Received: 4 July 2024 | Revised: 21 September 2024 | Accepted: 7 October 2024

DOI: 10.1002/cncr.35874

CONSENSUS STATEMENT

Consensus guideline for the management of patients with appendiceal tumors, part 2: Appendiceal tumors with peritoneal involvement

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Abstract

Background: Appendiceal tumors comprise a heterogeneous group of tumors that frequently disseminate to the peritoneum. Management of appendiceal tumors is

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.

This article is co-published in the journals *Cancer* and *Annals of Surgical Oncology*. https://doi.org/10.1002/cncr.35874 or https://doi.org/10.1245/s10434-025-17364-z.

lacking high-quality data given their rarity and heterogeneity. In general, appendiceal tumor treatment is extrapolated in part from colorectal cancer or pooled studies, without definitive evidence of disease-specific benefit. Many practices are controversial and vary widely between institutions. A national consensus update of best management practices for appendiceal malignancies was performed to better standardize care. Herein, the authors present recommendations for the management of appendiceal tumors with peritoneal involvement.

Methods: As previously described, modified Delphi consensus was performed to update the previous 2018 Chicago Consensus guideline. Recommendations were supported by using rapid systematic reviews of key issues in surgical and systemic therapy. Key pathology concepts and recommendations were synthesized in collaboration with content experts.

Results: A consensus-based pathway was generated for any type of non-neuroendocrine appendiceal tumor with peritoneal involvement. The first round of Delphi consensus included 138 participants, of whom 133 (96%) participated in the second round, and greater than 90% consensus was achieved for all pathway blocks. Key items included recommending evaluation for cytoreduction to most patients with low-grade peritoneal disease who are surgical candidates and to many patients with high-grade disease, as well as timing of systemic chemotherapy and surveillance protocols. Common pitfalls in pathologic classification and their clinical implications are also presented.

Conclusions: These consensus recommendations provide guidance regarding the management of appendiceal tumors with peritoneal involvement, including a review of current evidence in the management of recurrent and unresectable disease.

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

INTRODUCTION

Appendiceal tumors are a diverse group of rare, heterogeneous tumors. Minimal data are available to guide management and are rarely prospective, so expert consensus guidelines remain a necessity to direct care, as was previously done in the 2018 Chicago Consensus.[1–5] Part 1 of the 2024 consensus guideline update presented management for localized appendiceal tumors.[6] This second part presents management of appendiceal tumors with peritoneal involvement.

Approximately 40%–50% of appendiceal tumors present with distant disease at diagnosis, most often mucinous tumor deposits in the peritoneum called *pseudomyxoma peritonei* (PMP).[7–9] Estimates of median overall survival (OS) range widely, in part because of diverse tumor biology. The median OS for patients with well differentiated mucinous peritoneal disease has been reported to approach 74–78 months. Moderately differentiated mucinous peritoneal disease exhibits a median OS of 13–66 months, poorly differentiated mucinous peritoneal disease has a median OS as low as 12–18 months when reported separately, and nonmucinous disease lower still, with a median OS of 6–27 months, depending on grade.[10–18] Some studies report prolonged survival times, but these are generally in the context of more limited cohorts of individuals who are offered or undergo surgery, and some do not distinguish between tumor types and grades.[4, 10–12, 19–30] The survival of patients who have goblet cell adenocarcinoma (GCA) with peritoneal involvement also differs by grade, from a median OS of 98 months for grade 1 and 2 disease to 33 months for grade 3 disease.[31]

Although estimates vary widely, recurrence is common, with approximately 25% of all patients developing recurrence in the first 1–3 years after surgery.[32–34] Rates are higher with increasing peritoneal disease extent and grade.[35–39] In one of the largest studies of recurrence after cytoreduction, 60% of patients with low-grade tumors and 20% of patients with high-grade tumors were disease-free at 6 years.[40]

MATERIALS AND METHODS

The methods, including the modified Delphi process for the 2024 consensus update of the 2018 Chicago Consensus guidelines, have been previously described in detail in an open-access, online

repository, in the Supporting Methods, and in the part 1 appendiceal tumors guideline.[6, 41]

Consensus group structure

The Appendiceal Tumor Working Group included 14 multidisciplinary cancer care specialists and a physician scientist with demonstrated expertise in systematic reviews. Two steering committee core members coordinated and revised the pathways (F.M., E.G.). Sixteen trainees (medical students, residents, and fellows) conducted the rapid reviews. Updated pathology recommendations were developed collaboratively with members of the consensus group who had gastrointestinal pathology expertise.

Rapid review of the literature

Rapid reviews were conducted of Medline, as described in the Supporting Methods and the part 1 guideline for the management of localized appendiceal tumors.[6,41] Key question 1 addressed the optimal timing of systemic chemotherapy relative to cytoreduction in non–low-grade peritoneal disease of appendiceal origin. The latter two of the three key questions address the following (for detailed search strategies, see Tables S1 and S2).

1. In patients with unresectable pseudomyxoma peritonei, which management approaches offer the best symptom control and survival benefit (surgical interventions vs. systemic therapy vs. conservative management)? (PROSPERO CRD42023463230)
2. In patients with recurrent peritoneal disease after initial cytoreductive surgery for appendiceal tumors, is repeat cytoreduction with or without hyperthermic intraperitoneal chemotherapy safe and superior to systemic therapy alone or observation? (PROSPERO CRD42023463240)

Reviews were conducted and data extracted according to the published protocols and methods detailed in the Supporting Methods and also is available in an online repository and in the part 1 appendiceal tumors guideline, in which key question 1 is also summarized.[6, 41]

RESULTS

Pathways

Of 138 specialists who voted on the clinical pathway for appendiceal tumors with peritoneal involvement, 133 (96%) participated in the second round. The group comprised 96 (70%) surgical oncologists, 20 (14%) medical oncologists, 15 (11%) pathologists, and seven (5%) specialists from other disciplines and patient advocates. The blocks are summarized below with supporting literature incorporated where appropriate.

Rapid reviews

Key question 2: Management of unresectable appendiceal malignancy

For key question 2, 1473 abstracts were screened, 103 were included for full-text review, and 15 were selected for final inclusion, reporting outcomes of any intervention for the management of initially unresectable PMP of appendiceal origin of any grade. Inclusion and exclusion criteria are detailed in the key question 2 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and key (Figure S1 and Table S3). Most exclusions were for overlap with key question 3: recurrent disease. Outcomes were OS and progression-free survival, eligibility for and completeness of cytoreduction, and adverse events. Although not amenable to meta-analysis, the included heterogeneous studies explored a range of therapies for unresectable PMP. Included studies were retrospective and observational studies except for one—a single-arm, phase 2 trial. Six studies reported on systemic chemotherapy,[42–48] eight reported on incomplete cytoreduction or debulking,[49–56] and seven reported on intraperitoneal chemotherapy (IPCT),[45,47,48,50,52,54,56] with substantial overlap. The results are summarized in Table 1,[42–56] and quality assessment is provided in Table S4.

The included studies generally reported better outcomes for patients who underwent cytoreductive surgery (CRS) or major tumor debulking than those who did not, but all studies included here were observational and retrospective.[49,51,53,55,56] From the retrospective standpoint, surgery is most likely to have been offered to the same individuals who were already likely to have better outcomes—those with superior physiologic reserve, lower disease burden, and more indolent tumor biology—making it impossible to account for the true impact of selection bias.

For cohorts that included low-grade disease, six studies demonstrated either increased survival compared with observation or an acceptable survival and morbidity profile for tumor debulking or incomplete cytoreduction.[49–51, 53–55] IPCT was part of the treatment regimen in five retrospective, nonrandomized studies involving low-grade disease, two of which demonstrated a survival advantage of IPCT.[45,47,50,52,54]

For patients with high-grade disease, four included observational studies that reported either improved survival or eligibility for cytoreduction after upfront systemic therapy, although two studies did not explicitly report which outcomes were associated with high-grade versus low-grade disease; most strikingly, Baron et al. reported median OS of 26 months with systemic chemotherapy (SCT) compared with 12 months without.[42–44,46] Although Sugarbaker and Chang reported longer survival among patients undergoing upfront incomplete cytoreduction instead of SCT, as an observational study over 22 years, it is likely that patients with more indolent tumor biology underwent upfront surgery and that patients undergoing upfront SCT received regimens that would now be considered obsolete.[53] Three studies reported a survival benefit associated with IPCT, and another reported increased survival in patients undergoing iterative HIPEC (iHIPEC) in high-grade goblet cell disease.[45,48,50] As

TABLE 1 Key question 2: Management approaches for initially unresectable peritoneal surface malignancy of appendiceal origin.

Reference (country)	Population and inclusion criteria	Tumor grade/ type and disease burden	Interventions	Outcomes reported	Adverse events, grade 3/4
Studies of exclusively unresectable appendiceal cohorts					
Baron 2022[42] (US)	72 patients with high-grade PMP who underwent aborted/ palliative CRS; excluded deaths within 90 days of surgery	All high grade *SCT:* - 8/20 with SRCs 1/20 goblet cell *No SCT:* - 29/50 with SRCs - 8/50 goblet cell	*SCT:* - 20/72 with median 12 cycles of 5-FU/Cape ± oxaliplatin ± irinotecan - 10/20 with bevacizumab *No SCT:* - 52/72	*OS, repeat CRS* - Median OS 26 months for SCT vs. 12 months for no SCT (HR, 0.22; 95% CI, 0.08–0.66; $p = .007$) - 2/20 SCT group with reattempted CRS, 1/ 20 completed CRS	Grade 3-4 complications: 3/20 SCT vs. 3/ 52 no SCT
Choe 2015[43] (US)	130 patients treatment naive to SCT and not amenable to complete CRS because of extensive disease, progression after prior CRS, or assessed low benefit from surgery	37/130 well diff 43/130 mod diff 50/130 poor diff 33/130 with SRCs	*SCT with anti-VEGF or anti-EGFR:* - 59/130 total with bevacizumab, all 5-FU based - 5/130 with cetuximab, also 5-FU based - 1/130 with panitumumab *Standard SCT without biologic:* - 51/130 standard 5-FU–based or Cape-based 14/130 other	*OS, PFS, response* - Median PFS 9 months with bevacizumab vs. 4 months without biologic (HR, 0.69; 95% CI, 0.46–0.995; $p = .047$) - Median OS improved by 34 months with bevacizumab vs. without biologic (HR, 0.49; 95% CI, 0.25–0.94; $p = .03$) - Anti-EGFR associated with reduced median OS by 18–20 months - Response to SCT (imaging/clinical): 87% with bevacizumab vs. 60% without biologic	NR
Delhorme 2016[49] (France)	39 patients with unresectable disease	13/39 DPAM 12/39 PMCA-I 14/39 PMCA	*Debulking (incomplete CRS):* - 23/39 underwent >80% (major) debulking - 24/39 with prior CRS - 17/39 with prior SCT	*OS, PFS, symptom resolution* - Median OS, 55.5 months; 5-year OS, 46% - Median PFS, 20 months; 5-year PFS, 11% - Resolution of PMP-related symptoms in 14/39 patients	NR
Farquharson 2008[44] (UK)[a]	Phase 2 experimental trial 40 patients with unresectable PMP, adequate performance status, and life expectancy >3 months	27/40 DPAM 10/40 PMCA-I/ PMCA-D 3/40 PMCA	*SCT: Eight cycles every 3 weeks of:* Mitomycin C 7 mg/m^2 intravenously on day 1 and capecitabine 1250 mg/m^2 twice daily on days 1–14	*OS, attempt at CRS, and response* - 1-year OS, 84%; 2-yearr OS, 61% - Attempt at CRS, 2/40 - Response to SCT (imaging), 15/40 (38%)	Grade 3 events in 12/277 cycles, grade 4 events in 4/277 cycles
Mangieri 2022[50] (US)	93 patients with incomplete CRS (R2b or R2c)	39/93 low grade 48/93 high grade 6/93 NOS	*CRS-HIPEC:* 43/93 (mitomycin C or oxaliplatin) *CRS alone:* 50/93	*OS and PFS:* CRS-HIPEC vs. CRS alone *Median OS* - All: 2.3 vs. 1.2 years ($p = .016$) - Low-grade: 1.9 vs. 1.2 years ($p = .004$) - High-grade: 1.15 vs. 1.6 years ($p = .484$) *Median PFS* - All: 1.3 vs. 0.6 years ($p < .0001$)	NR

TABLE 1 (Continued)

Reference (country)	Population and inclusion criteria	Tumor grade/ type and disease burden	Interventions	Outcomes reported	Adverse events, grade 3/4
				- Low-grade: 1.80 vs. 0.63 years (p = .004) - High-grade: 1.19 vs. 0.43 years (p = .016)	
Murphy 2007[51] (UK)	40 patients not amenable to complete CRS	32/40 low grade 8/40 adenocarcinoma	*Open and close:* 6 *Major debulking:* 34 CC-2/CC-3	*Mortality and OS* - Open-and-close: 2/6 30-day mortality, 2/6; OS, 6 months Major debulking: 30-day mortality, 1/34; 2-year OS, 57%	NR for unresectable group
Shapiro 2010[45] (US)	54 patients not amenable to complete CRS because of extensive disease, progression after prior CRS, or assessed low benefit from surgery	24/54 well diff 11/54 mod diff 15/54 mod poor diff 4/54 undetermined 18/54 (33%) with SRCs	*SCT:* 38/54 received two cycles; most 5-FU–based or capecitabine-based ± platinum; some irinotecan regimens (7/54) and 5/54 gefitinib; 11/54 received biologic therapy *SCT and IPCT:* 16/54 also received IP mitomycin C	*OS and response* - Median OS, 40 months for SCT vs. not reached at 80 months for SCT + IPCT - 3-year OS, 50.6% for SCT vs. 73.4% for SCT + IPCT (p = .0495) - Response to SCT (imaging/clinical), 56% (no difference between groups)	NR
Sideris 2009[46] (Canada)	37 patients undergoing CRS + IPCT with curative intent, of which 12 patients deemed initially unresectable	NR for patients with unresectable disease	*SCT:* (6 months of FOLFOX/FOLFIRI) followed by CRS + HIPEC: 2/12 *Palliative surgery and SCT NOS:* 10/12	*Attempt at CRS* - Both patients who received 6 months of SCT underwent complete CRS + HIPEC; survival data not specified for unresectable disease	NR
Smeenk 2007[52] (Netherlands)	10 patients undergoing CRS ± IPCT for disease recurrence or progression after prior CRS	7/10 DPAM 3/10 PMCA-I	*Incomplete cytoreduction + HIPEC:* 1/10 later had SCT for recurrence; further results not specified	*Progression* - 7/10 progressed - 5/7 DPAM and 2/7 PMCA - Median PFS, 6–9 months based on extrapolated survival curve	NR
Sugarbaker & Chang 2022[53] (US)	264 patients with PMP and incomplete CRS	83/264 low to intermediate grade (LAMN/MACA-I) 85/264 grade 1–2 adenocarcinoma 73/264 grade 3 or with SRCs	*Incomplete CRS (CC-2/CC-3)* - SCT before CRS: 107/264 - HIPEC: 14/264 - EPIC: 147/264	*OS* - Median OS, 1.8 years for whole cohort - Median OS, 1.5 years for SCT before CRS vs. 2.0 years for no SCT before CRS (HR, 1.4; 95% CI, 1.1–1.8; p = .008)	2 post-procedural deaths in HIPEC + EPIC 26/264 with grade 4 complications
Trilling 2021[54] (Canada)	8 patients with low-grade PMP and predicted complete CRS after two sequential surgeries	4/8 DPAM 4/8 PMCA-I	*Two-step CRS-HIPEC* - First CRS: 8/8 CC-2 - Second CRS: 5/8 CC-0, 3/8 CC-1, 1/8 unresectable	*OS* - Median OS not reached at a median follow-up of 53.8 months - 3-year OS, 100%; 5-year OS, 85.7% - 1 patient lost to follow-up	NR

(Continues)

TABLE 1 (Continued)

Reference (country)	Population and inclusion criteria	Tumor grade/ type and disease burden	Interventions	Outcomes reported	Adverse events, grade 3/4
Vierra 2022[47] (US)	13 patients with PMP and ≥1 incomplete CRS ± SCT or HIPEC, receiving celecoxib-myrtol combination	9/13 low grade 4/13 high grade	*Celecoxib-myrtol* - 11/13 HIPEC - 7/13 with multiple previous cycles of SCT	*OS, PFS, response* - Median OS, 27 months - Median PFS, 16 months - Tumor marker response, 9/13	Mortality, 2/13 in 8 months; bowel obstructions in 3/13
Studies including unresectable appendiceal cohorts as a subpopulation compared with resectable cohorts					
Berger 2021[48] (US)	7 patients who underwent iterative HIPEC for high-grade appendiceal ex-goblet cell adenocarcinoma with unresectable peritoneal disease; after 3–6 months of SCT without progression	4/7 Tang B AEGA 3/7 Tang C AEGA	*Iterative HIPEC:* Open/ laparoscopic mitomycin C HIPEC, two to three cycles per patient Outcomes compared with institutional control groups of patients with high-grade appendiceal tumors who underwent - SCT only, $n = 16$ - Complete CRS-HIPEC, $n = 7$	*OS, CRS-HIPEC reattempt* - Median OS, 24.6 months for IHIPEC vs. 7.9 months for SCT only ($p = .005$) vs. 16.5 months for CRS-HIPEC ($p = .62$) - 2/7 re-attempted CRS-HIPEC, not complete - No significant change in PCI across IHIPEC intervals	*IHIPEC:* 0 procedural complications, 5 90-day readmissions across 4 patients
Dayal 2013[55] (UK)	205 patients who underwent maximal tumor debulking	61/205 high grade 3/205 with SRCs	Maximal tumor debulking	*OS* Median OS, 32.8 months; 3-year, 5-year, and 10-year OS, 47%, 30%, and 22%, respectively	167 complications 22/205 return to OR
Polanco 2016[56] (US)	97 patients with high-grade disease, of whom 21 underwent incomplete CRS (CC-2/ CC-3); compared outcomes in patients with high-volume vs. low-volume disease	All high grade; 32/97 had SRCs	CRS ± HIPEC: *High-volume disease* (SPCI ≥12) - 15/54 CC-2/CC-3 - 43/54 HIPEC - 32/54 prior SCT, 17/54 adjuvant SCT *Low volume disease* (SPCI <12) - 6/43 CC-2/CC-3 - 42/43 HIPEC - 31/43 prior SCT, 8/24 adjuvant SCT	*OS and PFS (not specified for CC-2/CC-3)* - Median OS, 17.42 months in high volume vs. 42.4 months in low volume ($p = .009$) - Median PFS, 9.6 months for high volume vs. 14.2 mo for low volume ($p = .002$) - Comparable median OS (56 vs. 52 months; $p = .73$) and PFS (20 vs. 19 months; $p = .39$) between high volume vs. low volume when CC-0 achieved	NR

Abbreviations: ±, with or without; 5-FU, 5-fluororacil; AEGA, adenocarcinoma ex-goblet cell adenocarcinoma; AM, acellular mucin; Cape, capecitabine; CC-0, complete cytoreduction score of zero; CC-2, complete cytoreduction score of 2; CC-3, complete cytoreduction score of 3; CI, confidence interval; CRS, cytoreductive surgery; DPAM, disseminated peritoneal adenomucinosis; EPIC, early postoperative intraperitoneal chemotherapy; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; HGMCP, high-grade mucinous carcinoma peritonei; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; IP, intraperitoneal; IHIPEC, iterative hyperthermic intraperitoneal chemotherapy; LAMN, low-grade appendiceal mucinous neoplasm; LGMCP, low-grade mucinous carcinoma peritonei; mod diff, moderately differentiated; NOS, not otherwise specified; NR, not reported; OR, operating room; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; PMCA, peritoneal mucinous carcinoma; PMCA-I, intermediate-grade peritoneal mucinous carcinoma (referring to Ronnett classification); PMCA-D, discordant peritoneal mucinous carcinoma; PMP, pseudomyxoma peritonei; poor diff, poorly differentiated; R2b, residual gross disease between 5 and 20 mm in size; R2c, residual gross disease greater than 20 mm in s; SCT, systemic chemotherapy; SPCI, simplified peritoneal carcinomatosis index; SRCs, signet ring cells; well diff, well differentiated.

[a]Except for the indicated study, all studies were retrospective cohort studies of prospectively collected data, whether in a prospective database or of previously recorded patient chart information.

the authors reporting on iHIPEC describe, the likely impact of selection bias, in terms of both the inclusion only of patients able to undergo multiple surgical procedures and the exclusion of individuals whose disease progressed during SCT, makes it difficult to generalize the benefit of iHIPEC.[48]

Another small study evaluated celecoxib-myrtol combination therapy along with IPCT for disease of any grade, with modest biochemical response in nine of 13 patients.[47] The inclusion of bevacizumab in systemic regimens has been associated with favorable progression-free survival and OS for any grade in one included study and in another more recent study by Hornstein et al., described in part 1.[43,57] A recent prospective, randomized trial with a crossover design, discussed in part 1, demonstrated that systemic chemotherapy with 5-fluroracil–based regimens was no better than observation in terms of survival for individuals presenting with unresectable low-grade mucinous disease.[3] Although excluded from the review because most participants had recurrent, not initially unresectable, disease, this supports our consensus that conventional cytotoxic chemotherapy regimens are unlikely to provide benefit for most patients who have unresectable low-grade peritoneal disease.

Key question 3: Repeat cytoreduction for recurrent appendiceal malignancy

For key question 3, 191 abstracts were screened, 36 were included for full-text review, and nine were selected for final inclusion, reporting outcomes of repeat cytoreduction for recurrent PMP of appendiceal origin of any grade after previous cytoreduction. Inclusion and exclusion criteria are detailed in the KQ3 PRISMA flow diagram (see Figure S2 and key in Table S5). Most exclusions were because of reporting outcomes collectively with nonappendiceal disease or overlap with other studies or key question 2, which evaluated initially unresectable rather than recurrent disease. Meta-analysis was not possible, but summation of outcomes, including OS and adverse events, support an OS advantage of repeat CRS for carefully selected patients with appendiceal tumors experiencing relapse after initial CRS versus with nonsurgical management. Results are summarized in Table 2,[32,58–65] and quality assessment is provided in Table S6. All were retrospective observational studies.

Notably, two high-quality comparative studies showed that outcomes of CRS are associated with tumor grade. Karpes et al. demonstrated improved OS in multivariable analysis among patients undergoing repeat CRS versus nonsurgical management for *peritoneal mucinous carcinoma* (PMCA; high-grade disease; hazard ratio, 0.57) but not for *disseminated peritoneal adenomucinosis* (DPAM; low-grade or acellular disease).[60] Lopez-Ramirez et al. compared outcomes between patients who underwent repeat CRS and a propensity score–matched cohort of patients who did not and noted a survival benefit of repeat CRS for both low-grade and high-grade disease (hazard ratio, 0.32 and 0.36, respectively), excluding those with signet ring cells.[61] The incidence of grade 3–4 postoperative adverse events after repeat CRS ranged from 14.0% to 44.1% across studies.[58,60,61]

It is difficult to separate selection and publication biases from the necessarily careful selection of candidates for repeat CRS. Collectively, the included studies suggest benefit from repeat CRS in terms of OS and also describe patient selection for repeat CRS for those with more favorable patient and disease characteristics, including younger age, better performance status, lower grade disease, longer intervals to disease recurrence, and less frequent elevation of tumor markers at recurrence.[32,58,60,62] This emphasizes the need for individualized decision making regarding repeat CRS by carefully weighing the risks and benefits of major surgery.

PATHOLOGIC CLASSIFICATION OF APPENDICEAL TUMORS

Survival and other key outcomes have been associated with the pathologic classification and grade of appendiceal tumors,.[15,16,66–69] Consequently, our consensus pathway recommendations are stratified by tumor pathology (Table 3). The evolution of pathologic classification systems informs understanding of their crosstalk and key interpretation issues that clinicians may encounter. Advances in molecular tumor biology may lead to improved understanding of tumor behavior and treatment response.

Historical perspective

Before the 1970s, the term *mucocele* was frequently used to describe dilated appendices filled with mucin, although the term was used inconsistently for neoplastic and non-neoplastic conditions.[70–74] Perforated mucoceles associated with extra-appendiceal mucin were typically called *malignant mucoceles*.[75] Over the next several decades, the concept of an appendiceal *adenoma*, or *cystadenoma* if cystically dilated, was transferred from colon to appendiceal tumor nomenclature, although these benign terms generated controversy when they ruptured and disseminated as PMP.[76,77] Biologically, classic PMP and carcinomatosis have different disease distribution, outcome, and tempo of progression, fueling debate over whether PMP should be considered a form of carcinomatosis; low-grade PMP, in addition to having a histologically bland appearance, coats the surfaces of organs, follows a pattern of peritoneal distribution known as the *redistribution phenomenon*, and is slowly progressive, whereas peritoneal carcinomatosis invades organs and is rapidly fatal.[26]

Some pathologists classified appendiceal lesions as ruptured adenomas and the peritoneal tumor as DPAM ("disseminated peritoneal adenomucinosis").[26] Other pathologists argued that neoplastic epithelium growing within the peritoneal cavity, by definition, is a form of malignant carcinomatosis and indicates malignant character of the primary.[77–81] In 1995, Carr and colleagues published a seminal work classifying appendiceal mucinous tumors as mucinous adenomas when confined to the mucosa and as

TABLE 2 Key question 3: Repeat cytoreductive surgery in the management of recurrent peritoneal disease.

		Intervention: Sample size		Outcomes Median OS, months				
Reference (country)	Population: Tumor/PMP grade	Repeat CRS	Nonsurgical	Repeat CRS	Nonsurgical	Log-rank *p*	OS: HR [95% CI]	Grade 3–4 adverse events after repeat CRS
Ahmadi 2021[58] (UK)[a]	Low-grade, high-grade, and adenocarcinoma	145	119	—	—	—	0.41 [0.23–0.74]	14.0% of 114; 41 unknown
Delhorme 2017[59] (France)	DPAM, PMCA-I, PMCA, and unknown	47	19	Not reached	~18[b]	<.05	—	37.9%
Karpes 2020[60] (Australia)[c]	DPAM	44	176	125.5	248.7	.15	1.11 [0.54–2.29]	44.1%
	PMCA	58	184	90.7	55.6	.03	0.57 [0.33–0.95]	
Lopez-Ramirez 2022[61] (US)[d]	Overall	55	55	80.2	36.2	<.001	—	27.3%
	LGMCP	36	36	174.1	51.9	<.001	0.32 [0.16–0.63]	—
	HGMCP	13	13	42.0	12.4	.02	0.36 [0.13–0.98]	—
	HGMCP-S	6	6	15.4	8.1	.61	0.84 [0.25–2.79]	—
Valenzuela 2022[62] (US)[e]	LAMN	58	85	227.1	54.5	<.001	—	—
Studies that included participants with recurrent appendiceal disease as a subcohort and also included progressive disease and/or nonappendiceal cohorts								
Kitai 2020[63] (Japan)	AM, DPAM, PMCA, PMCA-S	10	3	Not reached	~28[b]	<.05	—	—
Kong 2021[32] (Australia)[f]	AM	2	0	64.7	38.7	<.001	—	30% complications (not graded)
	Low grade	24	21					
	High grade	4	9					
Powers 2020[64] (US)	78.5% appendiceal, not otherwise specified	126	243	73	36	.001	—	30.7%
Yan 2007[65] (US)	DPAM, PMCA-I, PMCA	98	13	Not reached	~34[b]	<.001	—	—

Note: All studies were retrospective cohort studies of prospectively collected data, whether in a prospective database or of previously recorded patient chart information.

Abbreviations: AM, acellular mucin; CI, confidence interval; CRS, cytoreductive surgery; DPAM, disseminated peritoneal adenomucinosis; HGMCP, high-grade mucinous carcinoma peritonei; HR, hazard ratio; LAMN, low-grade appendiceal mucinous neoplasm; LGMCP, low-grade mucinous carcinoma peritonei; OS, overall survival; PMCA, peritoneal mucinous carcinoma; PMCA-I, intermediate-grade peritoneal mucinous carcinoma, referring to Ronnett classification; PMP, pseudomyxoma peritonei; -S, with signet ring cells.

[a]Patients with high tumor grade, early recurrence, and raised tumor markers at recurrence were less likely to have repeat surgery; there is potential overlap between intervention groups not otherwise specified or explained by study authors.

[b]Median OS was extrapolated from Kaplan–Meier curves.

[c]Patients who underwent repeat CRS were younger and underwent fewer complete cytoreductions.

[d]Propensity score-matched institutional controls for nonsurgical management.

[e]Patients who underwent repeat CRS were younger, had better performance status, underwent more complete initial CRS, and had a longer time to recurrence from initial CRS.

[f]Patients who were offered repeat CRS were younger and had more low-grade disease.

adenocarcinoma if associated with any growth of viable cells outside the appendix. Tumors that pushed into the underlying appendix wall or showed acellular mucin dissecting into the wall were classified as mucinous tumors of uncertain malignant potential to acknowledge the difficulty in recognizing subtle forms of invasion in some appendiceal tumors.[80]

TABLE 3 Pathology-based guidelines for management of appendiceal tumors.

Primary lesion	Primary tumor grade	Intraoperative findings in the peritoneum	Pathologic findings in the peritoneum: WHO classification and grade	Treatment		
				Primary resection	Peritoneal resection	Systemic therapy
LAMN[a]	Grade 1	No peritoneal disease	Not applicable	Resection	—	—
		Localized mucin	Acellular mucin		Observation if fully resected with primary	Surveillance
		Disseminated mucin			CRS ± IPCT	
		Localized or disseminated mucin	Grade 1 pseudomyxoma peritonei/mucinous carcinoma peritonei			
			Grade 2 pseudomyxoma peritonei/mucinous carcinoma peritonei[b]			Systemic chemotherapy
			Grade 3 pseudomyxoma peritonei/mucinous carcinoma peritonei[b]			
HAMN	Grade 2	No peritoneal disease	Not applicable	Resection	—	—
		Localized mucin	Acellular mucin		Can consider observation if fully resected with primary	Surveillance
		Disseminated mucin			CRS ± IPCT	
		Localized or disseminated mucin	Grade 1 pseudomyxoma peritonei/mucinous carcinoma peritonei			
			Grade 2 pseudomyxoma peritonei/mucinous carcinoma peritonei			Systemic chemotherapy
			Grade 3 pseudomyxoma peritonei/mucinous carcinoma peritonei[a]			
Mucinous adenocarcinoma	Grade 1[a] or 2	No peritoneal disease	Not applicable	Right hemicolectomy	—	Consider systemic chemotherapy in the case of high-risk features, such as lymph node involvement
		Localized mucin	Acellular mucin		Observation vs. CRS ± IPCT based on assessed risk of peritoneal disease progression	
		Disseminated mucin			CRS ± IPCT	
		Localized or disseminated mucin	Grade 1 pseudomyxoma peritonei/mucinous carcinoma peritonei			
			Grade 2 pseudomyxoma peritonei/mucinous carcinoma peritonei			Systemic chemotherapy

(Continues)

TABLE 3 (Continued)

Primary lesion	Primary tumor grade	Intraoperative findings in the peritoneum	Pathologic findings in the peritoneum: WHO classification and grade	Treatment		
				Primary resection	Peritoneal resection	Systemic therapy
			Grade 3 pseudomyxoma peritonei/mucinous carcinoma peritonei[a]			
Mucinous adenocarcinoma with signet ring cells[a]	Grade 3	No peritoneal disease	Not applicable	Right hemicolectomy[a]	—	Consider systemic chemotherapy in the case of high-risk features, such as lymph node involvement
		Localized mucin	Acellular mucin		Observation vs. CRS ± IPCT based on assessed risk of peritoneal disease progression	
		Disseminated mucin			CRS ± IPCT	Systemic chemotherapy
		Localized or disseminated mucin	Grade 1 pseudomyxoma peritonei/mucinous carcinoma peritonei[b]			
			Grade 2 pseudomyxoma peritonei/mucinous carcinoma peritonei			
			Grade 3 pseudomyxoma peritonei/mucinous carcinoma peritonei[a]			
Nonmucinous adenocarcinoma or goblet cell adenocarcinoma	Any grade	No peritoneal disease	Not applicable	Right hemicolectomy	Observation	Systemic chemotherapy
		Peritoneal disease	Any grade		CRS ± IPCT	

Abbreviations: ±, with or without; CRS, cyroreductive surgery; HMAN, high-grade appendiceal mucinous neoplasm; IPCT, intraperitoneal chemotherapy; LMAN, low-grade appendiceal mucinous neoplasm; WHO, World Health Organization.

[a]The presence of signet ring cells should be specifically reviewed.

[b]It is unlikely to see extreme discordance, such as LAMN with grade 3 peritoneal disease or adenocarcinoma with signet ring cells and grade 1 peritoneal disease, but all combinations have been included for completeness. In grade 2/3 peritoneal disease, even if the primary presents as LAMN or HAMN, the diagnosis would be considered adenocarcinoma with background LAMN/HAMN because the predominant disease is invasive.

In 2003, Misdraji and colleagues coined the term *low-grade appendiceal mucinous neoplasm* (LAMN) to describe the full spectrum of these tumors, arguing that the tumors with pushing type invasion that are classified variably as cystadenoma, mucinous neoplasm of uncertain malignant potential, and even adenocarcinoma were histologically indistinguishable, whether or not they had peritoneal spread.[82] Subsequently, the term *high-grade appendiceal mucinous neoplasm* (HAMN) was introduced for tumors with pushing invasion but high-grade cytology.[83] LAMN and HAMN are now recognized as the tumors most often responsible for PMP, and the presence of PMP no longer mandates classification as adenocarcinoma. Rather, to qualify as adenocarcinoma, a tumor must demonstrate infiltrative-type invasion typical of adenocarcinomas elsewhere in the gastrointestinal tract.

Commensurate with changes in primary tumor nomenclature, the terminology and grading of PMP evolved. Historically, the term PMP was reserved for the clinical syndrome of progressive mucinous ascites and was most often applied to peritoneal tumors with abundant mucin, dissecting fibrosis, and occasional neoplastic but cytologically bland mucinous epithelial cells.[84] Ronnett and coinvestigators coined the term DPAM for low-grade PMP and PMCA for high-grade PMP that had a worse prognosis, with a third category for intermediate or discordant lesions (PMCA-I/D).[26] Some pathologists did not accept DPAM for low-grade PMP and reported all PMP using malignant terms, such as *low-grade mucinous carcinoma peritonei* (MCP) or *high-grade MCP*. [84] Over the ensuing years, studies demonstrated that the presence of signet ring cells in PMP conferred a worse prognosis, and this led to the current three-tier grading

system, reserving grade 3 for tumors with signet ring cells.[23] In the past few years, the World Health Organization (WHO), in an attempt to introduce universally acceptable terminology, adopted the term PMP for all peritoneal mucinous tumors, regardless of grade.[85] MCP is an acceptable alternative term.

Finally, another tumor with evolving nomenclature is *goblet cell adenocarcinoma*. This unique tumor is composed of tubules of goblet-like cells, enterocyte-like cells, and occasional Paneth-like cells. These tumors show variable neuroendocrine differentiation by immunohistochemistry and thus are considered to be amphicrine tumors, exhibiting both endocrine and exocrine differentiation.[86] Classic goblet cell tumors are low grade but can dedifferentiate; and, as high-grade tumors, they resemble poorly differentiated adenocarcinomas or signet ring cell carcinoma.[87] Before 1990, the full spectrum of tumor grades was classified as *goblet cell carcinoid* to reflect their bland appearance and their circumferential infiltration without formation of a clear mass lesion, but this labeling resulted in their behavior being poorly predicted by their nomenclature.[88] In 1990, Burke et al. published the first grading system for these tumors.[87] Tumors with less than 25% *carcinomatous* growth were classified as biologically indolent *goblet cell carcinoid*, whereas those with greater than 50% carcinomatous growth were classified as mixed carcinoid-adenocarcinoma. In 2008, Tang and coinvestigators proposed the classification of low-grade tumors as *goblet cell carcinoid* and of high-grade tumors as *adenocarcinoma ex-goblet cell carcinoid*, with two subtypes.[89] Unfortunately, the term "adenocarcinoma ex-goblet cell carcinoid" gave the impression that adenocarcinoma is arising from an endocrine tumor, which is not the case, and perpetuated confusion regarding whether neuroendocrine staging systems or therapies should be applied. Yozu and colleagues reclassified these tumors as *goblet cell adenocarcinoma* in 2018, in recognition of their closer alignment to adenocarcinoma than neuroendocrine tumors.[90] They also proposed a grading system for these tumors depending on the extent that the tumor recapitulates low-grade tubular morphology. The most recent WHO classification adopted this nomenclature and grading system.[91]

Interpreting the crosstalk between classification systems

Although the WHO 2019 classification (fifth edition) should be used as the mainstay of appendiceal tumor classification to facilitate uniform clinical management and investigation, prior terminology still will be frequently encountered. Therefore, it is necessary for clinicians to understand the crosstalk between classification schemes to appropriately stratify patients to risk and treatment groups. Expert interpretation of this crosstalk is presented in Table 4, although perfect alignment between classification schemes is not feasible because of different histologic criteria, weighting, and thresholds.[24,26,36,82,83,85,91–95]

Low-grade appendiceal mucinous neoplasm is the WHO term for a low-grade mucinous tumor that shows pushing-type invasion.[91] Historical diagnoses, including appendiceal adenoma or cystadenoma (listed in the leftmost column of Table 4), likely indicate LAMN by today's standards, particularly a diagnosis of ruptured appendiceal adenoma. HAMN is the current terminology for what was often described as noninvasive adenocarcinoma or cystadenocarcinoma in prior publications.[36,82,83,96]

By today's standards, including the WHO classification, a diagnosis of adenocarcinoma in the appendix requires at least focal infiltrative invasion in the appendix itself. However, as codified in the 1995 report by Carr et al., the diagnosis of adenocarcinoma has been used for any tumor associated with PMP; consequently, some pathologists may still incorrectly diagnose tumors with PMP as adenocarcinoma.[80] To confirm a WHO system diagnosis of adenocarcinoma, infiltrative type invasion in the appendix itself must be present.[91] Table 4 indicates how each classification system defines adenocarcinoma.

GCA is the current terminology for all three grades of goblet cell tumor. In the article by Burke et al., goblet cell carcinoid corresponds to GCA grade 1, whereas mixed carcinoid-adenocarcinoma is equivalent to GCA grade 3.[87] The Tang classification is more difficult to translate into WHO terminology.[89] The goblet cell carcinoid in that classification is roughly equivalent to GCA grade 1; adenocarcinoma ex-goblet cell carcinoid, signet ring cell type, corresponds to GCA grade 1 or 2, depending on the extent of disorganization; and adenocarcinoma ex-goblet cell carcinoid, poorly differentiated carcinoma type, likely translates to GCA grade 3, depending on the extent of poorly differentiated carcinoma. Table 4 does not expound upon the specific grades because our treatment recommendations do not differ among grades, but the table also lists the historical terminology used for GCA.

Pseudomyxoma peritonei grade 1 corresponds to DPAM in the Ronnett classification and grade 2 and 3 correspond to PMCA.[26] The intermediate category (PMCA-I) might be described as PMP grade 1 to focal 2. In the Peritoneal Surface Oncology Group International system, low-grade MCP is equivalent to PMP grade 1, high-grade MCP is equivalent to PMP grade 2, and high-grade MCP with signet ring cells is equivalent to PMP grade 3, as indicated in Table 4.[83]

Key principles of pathologic interpretation for the clinician

Clinicians caring for patients with appendiceal tumors should be aware that discordant evaluation is very common, with potential impact on clinical management.[97–99] Review by an expert gastrointestinal pathologist should be considered, particularly if certain common pitfalls may have affected the patient's initial evaluation.

Postinflammatory mucosal hyperplasia or diverticular disease of the appendix may mimic LAMN.[100] If a patient is diagnosed with perforated LAMN without PMP, particularly in an interval appendectomy specimen, expert review is suggested because many of these cases may indeed be benign mimics of LAMN. Similarly, if two tumor types are reported in the appendix, such as a neuroendocrine

TABLE 4 Crosstalk of classification terminology for appendiceal tumors.

	Classification schemes and nomenclature for primary appendiceal mucinous tumors							
Primary tumor	**Historic terminology**	**Carr 1995[81]**	**Misdraji 2003[83]**	**Pai 2009[35]**	**PSOGI 2016[83]**	**AJCC 2017 (8th edition)[93]**	**WHO 2019 (5th edition)[86]**	**AJCC 2024 (version 9)[93]**
Low-grade mucinous neoplasm confined to the appendix	Mucinous adenoma, mucinous cystadenoma grade 1 noninvasive papillary adenocarcinoma of the appendix	Mucinous adenoma (confined to mucosa with intact muscularis mucosae)	Low-grade appendiceal mucinous neoplasm (LAMN)	Mucinous adenoma	LAMN (favor use of TNM staging)	LAMN (Tis, T3)	LAMN	LAMN (Tis if confined within subserosa, T3 for involvement of subserosa)
Mucinous tumors of uncertain malignant potential pushing mural invasion or acellular mucin pools on serosa	Intermediate category of mucinous borderline tumor of the appendix Appendiceal mucinous neoplasm of uncertain malignant potential	Low-grade mucinous neoplasm with acellular extra-appendiceal mucin		Low-grade mucinous neoplasm with low risk of recurrence		LAMN (T4a; T4b if invading other structures)		LAMN (T4a; T4b if invading other structures)
Low-grade mucinous neoplasm with extra-appendiceal neoplastic epithelium		Mucinous adenocarcinoma		Low-grade mucinous neoplasm with high risk of recurrence				
Appendiceal mucinous neoplasms + high-grade cytology or complex architecture	Mucinous cystadenocarcinoma		Noninvasive mucinous adenocarcinoma	Mucinous adenocarcinoma	High-grade appendiceal neoplasm (HAMN)	HAMN	HAMN	HAMN (T1–T4; no Tis)
Positive for destructive invasion			Mucinous adenocarcinoma		Mucinous adenocarcinoma	Mucinous adenocarcinoma (T1–T4; no Tis)	Mucinous adenocarcinoma	Mucinous adenocarcinoma (T1–T4; no Tis)

	Classification schemes and nomenclature for mucinous peritoneal disease associated with appendiceal tumors								
Peritoneal disease	**Ronnett 1995[17]**	**Bradley 2006[85]**	**WHO 2010 (4th edition)[95]**	**AJCC 2010 (7th edition)[96]**	**Davison 2014[14]**	**PSOGI 2016 [84]**	**AJCC 2017 (8th edition)[93]**	**WHO 2019 (5th edition)[86]**	**AJCC 2024 (version 9)[93]**
Acellular mucin	Disseminated peritoneal adenomucinosis (DPAM)	NA	NA	Grade 1 (well differentiated, low grade) mucinous adenocarcinoma	G1 (lack any adverse histologic feature)	NA	NA (M1a)	NA	NA (M1a)
Low grade		Mucinous carcinoma peritonei-low grade (MCP-L)	Low-grade mucinous carcinoma peritonei			Low-grade mucinous carcinoma peritonei (DPAM)	Well differentiated mucinous tumor, grade 1 (M1b)	Pseudomyxoma peritonei, grade 1	Well differentiated mucinous tumor, grade 1 (M1b)
Intermediate grade	Peritoneal mucinous carcinomatosis (PMCA)-intermediate/ discordant (PMCA-I/D)		High-grade mucinous carcinoma peritonei	Grade 2 (moderately differentiated, high grade) mucinous adenocarcinoma	Grade 2 (at least one adverse histologic feature)	High-grade mucinous carcinoma peritonei (PMCA)	Moderately differentiated mucinous tumor, grade 2 (M1b)	Pseudomyxoma peritonei, grade 2 (M1b)	Moderately differentiated mucinous tumor, grade 2 (M1b)

TABLE 4 (Continued)

Peritoneal disease	Classification schemes and nomenclature for mucinous peritoneal disease associated with appendiceal tumors								
	Ronnett 1995[17]	Bradley 2006[85]	WHO 2010 (4th edition)[95]	AJCC 2010 (7th edition)[96]	Davison 2014[14]	PSOGI 2016 [84]	AJCC 2017 (8th edition)[93]	WHO 2019 (5th edition)[86]	AJCC 2024 (version 9)[93]
High grade	PMCA	Mucinous carcinoma peritonei-high grade (MCP-H)		Grade 3 (poorly differentiated, high grade) mucinous adenocarcinoma	Grade 3 (signet ring cell component)	High-grade mucinous carcinoma peritonei with signet ring cells (PMCA-S)	Poorly differentiated mucinous tumor, grade 3 (usually has signet ring cells) (M1b)	Pseudomyxoma peritonei, grade 3 (signet ring cells or sheets of tumor cells)	Poorly differentiated mucinous tumor, grade 3 (usually has >10% signet ring cells; M1b)
High grade with signet ring cells	PMCA-I/D or PMCA								

Primary tumor	Classification schemes and nomenclature for primary appendiceal goblet cell tumors								
	Historic terminology	Carr 1995[81]	WHO 2010 (4th edition)[95]	AJCC 2010 (7th edition)[96]	Davison 2014[14]	PSOGI 2016 [84]	AJCC 2017 (8th edition)[93]	WHO 2019 (5th edition)[86]	AJCC 2024 (version 9)[93]
Amphicrine neoplasm containing goblet-like mucinous cells	Mixed carcinoid-adenocarcinoma Mixed adenoneuroendocrine tumor/carcinoma Goblet cell carcinoid/ carcinoma, crypt cell carcinoma Microglandular adenocarcinoma (Mixed) adenocarcinoid Adenocarcinoma ex-goblet cell carcinoid/ adenocarcinoma	(Tumors with clearly invasive components only) Mixed carcinoid-adenocarcinomas	Proposed mixed adenoneuroendocrine carcinoma, goblet cell carcinoid	Goblet cell carcinoids; grades 1 (low), 2, or 3 (high)	No changes proposed	Goblet cell tumor or goblet cell carcinoid; adenocarcinoma ex-goblet cell Carcinoid acceptable and preferred to mixed adenoneuroendocrine carcinoma	Goblet cell carcinoids	Goblet cell adenocarcinoma Grade 1 (low), 2, or 3 (high) based on proportion of high- and low-grade patterns (Misdraji 2019[91])	Goblet cell adenocarcinoma; grades 1 (low), 2, or 3 (high)[159]

Abbreviations: AJCC, American Joint Committee on Cancer; NA, not applicable/available; PSOGI, Peritoneal Surface Oncology Group International; Tis, tumor in situ; TNM, tumor, lymph node, metastases classification.

tumor and LAMN, obstructive hyperplastic changes in the appendiceal mucosa may have been misinterpreted as LAMN. Some diagnoses are prone to confusion by nonexpert pathologists, such as serrated polyps and LAMN or LAMN and HAMN, and expert review is suggested if the distinctions between diagnoses would affect the treatment plan.[83,101,102] Nonmucinous adenocarcinomas may be difficult to differentiate on a purely histologic basis from right-sided colon cancers, particularly in patients with obliterated or obscured anatomy, but have significantly different biology.[103–105] Specifically, signet ring cell carcinoma and high-grade GCA have similar appearances and may even be mistaken for metastatic disease from other primary sites, and the clinician should have a low threshold for requesting additional pathology review in any of these instances.[106,107]

In terms of peritoneal disease, the location and extent of extra-appendiceal mucin and neoplastic epithelium determines the appropriate management algorithm. In this consensus guideline, where recommendations refer specifically to localized acellular mucin, we recommend a definition of disease limited to the meso-appendiceal fold and peri-appendiceal recesses, and we recommend referring to the peritoneal disease pathway for any cellular or more widespread mucinous disease.[6] Difficulty in making this determination may arise on the surgeon's side because of intraoperative obstacles, such as inflammation that obscures anatomy, but may also be caused by challenges with pathologic evaluation; in the latter case, secondary review may be helpful.

A diagnosis of PMP with signet ring cells should be carefully considered because degenerating cells may masquerade as pseudo signet ring cells in low-grade PMP.[108] The American Joint Committee on Cancer, as of version 9 of their cancer staging manual, recommends at least 10% signet ring cells to classify disease as grade 3, but this threshold has not been implemented by the WHO.[23,93] The grade of the appendiceal primary and the peritoneal tumor is usually concordant, thus if reported as discordant (such as high-grade PMP with signet ring cells with an associated low-grade primary tumor), expert review is prudent.[109] Prognosis and management follow the grade of the peritoneal disease if discordant.[68,110]

An ongoing issue in the evaluation of PMP is the assessment of disease progression and treatment effect, which affects the evaluation of patients for surgery. The Peritoneal Regression Grading Score was proposed to address this issue using an aggregate measure of intraoperative macroscopic findings and histologic features from biopsies in each of four quadrants, although, to date, it has only been validated in combination with peritoneal cytology.[111,112]

Molecular characteristics of appendiceal tumors

Rapidly accelerating genomic research suggests that appendiceal tumor genomics may be prognostic and predictive of tumor behavior, pathologic appearance, and patient outcomes.

Some major single mutations in appendiceal tumors have been well characterized. Appendiceal tumors are commonly mutated in KRAS, GNAS, TP53, APC, and SMAD4, with relative frequencies distinct from those of colorectal cancer and clear differences between appendiceal tumors with goblet cell versus mucinous histology.[113] GNAS mutation has consistently been associated with low-grade mucinous tumors, and TP53 is associated with high-grade tumors and a worse overall prognosis.[114] Alterations in the expression of genes associated with stem cell–like behavior have also been associated with a poor prognosis.[115,116]

Molecular subtypes that integrate variant patterns may explain tumorigenesis, survival, and treatment response.[116,117] One key study generated four molecular subtypes of appendiceal adenocarcinoma. Tumors that were RAS-mutation–predominant had the most favorable survival, GNAS-mutated tumors exhibited treatment resistance and high peritoneal disease burden, and TP53-predominant tumors were associated with a stromally invasive phenotype, chromosomal instability, and poor outcomes.[118] Molecular subtype was independently associated with survival and improved tumor classification beyond histopathologic grade.[118] Outcomes of mucinous neoplasms may be predicted in part by the expression and enrichment of immune-related genes.[115] Machine-learning approaches are increasingly being explored as methods for more novel and objective cluster identification, with the goal of identifying further drivers of tumorigenesis.[119]

Pathology-based treatment guidelines

Primary and peritoneal grades and types of appendiceal tumors have been arranged into a grid of all possible combinations in Table 3, with the corresponding treatment recommendations for surgical resection of the primary, cytoreduction, and systemic chemotherapy. Nonmucinous adenocarcinomas and GCAs are addressed together, as in the consensus pathway. Neuroendocrine tumors are not addressed in this guideline.

All three consensus pathways, including those described in part 1, are summarized in this table; the recommendations will not be recapitulated in full here; however, notably, for appendiceal mucinous neoplasms, the primary should be resected to negative margins in the least invasive, safe fashion. For LAMN, extra-appendiceal acellular mucin that is localized to the meso-appendiceal fold and peri-appendiceal recesses can be managed by complete resection alone. If extra-appendiceal mucin is cellular or more extensively disseminated, cytoreduction with or without IPCT should be offered to surgical candidates.[13,15,120–126] Recommendations for HAMN differ from those for LAMN only in that cytoreduction may be considered in localized extra-appendiceal acellular mucin, given the higher rates of progression and recurrence.[30] Cytotoxic chemotherapy should be considered only for grade 2 or 3 peritoneal disease because as minimal benefit has been demonstrated for grade 1 disease.[57,127–133] New

modalities are being investigated for unresectable and progressive disease, as discussed in part 1, such as systemic combination regimens, including immunotherapy, anti-VEGF agents, and other therapies.[57]

For mucinous adenocarcinoma, right hemicolectomy should be performed, with the exception of well differentiated (grade 1) adenocarcinoma confined to the appendix, as described in part 1.[24,134–136] Cytoreduction with or without IPCT may be considered for localized acellular mucin based on the patient's assessed risk of peritoneal disease progression; it should be pursued for disseminated acellular mucin and all cellular mucin.[13,15,120–126] Systemic chemotherapy should be considered if the primary adenocarcinoma has high-risk features, as described in the part 1 guideline, including lymph node involvement or signet ring cells, or for grade 2 or 3 peritoneal disease.[10,18,29,45,69,127–133, 137–140]

For GCA or nonmucinous adenocarcinoma, right hemicolectomy should be performed. If any peritoneal disease is present, cytoreduction should be performed. Systemic chemotherapy should be administered before cytoreduction if possible. [18,127–133]

APPENDICEAL TUMORS WITH PERITONEAL DISEASE

Consensus results and updates

The pathway's nine final main blocks are summarized below (Figure 1). The most important update from 2018 is the stratification of recommendations by pathologic grade of peritoneal involvement for mucinous disease. All nonmucinous disease is grouped together. An overarching change in treatment recommendations is the preference in most instances for a period of SCT before cytoreduction. As with localized tumors, initial workup recommendations are more comprehensive, and surveillance recommendations are unified and updated. A tenth block describing novel therapies was proposed for the Delphi 1 consensus voting but was discarded because many of the 77% who approved of the content expressed a preference to exclude novel therapies from a guideline algorithm; the round 1 version of the pathway is included as Figure S3. Consensus was defined as agreement of at least 90%,

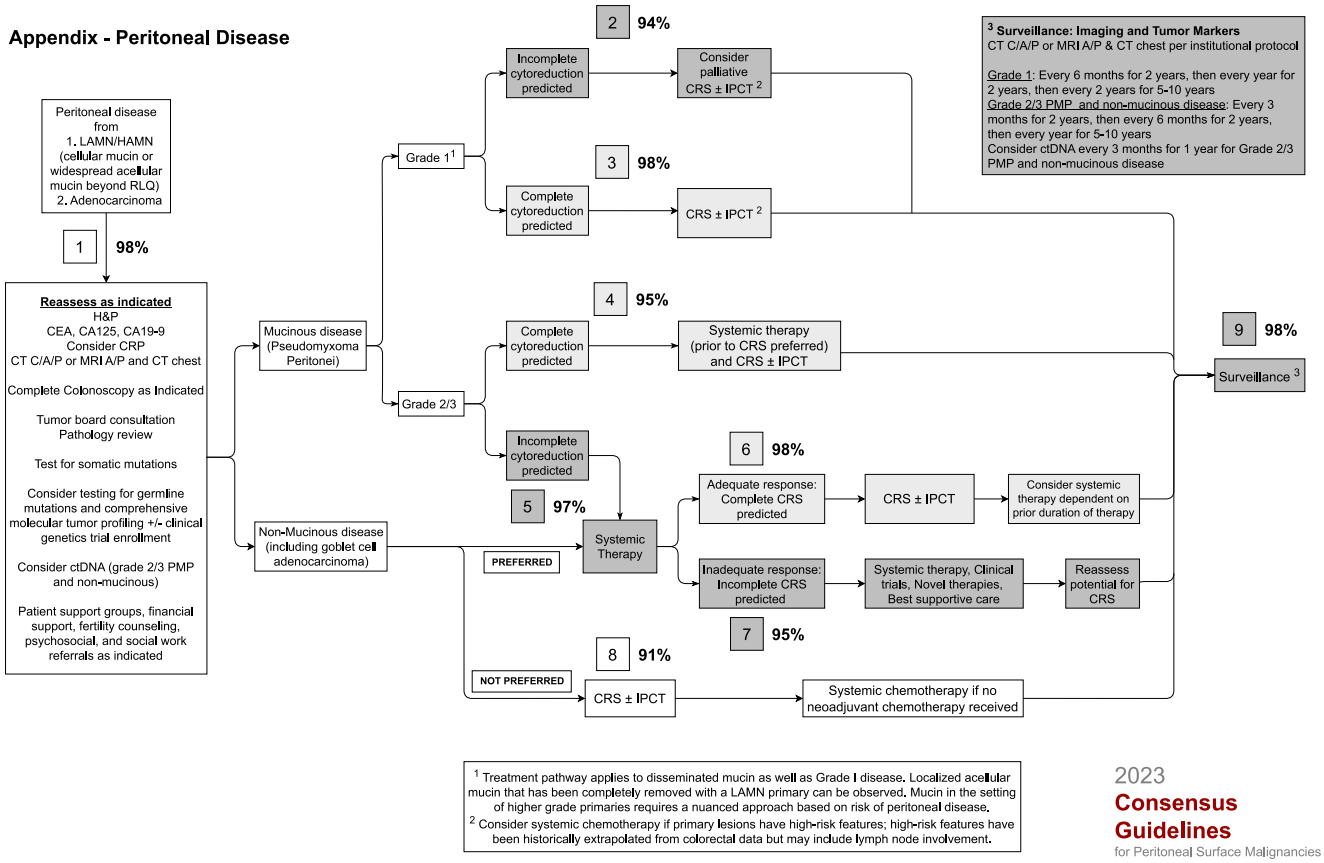

FIGURE 1 Appendiceal tumors with peritoneal disease pathway. CA 19-9 indicates carbohydrate antigen 19-9; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CRS, cytoreductive surgery; CT, computed tomography, CT C/A/P, computed tomography of chest/abdomen/pelvis; ctDNA, circulating tumor DNA; GCA, goblet cell adenocarcinoma; 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 abdomen/pelvis; PCI, peritoneal carcinomatosis index; PMP, pseudomyxoma peritonei; RLQ, right lower quadrant.

TABLE 5 Appendiceal tumors with peritoneal involvement: Delphi round 1 and 2 agreement (% agreement includes agree and strongly agree).

	No. of participants						
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Total	% Agree
Delphi round 1							
Block 1	96	36	4	2	0	138	96%
Block 2	74	41	13	8	2	138	83%
Block 3	100	33	5	0	0	138	96%
Block 4	81	40	11	5	1	138	88%
Block 5	92	37	7	2	0	138	93%
Block 6	94	39	5	0	0	138	96%
Block 7	86	43	8	1	0	138	93%
Block 8	74	39	13	9	3	138	82%
Block 9	74	47	9	8	0	138	88%
Block 10[a]	63	43	27	3	2	138	77%
Delphi round 2							
Block 1	121	9	1	2	0	133	98%
Block 2	119	6	6	1	1	133	94%
Block 3	127	3	3	0	0	133	98%
Block 4	120	6	4	2	1	133	95%
Block 5	125	4	3	1	0	133	97%
Block 6	125	6	2	0	0	133	98%
Block 7	122	5	3	2	1	133	95%
Block 8	108	13	6	5	1	133	91%
Block 9	125	6	1	0	1	133	98%

[a]Block 10 was removed despite >75% agreement with the content because even those who agreed with the content believed it should not be included as part of the algorithm.

which was achieved across all blocks and can be reviewed in Table 5.

Block 1

Peritoneal disease of appendiceal origin may present at initial diagnosis, or as progression or recurrence of previously diagnosed disease. If noted intraoperatively, biopsies should be taken at that time; otherwise, laparoscopy should be considered to obtain a tissue diagnosis.

Workup should include either a complete (if index diagnosis) or appropriately updated full history and physical examination, including family and personal cancer history and risk factors; tumor markers including, carcinoembryonic antigen (CEA), cancer antigen 125, and carbohydrate antigen 19-9, in addition to consideration of C-reactive protein (CRP); and completion chest and abdominopelvic cross-sectional imaging.[141–145] A recent study of more than 1300 patients with appendiceal adenocarcinoma demonstrated an association between each of CEA, cancer antigen 125, and carbohydrate antigen 19-9 with OS, supporting their inclusion in the workup.[146] 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, including progression-free survival and aborted HIPEC.[145,147] Colonoscopy should be recent or updated.[148,149] Genomic testing for advanced cancers may include somatic variant profiling with consideration for further germline variant evaluation.[150,151] For non-low–grade disease, circulating tumor DNA testing should be considered at baseline for future surveillance purposes.[152]

As with all appendiceal tumors, patients should be discussed in tumor board, and pathology should be reviewed by an expert pathologist. Patients should be evaluated for additional support needs, including patient support groups, social work, financial support, psychosocial support, and fertility counseling.

% Agreement: Round 1, 96%; round 2, 98%

Block 2

Blocks 2 and 3 address grade 1 PMP and disseminated acellular mucin associated with any primary other than grade 3 adenocarcinoma. (Of note, this does not include localized peritoneal involvement of LAMN

or HAMN, which is defined as disease limited to the meso-appendiceal fold and peri-appendiceal recess and is addressed in the localized AMN pathway in the part 1 guideline.[6]) A plan of care must be nuanced based on the risk of peritoneal disease suggested by pathologic features and the patients surgical fitness and risk profile. In block 2, palliative or temporizing cytoreduction and IPCT should be considered even if incomplete cytoreduction is predicted.

Cytoreduction should include right hemicolectomy for most adenocarcinomas, although more limited resection may be considered for well differentiated mucinous primaries if hemicolectomy is not necessary to achieve complete cytoreduction because the limited body of evidence has not demonstrated survival benefit of hemicolectomy in these instances.[24,123–125,134–136,153] When full segmental colectomy is not necessary for complete cytoreduction, some form of regional lymph node sampling, such as meso-appendiceal node examination, should be considered to provide prognostic information and guide the role of systemic chemotherapy.[137,153]

Systemic chemotherapy has generally not been shown to improve outcomes in grade 1 disease. However, if the primary tumor has high-risk features, such as lymph node involvement, as noted above, or high-grade or signet ring cell histology, SCT is indicated, as described in part 1. If the primary is identified as grade 3 before cytoreduction, the consensus recommendation is for preoperative chemotherapy, as in block 4.[10,18,29,45,69,137–140]

There is neither adequate data nor consensus at this time to unilaterally recommend local resection only, more invasive CRS with or without IPCT, or SCT for the treatment of limited acellular mucin in the right lower quadrant when the primary disease is adenocarcinoma; however, it may be reasonable to consider observation if fully resected in the absence of high-risk tumor features.

% Agreement: Round 1, 83%; round 2, 94%

Block 3

In block 3, for grade 1 disease with complete cytoreduction predicted, definitive cytoreduction and IPCT should be performed, including right hemicolectomy for adenocarcinoma.[13,15,24,120–126,134–136] Systemic chemotherapy is indicated if the primary tumor has high-risk or high-grade features.[10,18,29,45,69,137–140]

% Agreement: Round 1, 96%; round 2, 98%

Block 4

Block 4 addresses grade 2/3 peritoneal mucinous disease or any PMP with a grade 3 primary. If complete cytoreduction is predicted, then both CRS with or without IPCT and SCT should be carried out.[127–133] Upfront SCT is preferred by consensus to assess disease response, followed by planned complete cytoreduction, although this is not universal.

% Agreement: Round 1, 88%; round 2, 95%

Block 5

Block 5 addresses grade 2/3 peritoneal mucinous disease with incomplete cytoreduction predicted and nonmucinous peritoneal disease. In these cases, chemotherapy should be performed upfront and response assessed before further surgical planning. [18,127–133]

% Agreement: Round 1, 93%; round 2, 97%

Block 6

After a course of systemic chemotherapy, response should be assessed. If predicted incomplete cytoreduction converts to predicted complete cytoreduction, or if complete cytoreduction remains feasible, then CRS with or without IPCT should be pursued.[18,127–133] Total duration of chemotherapy ultimately must be determined by a medical oncologist with subject matter expertise but, in most cases, is recommended for a duration of 6 months and, if not completed preoperatively, should be completed postoperatively.[5,127,154]

% Agreement: Round 1, 96%; round 2, 98%

Block 7

After a course of chemotherapy, if incomplete cytoreduction is persistently predicted or disease has progressed substantially, patients with higher grade mucinous or any nonmucinous peritoneal pathology should not be offered CRS with or without IPCT as definitive therapy. Survival at 3 years after incomplete cytoreduction for high-grade malignancy is as low as 9%, and it is the consensus opinion that this is unlikely to justify the surgical risks for most patients.[155] Depending on the initial chemotherapy course and characteristics of disease progression, patients should be referred for further SCT, novel and/or clinical trial therapies, and/or best supportive care. As therapy progresses, patients should be evaluated at regular surveillance intervals for progression or potential for cytoreduction.

Systematic review does indicate that tumor debulking in appropriate surgical patients, whether it is destination therapy or a bridge to further surgery or IPCT, may have a survival or symptom-control benefit. Risks and benefits should be carefully considered on an individualized basis, and patients should be counseled that this is not a curative therapy.

% Agreement: Round 1, 93%; round 2, 95%

Block 8

Upfront CRS with or without IPCT is not preferred in nonmucinous peritoneal disease. However, if a patient undergoes upfront surgery, they should receive a full course of SCT postoperatively.

% Agreement: Round 1, 82%; round 2, 91%

Block 9

Surveillance proceeds after blocks 3, 4, 6, 7, or 8. Surveillance, as in every other pathway, includes cross-sectional imaging of the chest, abdomen, and pelvis at regular intervals by either magnetic resonance imaging or computed tomography; evaluation f tumor markers (CEA and any other markers that have been elevated during the disease course); and an updated history and physical examination.

For grade 1 peritoneal disease, imaging should be every 6 months for 2 years, then every year for 2 years, then every 2 years for 5–10 years. For all others, imaging should be every 3 months for 2 years, then every 6 months for 2 years, and then every year for 5–10 years. This generally follows the US HIPEC Collaborative, although our consensus recommends enhanced intensity of surveillance for higher risk grade 2/3 disease in the initial postinterventional phase.[156]

Consider monitoring circulating tumor DNA every 3 months for 1 year for grade 2/3 and nonmucinous disease. There is not yet strong evidence for its use in grade 1 disease.

% Agreement: Round 1, 88%; round 2, 98%

DISCUSSION

A chief benefit of this update is the unification of recommendations across a multidisciplinary consensus group and a single pathologic grading system, with guidance on how to relate current recommendations to previous classification schemes. Major updates are the new preferential recommendations for timing of chemotherapy and cytoreduction and the unified surveillance recommendations.

As in part 1, limitations of the consensus include the observational nature of the relevant body of evidence; very little prospective data address the nuances of PSM management. The role of IPCT remains controversial among consensus members, thus we provide no universal recommendation, but several studies in appendiceal tumors suggest benefit. Optimal timing and regimens of systemic chemotherapy are under ongoing investigation; and, although surgical interventions are generally associated with survival benefit, it is difficult to provide nuanced recommendations given the lack of evidence for standardized selection criteria and techniques and the extent of cytoreduction. However, the increased diversity in expertise represented in this consensus group is a major strength as is its systematic presentation of existing evidence for several of its key questions. Future directions, first, include prospective studies to test and refine the recommendations made by this consensus group as well as ongoing exploration of novel and targeted therapies, including accessible clinical trials.

CONCLUSION

Herein, we report an updated Delphi consensus of management guidelines concerning appendiceal tumors with peritoneal involvement. Importantly, this consensus group contained specialists across multiple cancer care disciplines and patient advocates. Cytoreduction remains the bedrock of up-front, definitive treatment in low-grade peritoneal disease. Individuals with high-grade disease should first undergo systemic therapy and, if peritoneal disease remains or becomes resectable, should be evaluated for cytoreduction. Supportive multidisciplinary therapies and palliative surgery should be considered whenever they offer a quality-of-life advantage. These key takeaways are summarized in Table S7.

AUTHOR CONTRIBUTIONS

Elizabeth L. Godfrey: Conceptualization; methodology; investigation; data curation; validation; formal analysis; project administration; visualization; writing—original draft; and writing—review and editing. **Forest Mahoney:** Conceptualization; methodology; data curation; investigation; validation; visualization; project administration; writing—original draft; writing—review and editing; and formal analysis. **Varun V. Bansal:** Conceptualization; methodology; data curation; validation; investigation; formal analysis; writing—review and editing; visualization; writing—original draft; and project administration. **David G. Su:** Conceptualization; methodology; project administration; and visualization. **David N. Hanna:** Data curation; investigation; formal analysis; and validation. **Felipe Lopez-Ramirez:** Data curation; validation; investigation; and formal analysis. **Ekaterina Baron:** Investigation; formal analysis; data curation; validation; and writing—review and editing. **Kiran K. Turaga:** Conceptualization; methodology; investigation; validation; resources; supervision; and project administration. **Al B. Benson III:** Visualization; writing—review and editing; investigation; conceptualization; and writing—original draft. **Namrata Setia:** Investigation; visualization; and writing—review and editing. **Joshua H. Winer:** Visualization; writing—review and editing; and investigation. **Craig G. Gunderson:** Validation; methodology; investigation; formal analysis; and writing—review and editing. **Rupen Shah:** Visualization; writing—review and editing; investigation; conceptualization; and writing—original draft. **Deepa R. Magge:** Visualization; writing—review and editing; writing—original draft; investigation; and conceptualization. **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. **Joseph Misdraji:** Conceptualization; validation; supervision; writing—review and editing; writing—original draft; project administration; investigation; and visualization. **Michael B. Foote:** Conceptualization; investigation; writing—original draft; visualization; and writing—review and editing. **Wenyi Luo:** Conceptualization; investigation; writing—original draft; writing—review and editing; validation; supervision; and visualization.

ACKNOWLEDGMENTS

We thank the Society of Surgical Oncology and the Advanced Cancer Therapies Organization Committees for facilitating dedicated meeting time and space for our group during their meetings. The Society of Surgical Oncology has reviewed and provided endorsement of the recommendations outlined within this document. We thank the Appendix Cancer Pseudomyxoma Peritonei Research Foundation and PMP Pals patient advocacy groups for their participation and perspectives on patient-facing needs. We appreciate the input from Alexandria Brackett, a medical librarian specialist at the Yale Harvey Cushing/John Hay Whitney Library, for her assistance in developing and reviewing the rapid review search strategies.

Varun V. Bansal was supported by a grant from the Irving Harris Foundation. David G. Su was supported by the National Institutes of Health Immuno-Oncology Yale Cancer Center Advanced Training Program (Grant/Award T32 CA233414). David N. Hanna was supported by the National Institutes of Health Vanderbilt Surgical Oncology Training Grant (T32 CA106183). John Paul Shen was supported by the Cancer Prevention & Research Institute of Texas (CPRIT) as a CPRIT Scholar in Cancer Research (Grant/Award RR180035) and by a Conquer Cancer Career Development Award.

CONFLICT OF INTEREST STATEMENT

Al B. Benson, III reports grants/contracts provided directly to his institution from Amgen, Astellas Pharma, Bristol Myers Squibb, Celgene Corporation, Elevar Therapeutics, Inc., Infinity Pharmaceuticals, ITM Solucin GmbH, MedImmune, Merck Sharp & Dohme, Mirati Therapeutics, Rafael Pharmaceuticals Inc., ST Pharm Company Ltd., Syncore, Taiho Pharmaceutical, Tyme Inc., and Xencor, personal grants/contracts from ITM Samsung Bioepsis, Janssen, Pfizer, and the Nathan Cummings Foundation; and service on advisory and/or data safety and monitoring boards for Astellas Pharma, Apexigen, Array Biopharma Inc., Bristol Myers Squibb Company, PrecisCA, Array (Pfizer); Novartis, Amgen, Terumo, Mirati, GlaxoSmithKline, Bayer, Aveo, Gusto, Boehringer Ingelheim, AbbVie, Artemida, White Swan, Harborside Press, Patient Resources LLC, Axis Medical Education, Envision Communications, Trialcard Incorp, Tempus Labs Inc., Aptitude Health, Therabionic, Clarivate Analytics US LLC, Tukysa, Natera, Janssen, AIM Immunotech, Nuvation Bio, Xencor, Janssen, Natera, Xenor, Boston Scientific, Tukysa, and Cardiff Oncology outside the submitted work. Kiran K. Turaga reports personal/consulting fees from Merck & Company outside the submitted work. Namrata Setia reports personal/consulting or speaking fees from Astellas Pharma and Bristol Myers Squibb Company outside the submitted work. Rupen Shah reports personal/consulting fees from Intuitive Surgical Inc. outside the submitted work. Cathy Eng reports personal/consulting fees from AbbVie, Amgen Inc., General Electric, Gilead Sciences (aka Gilead Foundation), GlaxoSmithKline, Janssen Pharmaceuticals, Merck & Company, Taiho Pharmaceutical, and Takeda Oncology outside the submitted work. Oliver S. Eng reports personal/consulting or speaking fees from Dilon Technologies Inc. and Tempus Labs Inc. outside the submitted work. Ardaman Shergill reports institutional research-related funding directly to her institution from Hutchison MediPharma, Merck, Verastem Oncology, Turning Point Therapeutics, Gritstone, Bolt Therapeutics, Bristol Myers Squibb Company, Pfizer, Astellas Pharma, Oncologie, Macogenics, Seattle Genetics, Amgen, Daiichi, Eli Lilly & Company, Jacobio, and Takeda Oncology; personal/consulting or advisory fees from Guardant Health, Ipsen, Merus, Natera, Pfizer, and Takeda Oncology; and support for travel and accommodation from Takeda Oncology outside the submitted work. John Paul Shen reports grants/contracts from Celsius Therapeutics and BostonGene; personal/consulting fees from Nadeno Nanoscience and Engine Bioscience; and holds a patent (issued) for small molecule GNAS inhibitors outside the submitted work. Michael B. Foote reports personal/consulting fees from Abbott Pharmaceuticals, Bristol Myers Squibb Company, and Genzyme outside the submitted work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: Godfrey E. L., Mahoney F, Bansal VV, et al. Consensus guideline for the management of patients with appendiceal tumors, part 2: appendiceal tumors with peritoneal involvement. *Cancer*. 2025;e35874. doi:10.1002/cncr.35874