence supports a survival benefit for systemic therapy in this population at this time. Use of systemic therapy may be indicated in the setting of a trial such as those described above or certain palliative care pathways (Hornstein 2024[70]).	
Appendiceal adenocarcinoma with resectable low-grade peritoneal involvement, found after definitive resection to have nodal involvement or high-risk features (described above)	Neoadjuvant/conversion	Not recommended	
	Adjuvant (after complete cytoreduction)	Consider • FOLFOX doublet chemotherapy • FOLFOXIRI or FOLFIRINOX triplet chemotherapy[a]	Regimens as described at left not previously attempted
Appendiceal adenocarcinoma with unresectable, low-grade peritoneal involvement, found to have nodal involvement or high-risk features with or without an attempt at debulking	Perioperative	Consider • FOLFOX or FOLFIRI doublet chemotherapy ± anti-VEGF • FOLFOXIRI or FOLFIRINOX triplet chemotherapy ± anti-VEGF[a]	
	Nonoperative or postoperative (after debulking) for disease control	Consider • FOLFOX doublet chemotherapy • FOLFOXIRI or FOLFIRINOX triplet chemotherapy[a] • If residual disease after cytoreduction, consider anti-VEGF agents	Regimens as described at left not previously attempted

(Continues)

TABLE 2 (Continued)

Tumor type and spread	Stage of therapy	Initial therapy	Subsequent therapy
Any resectable or unresectable appendiceal tumor with any high-grade peritoneal involvement	Neoadjuvant therapy/conversion (trial of response or empiric regimen)	FOLFOX or FOLFIRI doublet chemotherapy ± anti-VEGF FOLFOXIRI or FOLFIRINOX triplet chemotherapy ± anti-VEGF[a]	Regimens as described at left not previously attempted
	Perioperative therapy (borderline resectable or cytoreducible lesions)	FOLFOX or FOLFIRI doublet chemotherapy ± anti-VEGF FOLFOXIRI or FOLFIRINOX triplet chemotherapy ± anti-VEGF[a]	
	Adjuvant/postoperative (after CRS/HIPEC if residual disease OR incomplete preoperative regimen)	FOLFOX doublet chemotherapy FOLFOXIRI or FOLFIRINOX triplet chemotherapy[a] If residual disease after cytoreduction: consider anti-VEGF agents	Regimens as described at left not previously attempted

Abbreviations: ±, with or without; CRS, cytoreductive surgery; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; HIPEC, hyperthermic intraperitoneal chemotherapy.
[a]When triplet chemotherapy is considered, it must be with the understanding that adverse events are more common.

indicate no benefit from the use of 5-fluorouracil (5-FU)–based chemotherapy in this population, it is not recommended.[24,53,71–73]

When the primary lesion is an adenocarcinoma that has high-risk features without peritoneal involvement, up-front resection with consideration of adjuvant chemotherapy is preferred by expert consensus. High-risk features have largely been extrapolated from colorectal cancer literature without validation in appendiceal cohorts, including T4 tumor size, invasion of adjacent structures, inadequate lymph node yield, and tumor perforation. High-risk features that have been validated in appendiceal malignancy include lymph node involvement, signet ring cells, and less differentiated or nonmucinous histology.[52,54,63,73–78]

The rationale for this is partly mechanistic because tumors with poor biology are anticipated to have a higher likelihood of distant spread. Limited observational evidence has shown benefit associated with the use of adjuvant chemotherapy in node-positive, high-grade, and/or nonmucinous disease.[48,53,54,59,60,73–75,79] Others studies have shown minimal benefit or even detriment after adjuvant therapy; it is unclear how much of this variation reflects selection bias, because the patients who are most likely to undergo adjuvant therapy are those who are well enough to do so.[47,49,51,52,56] To our knowledge, no studies have comprehensively evaluated the role of modern neoadjuvant therapy for resectable appendix tumors without peritoneal involvement; current expert consensus opinion is not in favor of neoadjuvant therapy in that setting because it would delay definitive resection.

Cytotoxic chemotherapy for tumors with peritoneal disease

Pathologic grade typically dictates the role of chemotherapy in appendix tumors with peritoneal spread. If both the primary tumor and the associated peritoneal lesions are low grade, cytotoxic therapies are usually not indicated. When resectable, definitive resection should be pursued; when unresectable, palliative debulking may be considered. Cytotoxic systemic therapies may be a part of clinical trials or in care pathways focused on symptom control, but no evidence currently supports improved disease control or survival. If the peritoneal disease is low grade but the primary is found to have the high-risk features described above, adjuvant chemotherapy should be considered as for any high-grade primary.

For appendiceal tumors with high-grade peritoneal histology, the grade of the primary does not affect management; even where there is substantial discordance, such as a low-grade AMN (LAMN) or well differentiated adenocarcinoma (which would be vanishingly rare), the peritoneal pathology guides management. Some studies suggest some degree of disease response with systemic chemotherapy, with disease stability or improvement on imaging in 20%–75% of patients, and some patients with unresectable disease may become eligible for cytoreduction.[77,80–82] In one prospective trial, 50% of 34 patients receiving preoperative chemotherapy had disease stability or response on imaging that was confirmed by intraoperative findings, and of those 17 patients, nine (53%) had lower tumor grade on pathology than in samples from prior chemotherapy.[32] Amont observational studies, a subset supports modest disease control or response and increased survival after preoperative chemotherapy.[31–34,37,39,62]

However, this may not translate to cohort-wide overall, recurrence-free, or progression-free survival, because several of observational studies suggest a lack of benefit from preoperative chemotherapy in one or all of those domains.[31,33,34,36,41,42,44,47,50,52,54,56–58] Overall and disease-free survival are still poor, even with definitive cytoreduction; a large study of the US hyperthermic intraperitoneal chemotherapy (HIPEC) collaborative estimates 23.2% 5-year disease-free and 43.8% overall survival rates for high-grade appendiceal tumors with peritoneal involvement.[83] Some studies show a survival benefit from postoperative therapy, but there are conflicting data regarding its role or benefit.[48,52,53] This observation suggests that underlying disease-specific features that are poorly understood may be driving these treatment outcomes. Further research in this area may allow for directed management.

Weighing the existing evidence summarized above and in Table 1, which summarizes all studies included in the key question 1 rapid review, the expert consensus recommendation of the Peritoneal Surface Malignancy Consortium is to administer chemotherapy before attempting cytoreduction, or as definitive therapy if cytoreduction is not feasible, for high-grade peritoneal malignancy of appendiceal origin. When complete cytoreduction is predicted, systemic chemotherapy is useful for assessing disease biology and response; and when, incomplete cytoreduction is predicted (high peritoneal cancer index or other anatomic factors), it is recommended as conversion therapy. If cytoreduction or the preoperative regimen is incomplete, postoperative chemotherapy should be considered. There is no clear consensus on regimen timing; when studied, perioperative regimens reportedly have the potential to be more challenging for patients to complete than total preoperative regimens but may be worth considering, particularly when surgery must be expedited.[84]

Cytotoxic chemotherapy regimens

Systemic chemotherapy for appendiceal malignancies commonly relies on the intravenous 5-FU backbone or, less commonly, oral capecitabine, which is typically used in colorectal cancers. Regimens are typically either doublet, with oxaliplatin or irinotecan as the second agent, or triplet, with both; in patients unable to tolerate doublet or triplet chemotherapy, singlet chemotherapy may be used.[35,37–39,46,48,53,57,75,80,85,86] At this time, only small retrospective studies have been done, so no clear evidence suggests better outcomes with either regimen; however, there is higher toxicity with triplet regimens, mandating careful patient selection.[38] Most therapeutic regimens paired with definitive surgical management, whether preoperative, perioperative, or postoperative, are intended for a duration of 3–6 months; however, if definitive surgical management is not feasible, cytotoxic chemotherapy may be part of a long-term management strategy. Re-evaluation is generally performed every 3 months when intended to query disease biology or attempt conversion to resectable disease.[26,32,57]

Appendix tumor genetics and targeted and molecular therapies

The role of targeted and molecular therapies is not well defined in appendix tumors and is still largely extrapolated from colorectal and other gastrointestinal cancers, but recent studies have explored genetic profiles of appendiceal tumors in the hope of identifying effective targets. Four of the most common mutations in appendix cancer are *KRAS* (>70%), *GNAS* (50-70%), *TP53* (up to 40%), and *APC* (up to 20%). The relative frequency of these mutations is distinct from that of colorectal cancer, particularly in the paucity of *APC* and *TP53* mutations compared with 70%–80% of colorectal cancers. High microsatellite instability and mismatch-repair deficiency are relatively uncommon in appendix cancer (6%) as well.[66–68,87,88]

Like most patients who have solid tumors, all those with metastatic disease should receive next-generation sequencing for molecular profiling with an accepted next-generation sequencing panel to identify potential molecular targets. Retrospective data suggest that molecular information also may inform prognosis and/or predict therapy response, although targeted randomized studies in appendiceal cancer have not been performed.[65,66] When possible, tissue should be sent for tumor molecular profiling; circulating (blood) profiling may not be as sensitive.[89]

Germline variants, including those associated with hereditary cancer syndromes, have been detected at frequencies approaching 10%–12% in patients with appendiceal tumors, although these variants may be incidental to disease biology, and the relevance to therapeutic management is unknown.[88,89] Testing for germline variants may be considered, taking into account the individual's family history of cancer.

One molecularly targeted treatment that may be applicable to metastatic appendiceal cancer is anti-VEGF agents, most commonly bevacizumab, which has been associated with improved outcomes in some observational studies.[86] Anti-VEGF therapy may be considered for most settings in which systemic therapy is considered, with preference to those in which no resection or incomplete resection has taken place, although it should be avoided in patients assessed to be at risk of impending bowel obstruction or perforation, bleeding, or arterial thrombosis. Anti-EGFR agents have a more controversial role because they have unclear survival benefit in appendix cancer, and studies have raised concern for worse survival in patients with *RAS* mutations.[86,87]

Possible therapeutic options for less common mutations may be extrapolated from other cancers. The National Comprehensive Cancer Network guidelines for appendix cancer at the time of this writing are presented alongside colorectal cancer recommendations and recommend similar use of targeted therapies for druggable targets in late, previously treated, and/or metastatic settings, such as treating *BRAF V600E*-mutated tumors with combination anti-EGFR and anti-BRAF agents.[90] Deficient mismatch-repair and high microsatellite instability lesions may be treated with anti-PD1 or combination anti-PD1 and anti-CTLA4 therapy.[90] A recent trial investigated the effect of combination anti-PD1 (atezolizumab) and anti-VEGF (bevacizumab) therapy in 16 individuals with unresectable, predominantly low-grade mucinous appendiceal adenocarcinoma; disease control was achieved in 100% of individuals, with a progression-free survival of 18 months compared with 3 months of disease control on 5-FU–based regimens. This is a promising development for those with low-grade, unresectable disease.[70]

Genetic profiles of appendiceal tumors also influence the effectiveness of cytotoxic regimens. Patients with *GNAS*-mutation–predominant disease are much less likely to have a disease response to

chemotherapy, whereas as many as 50% of patients with *RAS*-mutation–predominant disease may respond.[66] In addition, some evidence may support the preferential use of irinotecan-containing regimens in *RAS* wild-type cancers.[65]

Regional chemotherapy regimens

Evidence suggests potential survival benefit from intraperitoneal chemotherapy with optimal cytoreduction for appendiceal neoplasms that have peritoneal involvement.[35,42,43,71,85,91–94] In general, the consensus recommendation is to consider intraperitoneal chemotherapy with optimal cytoreduction, but there are still variations in practice.

Table 3 summarizes regional regimens. Mitomycin C (MMC) is the most widely used agent.[35,71,76,91,94–108] Oxaliplatin is also common, given its known activity against gastrointestinal malignancies.[42,92,93,97,109] Oxaliplatin and MMC appeared to have similar hematologic outcomes in a randomized trial; MMC was more commonly associated with leukopenia, and oxaliplatin was associated with thrombocytopenia, and there was no difference in grade 3 and 4 adverse events.[97] Regimens involving irinotecan, cisplatin, and doxorubicin have been studied alone and with the addition of MMC or oxaliplatin.[43,76,106,109–114] Data are mixed regarding cisplatin-containing regimens, but irinotecan trends toward more inferior outcomes.[42,109]

In studies and centers that perform pressurized intraperitoneal aerosol chemotherapy, oxaliplatin is most common, followed by cisplatin and doxorubicin.[115,116] Currently, this consortium recommends pressurized intraperitoneal aerosol chemotherapy only in the setting of a clinical trial because early phase trials are still in progress. A few centers offer early postoperative intraperitoneal chemotherapy; when implemented, 5-FU is typically used, with some initially promising data.[42,117,118] The ICARUS trial (ClinicalTrials.gov identifier NT01815359) and other trials are ongoing to further assess the role for early postoperative intraperitoneal chemotherapy in appendiceal cancer.[119]

TABLE 3 Regional chemotherapy for appendiceal neoplasms.

Regional regimens	Currently in use
HIPEC	Mitomycin C Oxaliplatin Not recommended at this time: combinations based on irinotecan, cisplatin, doxorubicin
PIPAC	Oxaliplatin Cisplatin/doxorubicin
IP/EPIC	5-fluorouracil (FUDR) used in some centers

Note: The use of regional perfusion chemotherapy is extremely institution-specific and setting-specific, and there is neither adequate literature nor strong consensus regarding the most effective regimen or mode of administration. This table is included for reference into current practices at time of writing.

Abbreviations: EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal; PIPAC, pressurized intraperitoneal aerosol chemotherapy.

EPITHELIAL APPENDICEAL MUCINOUS NEOPLASMS

Consensus updates

One major change from the 2018 guideline (Figure 2) is more definitive recommendations for surveillance versus cytoreduction with or without intraperitoneal chemotherapy in disease that is otherwise localized but with limited regional spread. More specific recommendations address positive margins and perforation, with an emphasis on the most minimally invasive treatment possible to achieve negative margins.

Pathway components are designated by blocks, indicating critical areas of clinical decision making. Percentages (% agreement) at the end of each block description indicate agreement levels from the second Delphi round. The first-round version of the pathway may be referenced in Figure S1.

Block 1

When first detected on imaging or as a pathologic finding during or after appendectomy, initial workup of a suspected of AMN should include a detailed history and physical examination; tumor markers, including carcinoembryonic antigen, cancer antigen 125, cancer antigen 19-9, and consideration of CRP; and abdominopelvic cross-sectional imaging if not already performed. Although a less robust body of evidence supports the use of CRP as a biomarker compared with other markers, some association has been noted between CRP and outcomes for patients who have AMNs with peritoneal involvement, including progression-free survival in one study and aborted HIPEC in another.[120,121] Serum markers are useful for prognostication, monitoring treatment response, and identifying recurrence. Imaging is additionally useful for evaluating peritoneal and other distant disease sites and surgical planning.[120,122–124] Imaging findings that may be seen in appendiceal neoplasms include focal distal appendiceal dilatation, size >2 cm, curvilinear calcifications, wall irregularity, and absence of periappendiceal fat stranding; calcifications are specific but not sensitive.[125,126]

Colonoscopy should be performed to rule out synchronous lesions that might affect surgical planning, which occur in 14%–42% of this population.[127,128] Somatic and tumor genetic profiling may be considered, but minimal evidence exists for AMN.

Patients with AMNs should be discussed at multidisciplinary tumor board; whereas many AMNs can be treated with resection alone, imaging and treatment plan review can help prepare the care team for unexpected contingencies. Tissue samples should be reviewed by an expert pathologist. Patients should also be evaluated for additional support needs, which may include referral to patient

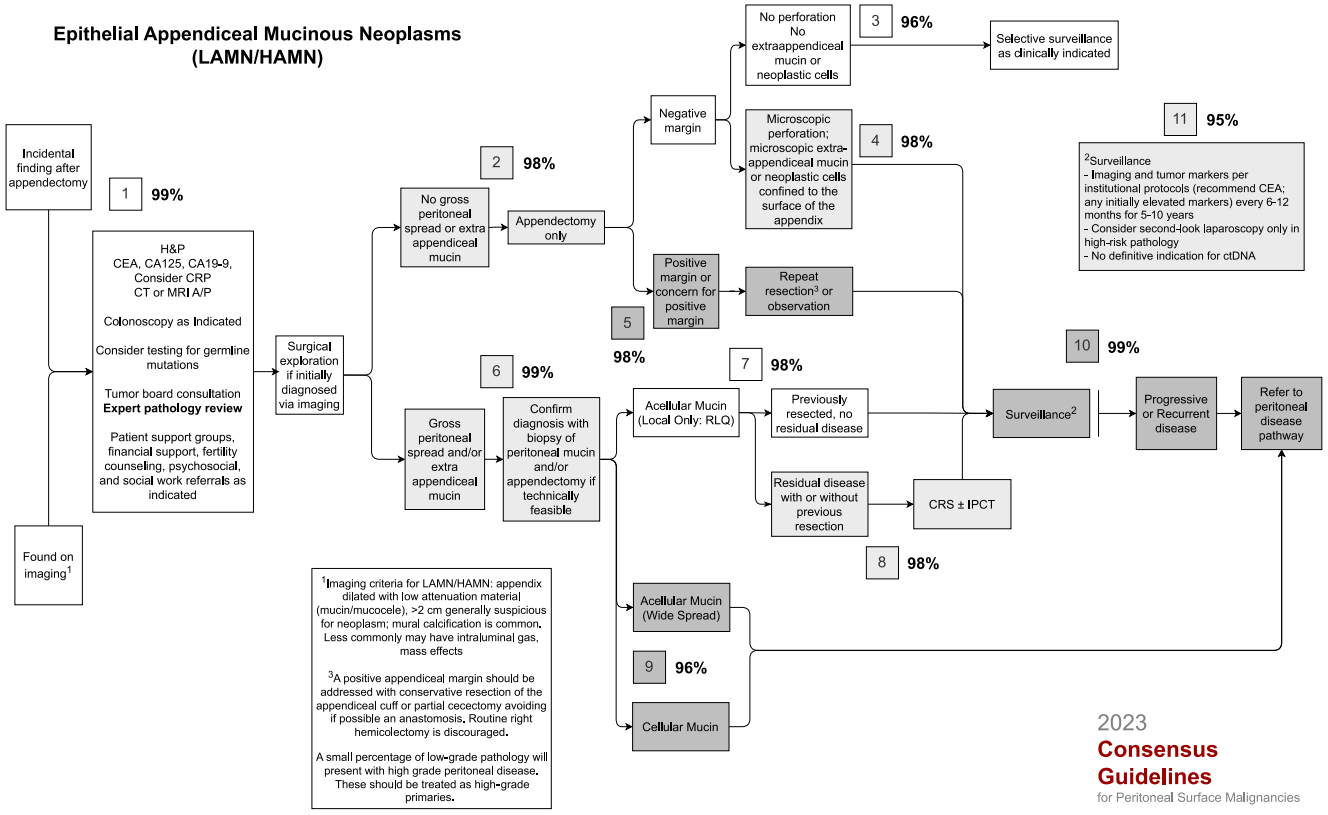

FIGURE 2 Epithelial appendiceal mucinous neoplasms (LAMN/HAMN) pathway. CA 19-9 indicates cancer antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; CRS, cytoreductive surgery; CT A/P, computed tomography of the abdomen/pelvis; ctDNA, circulating tumor DNA; H&P, history and physical examination; HAMN, high-grade appendiceal mucinous neoplasm; IPCT, intraperitoneal chemotherapy; LAMN, low-grade appendiceal mucinous neoplasm; MRI A/P, magnetic resonance imaging of the abdomen/pelvis; RLQ, right lower quadrant.

support groups, social work consultation, financial support resources, psychosocial support resources, and fertility counseling.

When AMNs are diagnosed by any nonsurgical means (typically imaging), the next step should be surgical exploration by the least invasive safe approach. In most patients, this will be diagnostic laparoscopy, depending on the surgeon's best judgement. If lesions suspicious for peritoneal disease are identified, biopsies should be taken.

% Agreement: First round, 93%; second round, 99%

Block 2

If no gross peritoneal spread of disease or macroscopic extra-appendiceal mucin is noted on surgical exploration, appendectomy alone should be performed to a negative margin.[129–131]

% Agreement: First round, 97%; second round, 98%

Block 3

If final surgical margins are negative, attention must be turned to the presence or absence of perforation and extra-appendiceal mucin or neoplastic cells. If all of the above are absent, surveillance can be used selectively. In many patients, surveillance will not be necessary; however, the risk of recurrence is never zero because it is possible for an AMN to perforate and then re-seal, leading to a theoretical increased risk of peritoneal progression or recurrence.[130–132]

% Agreement: First round, 93%; second round, 96%

Block 4

If final surgical margins are negative but microscopic perforation is noted or if there is microscopic extra-appendiceal mucin or neoplastic cells confined to the surface of the appendix, surveillance is indicated as described in block 11.[130–132] Microscopic extra-appendiceal mucin and neoplastic cells confined to the surface of the appendiceal specimen alone still constitute a negative margin.

% Agreement: First round, 94%; second round, 98%

Block 5

If final surgical margins are positive with viable neoplastic epithelial cells at the margin (not acellular mucin alone) or if there is concern for the same, repeat resection should be performed to a negative margin, although data suggest in some series that even gross resection may be adequate.[130–132] Historically, ileocecectomy or

cecectomy have been performed, but the consensus recommendation is to perform the most conservative resection possible, such as cuff resection. Anastomosis should be avoided if possible. Then, surveillance must be regularly performed. Observation may be considered for patients at high risk for surgical morbidity, in whom there may be less benefit from oncologic resection.

% Agreement: First round, 92%; second round, 98%

Block 6

If, on index surgical exploration, gross peritoneal spread or extra-appendiceal mucin is noted, a definitive diagnosis must be confirmed. Biopsy of the sites of peritoneal spread and appendectomy should be performed if technically feasible, such that pathologic review can clearly confirm diagnosis and disease grade to guide therapy.

% Agreement: First round, 97%; second round, 99%

Block 7

If extra-appendiceal disease is limited to localized acellular mucin only by direct visualization, and all disease is completely resected (the equivalent of a complete/adequate cytoreduction), no further surgical management is indicated. The rate of recurrence is as low as 4%.[133] The definition of localized acellular mucin ultimately depends on intraoperative surgeon judgement, but we recommend defining this as disease limited to the meso-appendiceal fold and periappendiceal recesses. Regular surveillance is recommended according to block 11.[134]

% Agreement: First round, 96%; second round, 98%

Block 8

If extra-appendiceal disease is limited to acellular mucin in the right lower quadrant but residual disease is left at the time of initial exploration with or without an attempt at resection (such as in those patients referred from outside institutions or with otherwise previous incomplete cytoreduction), evaluation should be initiated for cytoreduction with or without intraperitoneal chemotherapy; given the limited data on recurrence in this subpopulation, this is primarily an expert consensus-based recommendation.

% Agreement: First round, 95%; second round, 98%

Block 9

If surgical exploration reveals extra-appendiceal acellular mucin that is more widely disseminated than the periappendiceal region or cellular mucin, refer to the peritoneal disease pathway because a more comprehensive approach focused on regionally advanced disease must be pursued. Recurrence estimates for localized cellular mucin (any grade) range widely from 33% to 75%, comparable to disseminated disease, justifying a more aggressive approach.[133,135]

% Agreement: First round, 96%; second round, 96%

Block 10

If there is evidence of recurrent or progressive disease during surveillance, by definition, this would be peritoneal disease, and care should progress to the peritoneal pathway.

% Agreement: First round, 96%; second round, 99%

Block 11

When indicated, surveillance should include regular interval history and physical examination as well as imaging studies and tumor markers. Either computed tomography or magnetic resonance imaging are acceptable; modality should be chosen for consistency and expertise in institutional practice because no clear evidence identifies the superior examination. Tumor markers should include carcinoembryonic antigen and any other markers that are noted to be elevated at initial evaluation or at any point in treatment. No studies provide strong evidence for duration and frequency, but a single retrospective study from the US HIPEC Collaborative demonstrated that imaging surveillance every 6–12 months was noninferior to more frequent schedules.[136] Recurrence is most common in the first 3 years postoperatively and plateaus at approximately 6 years.[137,138] Therefore, consensus recommends surveillance every 6–12 months for 5–10 years; higher grade lesions and any degree of peritoneal involvement are indications for more intense surveillance.

Because cross-sectional imaging is not sensitive for early peritoneal disease, high-risk pathologic features may merit second-look laparoscopy in select cases, but this should not be pursued for most patients with AMNs.[136] There is no definitive indication for circulating tumor DNA surveillance in AMNs.

% Agreement: First round, 91%; second round, 95%

APPENDICEAL ADENOCARCINOMA

Consensus results and updates

This pathway (Figure 3) summarizes recommendations for both mucinous and nonmucinous tumors, inclusive of goblet cell tumors but exclusive of neuroendocrine tumors. In addition to reorganization of peritoneal disease, other changes include updated criteria for

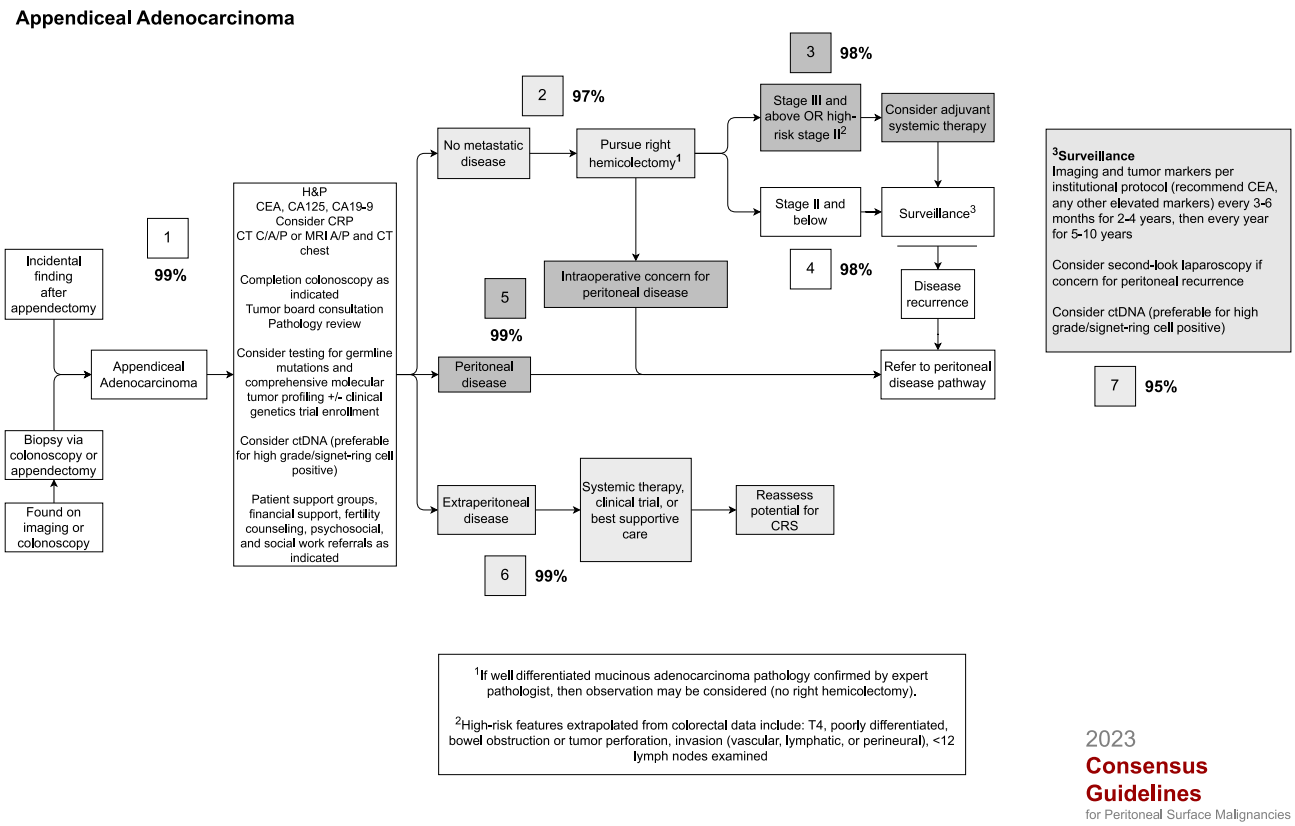

FIGURE 3 Appendiceal adenocarcinoma pathway. CA 19-9 indicates cancer antigen 19-9; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CRP, C-reactive protein; CRS, cytoreductive surgery; CT, computed tomography; CT C/A/P, computed tomography of the chest/abdomen/pelvis; ctDNA, circulating tumor DNA; H&P, history and physical examination; IPCT, intraperitoneal chemotherapy; MRI A/P, magnetic resonance imaging of the abdomen/pelvis; RLQ, right lower quadrant.

systemic chemotherapy, a more comprehensive initial workup, and cohesive surveillance recommendations.

Pathway components are designated by blocks, indicating critical areas of clinical decision making. Percentages (% agreement) at the end of each block description indicate agreement levels from the second Delphi round. The first-round version of the pathway may be referenced in Figure S2.

Block 1

Similar to AMN, appendiceal adenocarcinoma may be detected on diagnostic imaging or incidentally after appendectomy. Initial evaluation and management should mirror that of the AMN pathway.[127,128] As discussed above, germline testing may be considered in conjunction with family cancer history for research purposes and assessment of hereditary cancer risk.[88,89,139,140] Comprehensive tumor profiling should be considered to identify potential molecular targets.[120,122–124,139,140] Of note, circulating tumor DNA testing may be considered particularly for patients with high-grade or signet ring cell pathology because it is useful for prognostication, although evidence is limited in appendix cancer compared with metastatic colorectal cancer.[141]

% Agreement: First round, 96%; second round, 99%

Block 2

Right hemicolectomy with oncologic lymphadenectomy should be pursued for most cases of appendiceal adenocarcinoma in suitable surgical candidates. Currently, this is interpreted as the 12-node yield required in colon cancers. Observational data show a survival benefit with at least 10 nodes.[142] Although stage migration and limitations of current research may contribute to the observed benefit of right hemicolectomy, it has been associated with survival benefit in most mucinous adenocarcinomas with a stage <I and in any nonmucinous adenocarcinoma.[143,144]

The exception to this is well differentiated mucinous adenocarcinoma that is completely confined to the appendix with negative margins and no concern for more distant disease. The rate of lymph node positivity has been shown to be low in well differentiated and some moderately differentiated mucinous lesions, decreasing the survival benefit of right hemicolectomy.[74,129,145]

% Agreement: First round, 94%; second round, 97%

Block 3

Patients with stage III appendiceal adenocarcinoma (spread to at least one regional lymph node) or stage II appendiceal adenocarcinoma

with any high-risk features should be considered for adjuvant systemic chemotherapy after surgical resection.[52,54,60,63,74–79] High-risk features are summarized in the section above on systemic chemotherapy section.[52,54,63,73–78,142] Adjuvant chemotherapy regimens, described above in the section on systemic chemotherapy, typically last 3-6 months, depending on patient toleration, with a goal of 6 months of therapy.[26,32,57] Patients should be subsequently surveilled, as described in block 7.

% Agreement: First round, 91%; second round, 98%

Block 4

Patients who have stage I and II appendiceal adenocarcinoma without high-risk features, as defined above, should be surveilled after surgical resection, as described in block 7, because insufficient evidence supports the benefit of systemic chemotherapy in completely resected, low-risk lesions.[73]

% Agreement: First round, 96%; second round, 98%

Block 5

If recurrent disease is detected on initial diagnostic workup or during surgical resection, management should follow the pathway described for appendiceal tumors with peritoneal disease, which will be presented in a separate article and will address both peritoneal and extraperitoneal disease.

% Agreement: First round, 97%; second round, 99%

Block 6

Although not an absolute contraindication to resection in oligometastatic disease, appendiceal adenocarcinoma with extraperitoneal spread at diagnosis is a poor prognostic indicator, and patients presenting in this setting are unlikely to be candidates for definitive surgical resection.[146] Through joint decision making, clinicians and patients may consider systemic chemotherapy, clinical trials, or best supportive care alone. Multidisciplinary oncologic care, including consideration of a palliative consultation, is recommended. Surgical intervention may be appropriate for symptom control. Depending on response to intervention, patients may be re-evaluated for debulking or more definitive cytoreductive surgery.

% Agreement: First round, 96%; second round, 99%

Block 7

Imaging and clinical surveillance with the same elements as for AMN are recommended at a frequency of every 3–6 months for 2–4 years and annually thereafter for 5–10 years. This is more frequent than recommended for AMNs, given the higher recurrence rates in this population in the first year after resection, but it is similar to surveillance for higher grade colorectal disease.[136–138] Like with AMN, cross-sectional imaging is not sensitive for early peritoneal disease, thus second-look laparoscopy may be considered when there is concern for peritoneal recurrence.[136] Again, interval testing for circulating tumor DNA levels should also be considered, particularly for patients with high-grade or signet ring–positive pathology.[141]

% Agreement: First round, 90%; second round, 95%

DISCUSSION

This text summarizes two of three consensus guideline pathways regarding the management of appendiceal tumors without peritoneal involvement. Consensus across all blocks was achieved after two rounds of review by a multidisciplinary group.

Most evidence regarding the treatment of appendiceal malignancy remains observational at best; however, the volume of data has increased, and understanding of the role of systemic chemotherapy has incrementally improved. One of the chief benefits of this update is the unification of recommendations across consensus group members in multiple different cancer care disciplines and across a single, unified pathologic grading system. Major changes in recommendations for localized disease are the new preferential recommendations for margin resection only for LAMN (avoiding segmental resections and anastomoses when possible) and clarified recommendations regarding chemotherapy.

Limitations of the consensus include the retrospective and observational nature of most literature in appendiceal malignancy management. The role of intraperitoneal chemotherapy remains highly controversial among consensus members, thus no explicit recommendation is presented here. The increased diversity in expertise represented in this consensus group is a major strength.

Comparison with other international guidelines

Both the American Society of Colorectal Surgeons (2019) and the Peritoneal Surface Oncology Group International (2021) have published their own consensus guidelines since the development of the Chicago Consensus, but both have limitations.[147,148] The American Society of Colon and Rectal Surgeons guidelines are surgeon-focused, whereas the Peritoneal Surface Oncology Group International (PSOGI) guidelines are more relevant to the European practice environment and do not expand upon certain grade-by-grade distinctions in management, which have been demonstrated to be clinically relevant. The PSOGI guidelines focus on peritoneal disease but also include some guidelines relevant to localized disease, as here. Primarily, they sit within the larger ecosystem of common PSOGI terminology and rely on the PSOGI pathologic classification system.[147] The initial evaluation guidelines are similar to those in this consensus, except neither CRP testing nor any genetic workup is

recommended. Surgical recommendations, including trocar placement (midline to allow for port excision), are more specific, although diagnostic laparoscopy is not as strongly recommended before resection; our consortium guidelines essentially require tissue diagnosis.

PSOGI presents recommendations separately for goblet cell adenocarcinoma instead of their inclusion in this consensus along with other nonmucinous adenocarcinomas. PSOGI suggests that hemicolectomy may not be necessary in the lowest grade tumors (World Health Organization grade 1 goblet cell adenocarcinoma or Tang A) confined to the appendix without high-risk features; whereas, currently, our group currently recommends right hemicolectomy without exception. Conversely, PSOGI supports consideration of right hemicolectomy for high-grade AMN even without peritoneal disease, whereas our consortium favors resection to negative margins only. The PSOGI consensus also suggests that perforation may be an indication to consider cytoreduction, but our group recommends cytoreduction only if there is demonstrable peritoneal disease of either cellular character or outside the immediate periappendiceal region. In terms of systemic chemotherapy, PSOGI specifically recommends a 5-FU backbone and an alkylating agent as well as neoangiogenesis inhibitors when resection is incomplete or not performed; indications are generally similar, although no preference is given for preoperative versus postoperative timing.[147]

The American Society of Colon and Rectal Surgeons guidelines are from a focused surgical perspective with some salient differences, including that no exception to hemicolectomy is made for well differentiated and otherwise localized adenocarcinoma. Recommendations regarding systemic chemotherapy are very limited and only extend to unlikely benefit in low-grade lesions and possible benefit in high-grade AMN.[148]

The Peritoneal Malignancies Oncoteam of the Italian Society of Surgical Oncology recently published recommendations as well. Their recommendations overlap in most areas with the PSOGI recommendations, including using PSOGI terminology, considering hemicolectomy for high-grade AMN, and pursuing cecectomy or ileocecectomy for margin involvement in LAMN instead of conservative margin resection alone. Similarly, when cellularity or dissemination of peritoneal mucin is required to consider cytoreduction in the PS Consortium guidelines, perforation alone is grounds for considering cytoreductive surgery/HIPEC in the Italian Society of Surgical Oncology consensus.[149]

Patient perspective

Advocacy groups, including PMP (pseudomyxoma peritonei) Pals and the Appendix Cancer Pseudomyxoma Peritonei Research Foundation are key resources, both directly to patients and families, and indirectly by engaging with research initiatives and guiding clinical practice. Diagnosis with rare malignancies like appendix tumors often leaves patients and their caregivers feeling abandoned and without options. Moreover, the process of treating appendiceal cancer is far from benign, with long-lasting effects on physical, sexual, and mental health for which patients and families are often not adequately prepared. Respondents identified strong community as crucial to alleviating those feelings, including close relationships with a network of oncologists, surgeons, advocacy groups, and family and, for some, integration of alternative, holistic, and palliative practitioners into routine care. The multidisciplinary nature of this consensus seeks to produce a cohesive approach that facilitates an integrated support network.

Responses from advocacy groups emphasize that quality of life and survival are paramount in deciding on treatment modalities but that those decisions are not always obvious, especially during surveillance following surgery. One respondent described the experience as a "vast wasteland," with patients "left to wander a 5-year journey with little on the horizon." Well designed, accessible online resources are key roadmaps for many, whereas it is access to clinical trials that often provides direction to that journey by offering hope and a sense of autonomy. However, patient and caregiver advocates report struggling to navigate this process because of the constraints of geography and medical insurance. Although this guideline emphasizes referral to clinical trials, equitable access to trials for all has not been achieved. Patient advocates emphasize that current research and scholarship involving appendiceal malignancies would benefit from a louder patient voice, whether it is in choosing the study design, deciding on the outcomes of interest, or educational initiatives and communication. Ultimately, improving the patient's experience hinges on clarifying the treatment journey, limiting isolation, and fostering hope where possible.

Future scope and limitations

Recommendations related to systemic chemotherapy are in need of ongoing study because outcomes remain poor, particularly in patients with high-grade disease. A clear need remains for judiciously designed, prospective trials to identify the optimal sequence and delivery of treatment modalities for patients with appendiceal tumors; some are in current development, particularly to investigate the neoadjuvant setting. Most randomized trial schemata are difficult to use in this patient population; however, recent work using crossover designs has shown promise.[69] Multiinstitutional prospective studies will be crucial to validate and further refine the recommendations of this consensus group. Further work is also needed to explore quality-of-life outcomes for patients with appendix tumors because the relative rarity of their disease leaves them with less support than individuals facing more common cancers.

CONCLUSIONS

In conclusion, herein we report an updated Delphi consensus of management guidelines concerning appendiceal tumors without peritoneal involvement. Importantly, this consensus group contained specialists across multiple disciplines relevant to cancer care, including medical oncologists, surgical oncologists, pathologists, radiologists, palliative care specialists, and patient advocates. Surgical resection remains the primary modality of up-front definitive treatment in presentations without peritoneal involvement. Systemic chemotherapy should be considered for high-risk pathologies. Regular surveillance should be performed for all patients with appendiceal tumors, save the lowest grade, lowest risk LAMNs after complete resection with no additional risk factors.

AUTHOR CONTRIBUTIONS

Elizabeth L. Godfrey: Conceptualization; methodology; investigation; writing—original draft; writing—review and editing; validation; formal analysis; project administration; data curation; and visualization. **Forest Mahoney:** Conceptualization; methodology; investigation; writing—original draft; writing—review and editing; data curation; project administration; formal analysis; validation; and visualization. **Varun V. Bansal:** Conceptualization; investigation; writing—original draft; methodology; validation; writing—review and editing; visualization; formal analysis; project administration; and data curation. **David G. Su:** Conceptualization; methodology; project administration; and visualization. **David N. Hanna:** Investigation; formal analysis; validation; and data curation. **Felipe Lopez-Ramirez:** Investigation; validation; formal analysis; and data curation. **Ekaterina Baron:** Data curation; formal analysis; validation; and investigation. **Kiran K. Turaga:** Supervision; resources; project administration; conceptualization; investigation; methodology; and validation. **Al B. Benson:** Visualization; writing—review and editing; investigation; conceptualization, and writing—original draft. **James Cusack:** Visualization; writing—review and editing; investigation; conceptualization; and writing—original draft. **Joshua H. Winer:** Visualization; writing—review and editing; and investigation. **Craig G. Gunderson:** Validation; writing—review and editing; methodology; investigation; and formal analysis. **Joseph Misdraji:** Methodology; writing—review and editing; and writing—original draft. **Rupen Shah:** Visualization; writing—review and editing; investigation; conceptualization; and writing—original draft. **Deepa R. Magge:** Visualization; writing—review and editing; investigation; conceptualization; and writing—original draft. **Ian Solsky:** Writing—original draft; writing—review and editing; and visualization. **Cathy Eng:** Writing—original draft; writing—review and editing; visualization; conceptualization; and investigation. **Oliver S. Eng:** Conceptualization; investigation; writing—original draft; writing—review and editing; and visualization. **Ardaman Shergill:** Conceptualization; investigation; writing—original draft; writing—review and editing; and visualization. **John Paul Shen:** Conceptualization; investigation; writing—original draft; writing—review and editing; and visualization. **Michael B. Foote:** Conceptualization; investigation; writing—original draft; visualization; and writing—review and editing.

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DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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