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CONSENSUS STATEMENT

# Consensus guideline for the management of colorectal cancer with peritoneal metastases

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## Abstract

The peritoneum is a common site of metastases from colorectal cancer (CRC), yet controversy exists regarding optimal treatment strategies. These guidelines describe the results of a national consensus addressing the management of CRC with peritoneal metastases (CRC-PM). An update of the 2018 Chicago consensus guidelines was conducted with a modified Delphi technique. Two rounds of voting were performed to assess agreement levels on two clinical management pathways regarding synchronous and metachronous CRC-PM. Supporting evidence was evaluated via rapid literature reviews. The overall level of evidence was low in the existing literature. Of 145 participants in the first round, 136 (96.8%) responded in the second round. Over 90% consensus was achieved in most pathway blocks. For both pathways, early referral to a peritoneal surface malignancy center should be made for patients with CRC-PM. For the synchronous pathway, upfront cytoreductive surgery was deemphasized in favor of systemic therapy. For the metachronous pathway, risk stratification via clinical and pathological features was revised. For both pathways, surveillance strategies were added, including only a weak recommendation for circulating tumor DNA testing, given limited evidence of its utility in detecting and monitoring PM. The consensus-driven clinical pathways provide valuable guidance for the management of CRC-PM. There remains a need for high-quality evidence and prospective multicenter trials in this domain.

**KEYWORDS**
circulating tumor DNA (ctDNA), colon cancer, colorectal cancer, cytoreductive surgery, guidelines, intraperitoneal chemotherapy, peritoneal surface malignancies, peritoneal surface neoplasms, rectal cancer

## INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent malignancy globally and the second leading cause of cancer-related mortality, with 1.8 million new cases diagnosed annually worldwide.[1,2] Notably, there is a concerning trend in the rise of early-onset CRC, which often presents with advanced disease in younger patients.[3,4] Peritoneal metastases (PM) develop in approximately 5%–15% of patients with CRC within their disease course. Approximately half of these cases present synchronously with an intact primary tumor, and the other half present metachronously in the setting of relapse.[1,5,6] However, the incidence of PM might be underestimated because not all high-risk patients undergo diagnostic laparoscopy; this is evidenced by the frequency of PM noted at autopsy.[7,8] CRC with PM (CRC-PM) has a worse prognosis compared to other metastatic sites, and is associated with malnutrition, bowel obstruction, and other complications.[9] As highlighted in a systematic review of clinical trials regarding systemic therapies for metastatic CRC, patients with PM face a poor prognosis, with a median overall survival of approximately 16 months.[10]

Multiple studies have shown promise with cytoreductive surgery (CRS) for CRC-PM, with a median overall survival exceeding 40 months for patients receiving CRS and systemic chemotherapy in the PRODIGE 7 trial.[11] Some studies have also shown benefit with intraperitoneal chemotherapy (IPCT) and systemic chemotherapy compared to systemic chemotherapy alone.[12–16] Yet several controversies exist regarding management strategies, including the utility of IPCT in therapeutic and prophylactic treatment strategies, optimal sequences and regimens of systemic therapies, and surveillance modalities. The exclusion of patients with PM from large clinical trials, likely because of challenges with the use of the Response Evaluation Criteria in Solid Tumors to assess disease response, precludes a better understanding of these questions.[7]

Given the scarcity of evidence guiding treatment decisions, limited standardized pathways exist for managing CRC-PM. This article builds upon the 2018 Chicago consensus guidelines on the management of colorectal metastases, and reports a multidisciplinary consensus aimed at outlining the clinical management of synchronous and metachronous CRC-PM.[17,18]

## METHODS

This initiative was part of a national multidisciplinary consortium group process aimed at streamlining guidelines for the care of patients with peritoneal surface malignancies (PSMs). The consensus and rapid review methodology have been described in detail in Supporting Information S1.[19] Major components are summarized below.

## Consensus group structure

In brief, the Colorectal Disease Working Group (CDWG) consisted of 10 experts (M.M.W., A.U., K.P.S.R., D.M.L., U.S., A.P.S., J.P.S., C.E., M.B. F., and J.M.B.). A team of 12 trainees, including eight surgical residents (K.S.S., F.A.G., J.W., J.T.B., E.P., S.C., L.E.S., and D.G.S.), two surgical oncology fellows (M.M.W. and N.B.), and two research fellows (V.V.B. and M.M.W.) conducted the rapid reviews. Two core group trainee members coordinated the effort (K.S.S. and F.A.G.).

## Modified Delphi process

A modified Delphi method with two rounds of voting was used to gather feedback regarding the clinical management pathways after preliminary synthesis of the major updates since 2018. Experts rated their agreement levels on a five-point Likert scale via a Qualtrics questionnaire. A 75% consensus threshold was set, and blocks with below 90% agreement underwent further review. Simultaneously, two summary tables outlining first-line systemic and regional therapies for CRC-PM were generated by the CDWG, with directed guidance from the medical oncologist in the working group. These tables were then included in the modified Delphi round 2 survey for general feedback from the entire PSM Consortium.

## Rapid review of the literature

The two key questions (KQs) were selected by the CDWG. A MEDLINE search via PubMed between January 2000 and August 2023 was performed for these two KQs.

KQ 1. In patients with CRC-PM undergoing CRS, what are the optimal sequences and regimens of systemic therapy (neoadjuvant, adjuvant, and perioperative)?

KQ 2. In patients with CRC-PM, does plasma-based liquid biopsy offer better sensitivity, specificity, and lead-time therapy compared with standard surveillance modalities in

a. detecting recurrence after CRS?
b. evaluating response to systemic therapies?

Search strategies were developed and reviewed by a medical librarian specialist (Tables S3–S5), and the review protocols were preregistered in PROSPERO (CRD42023471072 and CRD420234778690). The Covidence platform facilitated title and abstract screening, full-text review, and data extraction. Quality assessment was performed with the Newcastle Ottawa Scale for KQ 1 and the Quality Assessment of Diagnostic Accuracy Studies, version 2 tool for KQ 2a and KQ 2b.[20–24] Articles were screened by two reviewers, and conflicts were resolved by the trainee leads in the CDWG. The review was conducted in alignment with recommendations from the Cochrane Rapid Review Methods Groups, and reported in line with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines.[25,26]

## External/patient perspectives

Members of the Peritoneal Surface Oncology Group International (PSOGI; http://www.psogi.com/) Executive Council were invited to appraise the second version of the two pathways. Their comments were consolidated to evaluate alignment with global practices regarding the management of CRC-PM. Additionally, patients and caregivers from the COLONTOWN support group (https://colontown.org/) reviewed the treatment pathways, and offered insights regarding clinical trial enrollment, research outcomes, and available resources for patients with CRC-PM.

# RESULTS

Four pathways were initially proposed: (1) synchronous PM, (2) metachronous PM, (3) prophylactic IPCT for locally advanced CRC, and (4) recurrent CRC-PM post-CRS. However, because of insufficient data, guidelines for prophylactic IPCT and recurrent CRC-PM were not established. Hence, the focus of the current consensus and reviews is on synchronous and metachronous CRC-PM.

## Pathways and rapid reviews

In all, 145 experts voted in the first Delphi round, of which 136 (93.8%) responded in the second round. Of survey respondents, 101 (69.7%) were surgical oncologists, 25 (17.2%) were medical oncologists, 12 (8.3%) were pathologists, and seven (4.8%) belonged to other specialties. Given the low quality of the existing evidence in the literature, recommendations were based primarily on expert opinion. The synchronous and metachronous CRC-PM pathways were divided into 11 blocks (Figure 1) and 10 blocks (Figure 2), respectively.

The rapid reviews cumulatively revealed 2888 abstracts, of which 368 full texts were reviewed. Thirty-four studies were ultimately included for data extraction and quality assessment, and are cited in relevant sections of the article (PRISMA flow diagrams; Figures S1–S3).

## Summary of major changes

By building upon the 2018 Chicago consensus guidelines, the current approach involves a more stringent consensus and review methodology while engaging a larger spectrum of experts and patient advocates.[17,18] For both pathways, early referral to a PSM center was stressed. For the synchronous pathway, upfront CRS ± IPCT should only be considered in highly select patients, with systemic therapy being the preferred initial treatment. For the metachronous pathway, risk stratification via clinical and pathological features was revised by considering right-sided tumors and signet ring cell histology as high-risk features and removing younger age as a low-risk feature. For both pathways, repeat CRS ± IPCT can be considered in appropriately selected patients if recurrence is detected after initial CRS ± IPCT. For both pathways, surveillance recommendations were added, which

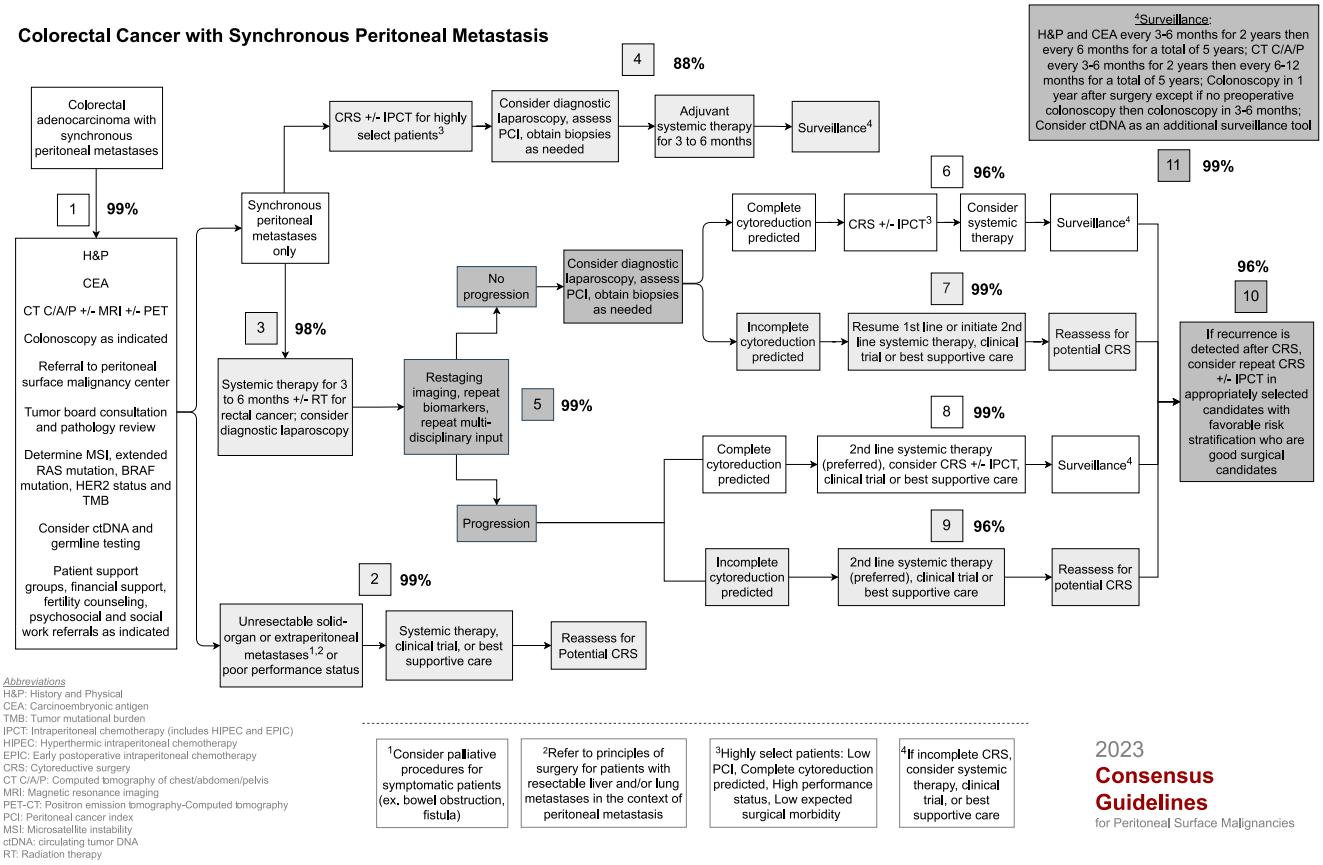


**FIGURE 1** Clinical pathway for the management of colorectal cancer with synchronous peritoneal metastases.

included only a weak recommendation for circulating tumor DNA (ctDNA) testing, given limited evidence of its accuracy for monitoring PM.

## CRC with synchronous PM pathway (Figure 1; Table 1)

### Block 1: Initial management and preoperative considerations

*Agreement: Round 1, 98%; round 2, 99%*

A cornerstone of initial management of CRC-PM is early referral to a PSM center. Centralization at high-volume centers is crucial because of the steep institutional learning curve associated with CRS ± IPCT,[27] and is associated with reduced postoperative morbidity and improved oncologic outcomes.[28]

Initial evaluation includes a thorough history and physical examination, diagnostic workup, and multidisciplinary tumor board discussion with expert radiology and pathology review. Recommended imaging includes computed tomography (CT) chest/abdomen/pelvis for all patients, pelvic magnetic resonance imaging (MRI) for rectal cancers, and positron emission tomography/computed tomography (PET-CT) as indicated. Notably, PET-CT and diffusion-weighted MRI may better characterize peritoneal lesions than standard CT, although signet ring cell carcinoma cannot be appreciated on PET-CT.[29] Colonoscopy should also be performed in all patients. Patients should be referred to patient support groups, financial support, fertility counseling, psychosocial support, and social workers as indicated.[30,31]

Standard molecular analysis should be conducted, which includes assessing for microsatellite instability, *RAS* mutations (*KRAS*, *NRAS*, and *HRAS*), *BRAF* mutations, *ERBB2* (formerly *HER2*) status, and tumor mutational burden by next-generation sequencing (NGS).[32,33] NGS also has the potential to identify sequence variations, such as *ERBB2* amplifications or *NTRK* gene fusions.[34]

Germline testing should be considered as indicated.[35] The prognostic significance of ctDNA is an active area of research but currently its role in preoperative risk stratification is less established than in postoperative surveillance.[36,37]

### Block 2: Nonoperative management

*Agreement: Round 1, 95%; round 2, 99%*

Nonoperative management is recommended for patients with poor performance status (PS) and patients with extensive solid organ or extraperitoneal metastases. For patients with poor PS, the risk of major surgery may outweigh potential benefits. It is important to discuss with patients and caregivers that CRS ± IPCT is a major abdominal surgery with serious postoperative morbidity rates ranging from 15% to 33% in patients with CRC-PM.[38] The management of malignant gastrointestinal obstruction, often indicating advanced and unresectable disease, is described in a separate

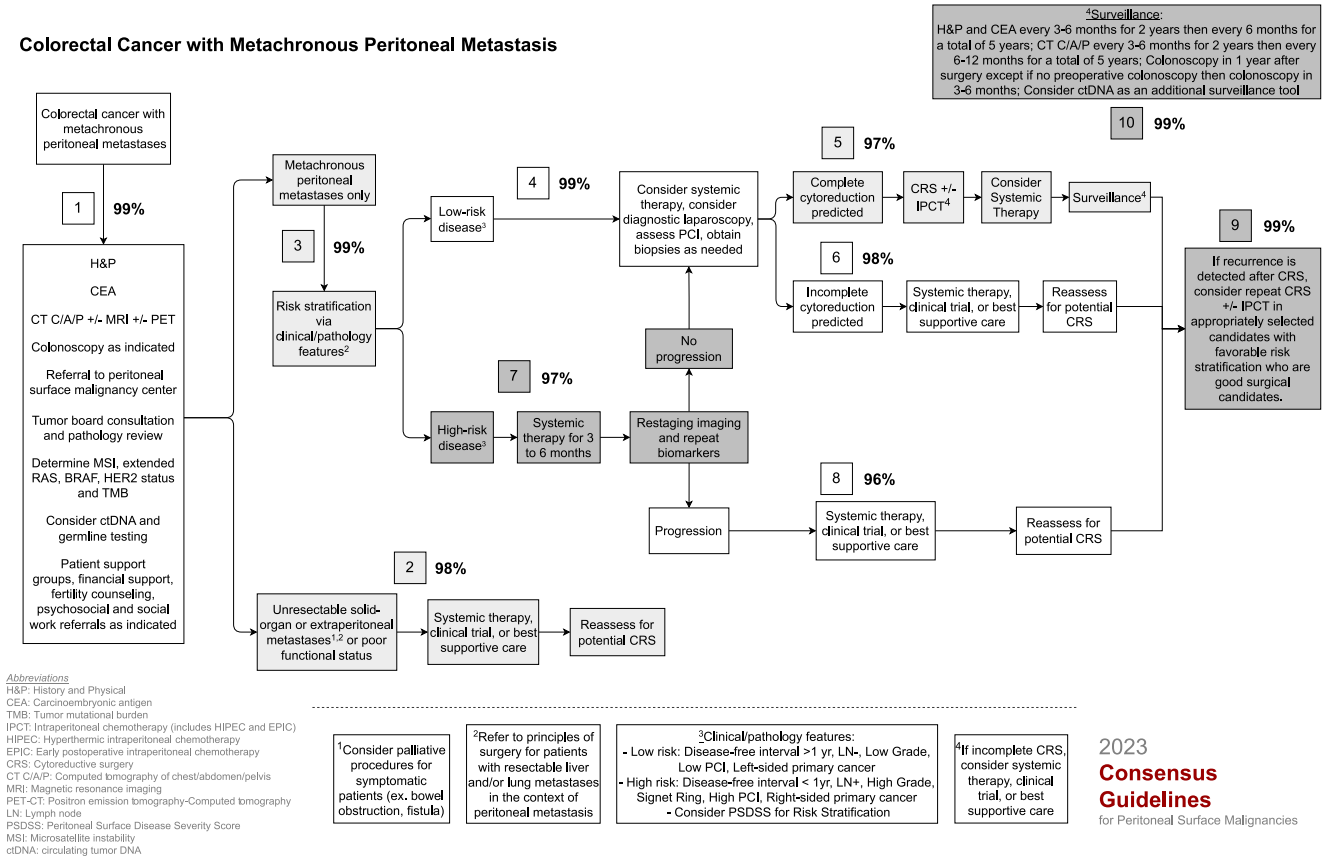


**FIGURE 2** Clinical pathway for the management of colorectal cancer with metachronous peritoneal metastases.

guideline by this consortium group.[39] Emerging evidence suggests that CRS ± IPCT may benefit patients with limited extraperitoneal disease but it requires careful consideration.[40] A recent systematic review of 20 studies revealed a mean overall survival of 26.4 months and a 5-year overall survival rate of 25% in patients receiving combined peritoneal and local treatment for PM and limited liver metastases.[41] Our consensus recommends avoidance of major hepatectomy with CRS. Combined CRS with minor hepatectomy could be considered in select patients with limited liver metastases amenable to a completeness of cytoreduction (CC) 0 resection and a peritoneal carcinomatosis index (PCI) of <19 amenable to a CC score of 0–1.[40] Although no strict cutoff for "limited" liver disease exists, CRS is discouraged in patients with more than four metastatic liver foci. Some experts suggest adding three PCI points for every liver metastasis on the basis of anecdotal experience.

Krukenberg tumors are metastatic tumors of the ovarian lining originating mostly from gastrointestinal adenocarcinomas.[42] Although historically deemed a terminal finding in CRC-PM, they do not necessarily preclude CRS. A retrospective study found that 52% of patients with CRC-PM undergoing CRS ± IPCT at a single institution had Krukenberg tumors, with no difference in disease-free survival compared to those without ovarian metastases.[43] Our group agreed that the presence of Krukenberg tumors, or their progression or nonresponse to systemic therapy, is not an absolute contraindication to CRS ± IPCT.

## Block 3: Preoperative systemic therapy

*Agreement: Round 1, 94%; round 2, 98%*

In the initial management of synchronous CRC-PM, systemic therapy is administered for 3–6 months to potentially downstage tumor burden and target systemic micrometastases. Additionally, radiation therapy can be considered for rectal cancers after multidisciplinary tumor board discussion. Details regarding systemic therapy regimens are summarized in Table 2.

There remains limited evidence regarding optimal systemic therapy in patients with resectable CRC-PM. Of 72 clinical trials for metastatic CRC from 2003 to 2016, only seven trials reported inclusion of patients with PM.[7] Our systematic review (Table 3; Table S1) synthesized findings from 13 observational studies, which reported receipt of systemic therapy for patients undergoing CRS for CRC-PM, with no published randomized controlled trials (RCTs) to date.[44–56] The timing, duration, and agents used for neoadjuvant chemotherapy varied across studies. Three studies (with <200 patients each) suggested a survival advantage of neoadjuvant therapy followed by CRS compared to upfront CRS.[46,47,54] Studies from the PSOGI Global Registry, with a sample size of more than 2000 patients, and the US HIPEC (hyperthermic intraperitoneal chemotherapy) Collaborative as well as several single-institution studies failed to demonstrate a benefit of neoadjuvant therapy.[44,45,48–53,55,56] Proponents of neoadjuvant therapy argue for its potential to reduce

**TABLE 1** Modified Delphi agreement table: Rounds 1 and 2 for colorectal cancer with synchronous and metachronous peritoneal metastases.

| Block | Strongly agree, No. | Agree, No. | Neither agree nor disagree, No. | Disagree, No. | Strongly disagree, No. | Total, No. | Agreement, % |
|---|---|---|---|---|---|---|---|
| Round 1 agreement for colorectal cancer with synchronous peritoneal metastases | | | | | | | |
| 1 | 106 | 36 | 2 | 0 | 1 | 145 | 98 |
| 2 | 111 | 27 | 5 | 2 | 0 | 145 | 95 |
| 3 | 94 | 43 | 6 | 2 | 0 | 145 | 94 |
| 4 | 67 | 45 | 20 | 13 | 0 | 145 | 77 |
| 5 | 95 | 42 | 6 | 2 | 0 | 145 | 94 |
| 6 | 90 | 44 | 8 | 3 | 0 | 145 | 92 |
| 7 | 86 | 49 | 9 | 1 | 0 | 145 | 93 |
| 8 | 69 | 50 | 17 | 9 | 0 | 145 | 82 |
| 9 | 90 | 45 | 5 | 5 | 0 | 145 | 93 |
| 10 | 76 | 49 | 15 | 5 | 0 | 145 | 86 |
| 11 | 77 | 50 | 12 | 5 | 1 | 145 | 88 |
| Round 2 agreement for colorectal cancer with synchronous peritoneal metastases | | | | | | | |
| 1 | 123 | 12 | 0 | 1 | 0 | 136 | 99 |
| 2 | 120 | 14 | 1 | 1 | 0 | 136 | 99 |
| 3 | 117 | 16 | 3 | 0 | 0 | 136 | 98 |
| 4 | 95 | 25 | 7 | 5 | 4 | 136 | 88 |
| 5 | 123 | 11 | 1 | 0 | 1 | 136 | 99 |
| 6 | 116 | 14 | 4 | 1 | 1 | 136 | 96 |
| 7 | 122 | 12 | 1 | 1 | 0 | 136 | 99 |
| 8 | 110 | 16 | 5 | 4 | 1 | 136 | 93 |
| 9 | 117 | 14 | 3 | 1 | 1 | 136 | 96 |
| 10 | 118 | 12 | 4 | 1 | 1 | 136 | 96 |
| 11 | 119 | 15 | 1 | 0 | 1 | 136 | 99 |
| Round 1 agreement for colorectal cancer with metachronous peritoneal metastases[a] | | | | | | | |
| 1 | 102 | 39 | 3 | 0 | 1 | 145 | 97 |
| 2 | 103 | 36 | 4 | 2 | 0 | 145 | 96 |
| 3 | 93 | 43 | 7 | 2 | 0 | 145 | 94 |
| 4 | 84 | 44 | 15 | 1 | 1 | 145 | 88 |
| 5 | 93 | 41 | 6 | 5 | 0 | 145 | 92 |
| 6 | 95 | 42 | 8 | 0 | 0 | 145 | 94 |
| 7 | 98 | 35 | 10 | 2 | 0 | 145 | 92 |
| 8 | 84 | 46 | 11 | 3 | 1 | 145 | 90 |
| 9 | 80 | 45 | 14 | 5 | 1 | 145 | 86 |
| Round 2 agreement for colorectal cancer with metachronous peritoneal metastases[a] | | | | | | | |
| 1 | 123 | 12 | 0 | 1 | 0 | 136 | 99 |
| 2 | 120 | 13 | 2 | 1 | 0 | 136 | 98 |
| 3 | 124 | 10 | 1 | 1 | 0 | 136 | 99 |
| 4 | 118 | 17 | 1 | 0 | 0 | 136 | 99 |
| 5 | 117 | 15 | 3 | 1 | 0 | 136 | 97 |

**TABLE 1** (Continued)

| Block | Strongly agree, No. | Agree, No. | Neither agree nor disagree, No. | Disagree, No. | Strongly disagree, No. | Total, No. | Agreement, % |
|---|---|---|---|---|---|---|---|
| 6 | 124 | 9 | 3 | 0 | 0 | 136 | 98 |
| 7 | 119 | 13 | 4 | 0 | 0 | 136 | 97 |
| 8 | 117 | 13 | 3 | 2 | 1 | 136 | 96 |
| 9 | 119 | 15 | 1 | 0 | 1 | 136 | 99 |

*Note*: Percent agreement includes agree and strongly agree.

[a]Block 10 was not subjected to consensus voting in the metachronous pathway because it was identical to the synchronous pathway.

PCI and increase complete cytoreduction rates, although this was not uniformly demonstrated across studies.[54]

Two studies sought to identify high-risk subgroups that may definitively benefit from preoperative or perioperative therapy, including lymph node–positive CRC-PM. Kuijpers et al. observed longer overall survival in 55 patients who received any perioperative chemotherapy compared to 16 patients without chemotherapy in conjunction with CRS-HIPEC (median, 30 vs. 14 months; $p = .015$).[49] However, this difference was attenuated after adjusting for major postoperative complications, which were higher in the group that did not receive any perioperative chemotherapy. Among patients who received any systemic chemotherapy, there was no survival difference according to the sequence of administration (neoadjuvant only, adjuvant only, or perioperative). Sugarbaker and Chang found no overall survival difference between 38 patients with neoadjuvant chemotherapy and 35 without (median, 2.3 vs. 2.9 years; $p = .94$).[52] Yet a notable benefit was seen in the subset of 11 patients with a complete or near-complete response to neoadjuvant chemotherapy.

By addressing these gaps, the CAIRO6 study is the first RCT evaluating perioperative systemic therapy and CRS-HIPEC versus CRS-HIPEC alone for resectable CRC-PM. The trial's phase 2 segment deemed perioperative systemic therapy safe and feasible, with a 38% major pathological response rate among patients receiving neoadjuvant therapy.[38] Results from the phase 3 randomized component of the trial are pending.[57]

Given the current lack of standardization in the selection of systemic regimens, our consortium group constructed a summary table delineating initial and subsequent systemic therapy regimens for CRC-PM (Table 2). In line with National Comprehensive Cancer Network (NCCN) recommendations, first-line treatment generally includes fluoropyrimidines, such as fluorouracil (5-FU) or capecitabine. Fluorouracil is combined with leucovorin (5-FU/LV) to potentiate its cytotoxic inhibitory effects. Oxaliplatin (FOLFOX or CAPOX), irinotecan (FOLFIRI or CAPIRI), or their combinations (FOLFOXIRI or CAPOXIRI) may augment this backbone regimen.

Anti–vascular endothelial growth factor antibodies, such as bevacizumab, may be added to first-line treatment. Anti–epidermal growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) are recommended to be added for pan-*RAS* wild-type (*KRAS* and *NRAS*) and *BRAF* wild-type metastatic CRC.[58] Transcriptional profiling has shown the potential to predict response to anti-EGFR antibodies, and might be superior to the historical right- and left-sided classification.[59,60] For robust patients, FOLFOXIRI and bevacizumab may be considered to maximize tumor response.[61] FOLFOXIRI and anti-EGFR therapy combinations have been shown to not improve overall survival on the basis of the TRIPLETE study.[62] Further line therapies, such as trifluridine-tipiracil plus bevacizumab, may be used in refractory metastatic CRC.[63] Immunotherapy is recommended as a first-line single-agent therapy for microsatellite instability–high or mismatch repair–deficient tumors.[64]

Diagnostic laparoscopy is commonly used for assessing PCI and estimating the ability to achieve a complete cytoreduction. It may be offered at diagnosis and/or after completion of induction chemotherapy to determine candidacy for CRS ± IPCT, and is generally reserved for patients with CRC-PM with a PCI of ≤19–25 amenable to complete or near-complete cytoreduction (CC 0–1 CRS).[11,40]

## Block 4: Upfront CRS ± IPCT

*Agreement: Round 1, 77%; round 2, 88%*

Consideration for upfront CRS ± IPCT is reserved for highly select patients with a high-performance status, low to moderate PCI, low expected surgical morbidity, and complete cytoreduction predicted. There is no universally accepted definition of low or moderate PCI, and tends to be surgeon and institution dependent. Extensive mesenteric deposits, small bowel deposits, or porta hepatis involvement might preclude complete cytoreduction. Patients with poorly differentiated histology, such as signet ring cell histology, should be treated with systemic therapy before CRS consideration.

This block had only 76% agreement in the first round, which improved to 87% in the second round after deemphasizing the treatment pathway and outlining selection criteria. After CRS, patients should receive adjuvant systemic therapy for 3–6 months followed by active surveillance. This recommendation is supported by observational data regarding upfront resection of isolated synchronous CRC-PM in 393 patients from the Netherlands Cancer Registry.[55] In a propensity score–matched analysis, adjuvant systemic chemotherapy was associated with improved overall survival compared to active surveillance (median, 39.2 vs. 24.8 months; $p = .006$).[55]

Postulated advantages of upfront surgery include avoiding systemic therapy–adverse events and reduced postoperative morbidity. In a multi-institutional French series, preoperative bevacizumab administration was associated with twice the rate of early complications after CRS ± IPCT for CRC-PM.[65] Additionally, patients may experience disease progression while on systemic therapy, which

**TABLE 2** Systemic therapy regimens for metastatic colorectal malignancy with peritoneal involvement.

| Type of CRC | Stage of therapy | Initial therapy | Subsequent therapy |
|---|---|---|---|
| Initially unresectable pMMR/MSS mCRC, left sided, RAS wild type | Definitive/ conversion chemotherapy | FOLFOX or FOLFIRI doublet chemotherapy ± anti-EGFR or anti-VEGF preferred [a]FOLFOXIRI triplet chemotherapy (up to 12 cycles) ± anti-VEGF may be considered followed by maintenance 5-FU/leucovorin/bevacizumab | Regimens as described at left were not previously attempted |
| Other initially unresectable pMMR/MSS mCRC | Definitive/ conversion chemotherapy | FOLFOX or FOLFIRI doublet chemotherapy ± anti-VEGF preferred [a]FOLFOXIRI triplet chemotherapy (up to 12 cycles) ± anti-VEGF may be considered followed by maintenance 5-FU/leucovorin/bevacizumab | Regimens as described at left were not previously attempted |
| Complete cytoreduction predicted pMMR/ MSS mCRC, left sided, RAS wild type | Neoadjuvant chemotherapy | FOLFOX or FOLFIRI doublet chemotherapy ± anti-EGFR or anti-VEGF preferred [a]FOLFOXIRI triplet chemotherapy (up to 12 cycles) ± anti-VEGF may be considered followed by maintenance 5-FU/leucovorin/bevacizumab | Regimens as described at left were not previously attempted |
| Complete cytoreduction predicted pMMR/ MSS mCRC | Neoadjuvant chemotherapy | FOLFOX or FOLFIRI doublet chemotherapy ± anti-VEGF preferred [a]FOLFOXIRI triplet chemotherapy (up to 12 cycles) ± anti-VEGF may be considered followed by maintenance 5-FU/leucovorin/bevacizumab | Regimens as described at left were not previously attempted |
| dMMR/MSI-H mCRC | Neoadjuvant/ adjuvant chemotherapy | Anti-PD1 ± anti–CTLA-4 or systemic chemotherapy as recommended above | Anti-PD1 ± anti–CTLA-4 if no IO given as first line |
| BRAF V600E mCRC | Neoadjuvant/ adjuvant chemotherapy | Systemic chemotherapy as recommended above | Anti-BRAF + anti-EGFR |
| HER2 | Neoadjuvant/ adjuvant chemotherapy | Systemic chemotherapy as recommended above | Anti-HER2 therapy |

Abbreviations: CRC, colorectal cancer; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; IO, immunotherapy; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability–high; MSS, microsatellite stable; pMMR, proficient mismatch repair; VEGF, vascular endothelial growth factor.

[a]Adverse events are more common with triplet chemotherapy.

renders them unresectable.[10] In the phase 2 component of the CAIRO6 trial, half of the patients declined trial participation because of concerns about systemic therapy's toxic effects and cancer becoming unresectable during neoadjuvant therapy. Despite this, all patients in the neoadjuvant arm proceeded to surgery, with comparable patient-reported outcomes between the study arms (perioperative systemic therapy with CRS-HIPEC and CRS-HIPEC alone).[38,66] Results of the phase 3 trial of CAIRO6 are pending, and may help address uncertainties surrounding upfront CRS.

## Block 5: Progression status after systemic therapy

*Agreement: Round 1, 94%; round 2, 99%*

After completion of systemic therapy, patients should be reevaluated to determine the response to systemic therapy via cross-sectional imaging and serum tumor markers. Measuring carcinoembryonic antigen (CEA) can aid in surgical decision-making, with elevated preoperative CEA levels (>5 mg/mL) suggesting disease progression.[67] ctDNA might be a marker of recurrence in patients with CRC-PM[68] but its utility in preoperative decision-making remains unproven. Diagnostic laparoscopy can be considered to reevaluate PCI. For patients with no evidence of progression of their metastatic CRC, candidacy for near-complete CRS should be determined.

## Block 6: No progression after systemic therapy with complete cytoreduction predicted

*Agreement: Round 1, 92%; round 2, 96%*

Patients with no progression after systemic therapy and with a complete cytoreduction predicted should proceed with CRS ± IPCT.

**TABLE 3** Key question 1: In patients with CRC-PM undergoing CRS, what are the optimal sequences and regimens of systemic therapy (neoadjuvant, adjuvant, or perioperative)?

| Study | Population | Systemic therapy regimens | Systemic therapy sequence; duration | Comparison | Sample size, No. | PCI, median; CC, % or R, % | Follow-up duration | OS; HR (95% CI) | Major adverse events, %[a] |
|---|---|---|---|---|---|---|---|---|---|
| Beal 2020[44] (USA) | Patients with CRC-PM undergoing CRS-HIPEC | FOLFOX, FOLFIRI, Bev, capecitabine, XELOX, 5-FU + leucovorin | NAC and/or AC; duration not specified | NAC versus no NAC (upfront CRS) | 298 | 12.1; CC0: 74.0; CC1: 15.8 | NR | NAC, 32.7 months versus no NAC, 22.0 months; adjusted, 0.8 (0.5–1.2) | 35.9 |
| Cashin 2023[45] (international) | Patients with CRC-PM undergoing CRS-HIPEC | FOLFOX, FOLFIRI, Bev, capecitabine, XELOX, 5-FU + leucovorin | NAC and/or AC; duration not specified | NAC versus no NAC (upfront CRS), AC versus no AC Propensity score matching used | 2093 | 10.1; CC0: 93; CC1: 5 | 10 years | NAC, 34.7 months versus no NAC, 37.0 months; 1.08 (0.88–1.32); AC, 45.7 months versus no AC, 37.0 months; 0.79 (0.64–0.97) | 33 |
| Ceelen 2014[46] (Belgium) | Patients with CRC-PM undergoing CRS-HIPEC | FOLFOX, FOLFIRI, Bev | NAC and/or AC; NAC, ≥3 months | NAC with Bev versus NAC without Bev versus no NAC | 166 | 4[b]; CC0: 47.6; CC1: 39.8 | 18 months | NAC with Bev, 39 months versus NAC without Bev, 22 months versus no NAC, 25 months; adjusted, NAC with Bev, 0.31 (0.12–0.83) | 35 |
| Devilee 2016[47] (The Netherlands) | Patients with CRC-PM undergoing CRS-HIPEC | Capecitabine, CAPOX, CAPOX + Bev, FOLFOX | NAC or AC; duration not specified | NAC versus AC | 91 | 6; CC0: 96; CC1: 4 | 28 months | NAC, not reached versus AC, 38.6 months; adjusted, 0.23 (0.07–0.75) | 18.7 |
| Hanna 2023[48] (USA) | Patients with CRC-PM undergoing CRS-HIPEC | FOLFOX ± Bev, FOLFIRI ± Bev, CAPOX | NAC, 6 months or NAC + AC (sandwich), 6 months | NAC versus sandwich | 79 | 11.4; CC0: 85.3; CC1: 8.8 | NR | NAC, 77 months versus sandwich, 61 months; adjusted, 0.96 (0.45–1.32) | NR |
| Kuijpers 2014[49] (The Netherlands) | Patients with lymph node–positive CRC-PM undergoing CRS-HIPEC | FOLFOX, FOLFIRI, Bev, capecitabine, XELOX, 5-FU + leucovorin | NAC and/or AC; duration not specified | Any periop chemo versus no chemo | 73 | 5[b]; ^R1: 87; R2a: 13 | 47 months | Any chemo, 30 months versus no chemo, 14 months[c]; no significant differences based on chemo sequence (NAC/AC) | 30.1 |
| Maillet 2016[50] (France) | Patients with isolated CRC-PM undergoing CRS-HIPEC | FOLFOX, FOLFIRI, Bev, cetuximab | NAC and/or AC; duration not specified | AC versus no AC | 221 | NR; CC0: 100 | 34 months | AC, 49 months versus no AC, 43 months; adjusted, 1.13 (0.7–1.84) | 44.8 |
| Noda 2023[51] (Japan) | Patients with CRC-PM undergoing CRS-HIPEC | 5-FU–based ± oxaliplatin ± irinotecan | NAC and/or AC; duration not specified | AC versus no AC | 123 | NR; R0: 26; R1: 13.8; R2: 59.3 | NR | 5-year OS rate, R0/R1 subgroup, AC, 48.2 versus no AC, 38.1; adjusted, 0.366 (0.137–0.997) | 21.1 |
| Repullo 2021[56] (Belgium) | Patients with CRC-PM with PCI <25 undergoing CRS-HIPEC | FOLFOX or FOLFIRI ± cetuximab or Bev | Periop within 3 months pre/post–CRS; ≥5 cycles | Periop chemo versus no chemo | 125 | 6; R0/R1: 100 | 54 months | Chemo, 43 months versus no chemo, 72 months; adjusted, 1.46 (0.87–2.47) | 21.6 |

(Continues)

**TABLE 3** (Continued)

| Study | Population | Systemic therapy regimens | Systemic therapy sequence; duration | Comparison | Sample size, No. | PCI, median; CC, % or R, % | Follow-up duration | OS; HR (95% CI) | Major adverse events, %[a] |
|---|---|---|---|---|---|---|---|---|---|
| Sugarbaker & Chang 2022[52] (USA) | Patients with lymph node–positive CRC with isolated PM undergoing CRS-HIPEC/EPIC | Not specified | NAC and/or AC; duration not specified | NAC versus no NAC (upfront CRS) | 73 | 13; CC0/CC1: 100 | NR | NAC, 2.3 years versus no NAC, 2.9 years; 1.00 (0.62–1.68) | 33.4 |
| van Eden 2017[53] (The Netherlands) | Patients with CRC-PM undergoing CRS-HIPEC | CAPOX or FOLFOX or not specified | NAC within 4 months/periop; AC within 3 months | NAC/periop versus AC versus chemo only before PC diagnosis (earlier chemo) | 280 | Range, 0–7[b]; R0/R1: 91; R2a: 8.1 | 29.8 months | NAC/periop, 36.9 months versus AC, 43.1 months versus earlier chemo, 34.0 months; adjusted, NAC/periop versus AC, 0.84 (0.53–1.35) | 30.0 |
| Zhou 2021[54] (China) | Patients with CRC-PM undergoing CRS-HIPEC | XELOX or FOLFOX or FOLFIRI ± Bev, 5-FU + leucovorin | NAC, >3 cycles and/or AC; duration not specified | NAC versus no NAC (upfront surgery) | 52 | 11.9; CC0/CC1: 59.6; CC2/CC3: 40.4 | 18.5 months | 2-year OS rate, NAC, 67.4 versus no NAC, 32.2; adjusted, 0.55 (0.22–1.39) | 34.6 |
| Rovers 2020[55] (The Netherlands) | Patients with isolated CRC-PM undergoing CRS-HIPEC | CAPOX or FOLFOX or 5-FU or capecitabine or not specified | No NAC (upfront CRS) ± AC; AC within 3 months | AC versus no AC (active surveillance) Propensity score matching used | 393 | NR; CC0/CC1: 100 | 25.9 months | AC, 39.2 months versus no AC, 24.8 months; 0.66 (0.49–0.88) | |

Abbreviations: AC, adjuvant chemotherapy; Bev, bevacizumab; CC, completeness of cytoreduction; cfDNA, cell-free DNA; chemo, chemotherapy; CI, confidence interval; CRC-PM, colorectal cancer with peritoneal metastases; CRLM, colorectal liver metastases; CRS, cytoreductive surgery; ctDNA, circulating tumor DNA; 5-FU, 5-fluorouracil; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; NAC, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; PCI, peritoneal cancer index; periop, perioperative; R, residual tumor classification; sandwich, neoadjuvant and adjuvant chemotherapy.

[a]Major adverse events are defined variably across studies between Clavien–Dindo and Common Terminology Criteria for Adverse Events 2–5.

[b]Uses a regional score and not PCI; ^R1, no residual macroscopic tumor; R2a, macroscopic residual tumor of <2.5 mm.

[c]Differences were attenuated when accounting for major postoperative complications (associated with a reduced likelihood of receiving AC).

Although the PRODIGE 7 trial did not demonstrate a survival benefit with oxaliplatin IPCT added to CRS, trial participants in both arms experienced a median overall survival of >44 months, which is higher than historical reports with systemic therapy alone.[10] Notably, more than 95% of patients in this trial received systemic therapy with CRS, with 219 of 265 patients (83%) receiving preoperative chemotherapy.[11] After CRS ± IPCT, additional systemic therapy should be considered, with the goal of completing at least a total of 6 months of systemic therapy. Patients should then be followed with an active surveillance program.

The cornerstone of curative-intent treatment for CRC-PM remains CRS, with the objective of resecting all visible tumor implants within the peritoneal cavity.[69] Diagnostic laparoscopy is essential for evaluating the PCI and determining the patient's candidacy for complete or near-complete cytoreduction (CC, 0–1). Contributing factors that reduce the likelihood of complete CRS, such as extensive mesenteric deposits, small bowel deposits, or porta hepatis involvement, must be considered. Minimally invasive approaches for cytoreduction may be used in select patients with low PCI.[70,71]

The role of IPCT in treating CRC-PM remains contentious, as highlighted in the 2018 Chicago consensus guidelines. Seminal evidence from the PRODIGE 7 trial, which compares CRS with oxaliplatin HIPEC for 30 min and CRS alone, failed to show a significant difference in overall survival (median, 41.7 vs. 41.2 months; $p = .99$), which led to our consensus group recommendation against short-duration, high-dose oxaliplatin HIPEC. The optimal drug dosing and duration are still uncertain, with some experts within our group favoring mitomycin C for ≥90 min, an approach yet to be tested in RCTs. Evidence from trials on prophylactic HIPEC for high-risk CRC cannot be directly applied to CRC-PM management because they focus on locally advanced tumors without PM, unlike CRS ± IPCT, which is administered with therapeutic intent. Trials have yielded conflicting evidence. HIPECT4 demonstrated improved locoregional recurrence-free survival with surgical resection and prophylactic mitomycin C HIPEC compared to resection alone, whereas the PROPHYLOCHIP and COLOPEC trials did not demonstrate a benefit with prophylactic oxaliplatin HIPEC.[72–74] Emerging evidence from the ICARuS trial sheds light on early postoperative intraperitoneal chemotherapy (EPIC) as an additional IPCT modality for CRC-PM and appendiceal cancer.[75] Prompted by the null findings of oxaliplatin HIPEC for CRC in PRODIGE 7, 75 patients with CRC were randomized to HIPEC ($n = 40$) versus EPIC ($n = 35$). Three-year progression-free survival did not significantly differ between treatment arms (median, 7.7 vs. 8.8 months; $p = .14$). Given the inconclusive evidence regarding IPCT for CRC-PM, decisions on its use should involve shared decision-making between patients and a multidisciplinary team.

As highlighted in our systematic review (Table 3; Table S1), evidence regarding adjuvant systemic chemotherapy after complete CRS for CRC-PM remains equivocal.[44–56] Its role is better established in patients undergoing upfront CRS without neoadjuvant therapy (block 3) but its role in a perioperative or "sandwich" regimen is more complex. Advocates of adjuvant systemic chemotherapy emphasize its role in preventing distant systemic relapse post-CRS because liver or lung metastases are more responsive to systemic treatments than isolated PM.[45] Notably, completing chemotherapeutic treatment as planned (typically >6 cycles), as opposed to partial treatment, is a critical prognostic factor for improved survival.[49,53] Our review also identified two important adjustments needed in studies investigating adjuvant systemic therapies.[45,50] The first is major postoperative morbidity, which may occur in more than 30% of patients undergoing CRS ± IPCT, and often precludes timely initiation of adjuvant systemic therapies. The second involves addressing immortal time bias, which may arise due to an imbalance in early postoperative deaths between study cohorts.

## Blocks 7–9: Incomplete cytoreduction predicted or complete cytoreduction predicted despite progression on systemic therapy

*Agreement: Round 1, 93%, 82%, and 93%; round 2, 99%, 93%, and 96%*

For patients with no disease progression after systemic therapy and with an incomplete cytoreduction predicted (block 7), first-line systemic therapy should be resumed. In cases of progression on first-line systemic therapy (blocks 7–9), initiating second-line therapies is preferred. CRS ± IPCT may only be considered in select patients amenable to complete cytoreduction (block 8). Offering best supportive care and appropriate clinical trials is essential while following an active surveillance protocol and reassessing candidacy for CRS.

An alternative for patients with unresectable PM is pressurized intraperitoneal aerosolized chemotherapy (PIPAC), which is primarily used palliatively in patients who are ineligible for CRS ± IPCT. Although current evidence highlights its safety and feasibility, further research into its efficacy is warranted.[76,77] As per current recommendations, PIPAC should be used only in a clinical trial setting.

## Block 10: Recurrence after CRS

*Agreement: Round 1, 86%; round 2, 96%*

Recurrence after CRS ± IPCT occurs in the peritoneum alone in approximately 60% of patients within 5 years after surgery.[78] It often prompts the need for additional systemic treatments, with repeat CRS ± IPCT being a potential option for select cases. Although much of the literature on repeat CRS ± IPCT focuses on appendiceal neoplasms, evidence supports its safety and feasibility in patients with CRC-PM.[79–86] Positive prognostic indicators for repeat CRS ± IPCT include a low PCI upon recurrence, an absence of extraperitoneal metastases, a disease-free interval exceeding 12 months, and no disease progression on systemic therapy.

### Block 11: Surveillance strategies

*Agreement: Round 1, 88%; round 2, 99%*

Aligning with the NCCN guidelines for metastatic CRC, recommended surveillance includes obtaining a history, physical examination, tumor markers (CEA), and cross-sectional imaging every 3–6 months for the first 2 years, and then every 6 months for a total of 5 years.[87,88] Per the NCCN guidelines, which align with the American Society of Colon and Rectal Surgeons (ASCRS) guidelines,[89] colonoscopy should be performed within 1 year after CRS, unless no preoperative colonoscopy was performed, in which case it should be done within 3–6 months.[90]

History, physical examination, and routine serum testing of CEA and carbohydrate antigen 19-9 can identify most recurrences of PM after CRS-HIPEC.[91] In a recent retrospective study of 253 patients with CRC-PM, patients with a normal CEA level pre– and post–CRS-HIPEC and those with an elevated preoperative level and normal postoperative level had better overall survival than those with CEA levels that remained elevated after CRS-HIPEC.[92]

Although ctDNA can be considered for surveillance in metastatic CRC, its role remains uncertain for patients with CRC-PM.[93] KQ 2a and KQ 2b addressed ctDNA as a surveillance tool postoperatively and while receiving systemic therapy, respectively. KQ 2a identified seven studies (Table 4; Table S2) yielding equivocal results regarding the utility of ctDNA in postoperative surveillance. Challenges include low detection rates and tissue–plasma discordance in PM compared to extraperitoneal metastases. This may be due to a plasma–peritoneal barrier limiting tumor DNA shedding, which contrasts with visceral metastatic sites that are well vascularized.[100–102] However, small retrospective series suggest higher diagnostic accuracy for postoperative relapse with ctDNA compared to standard markers.[96,98] The studies reviewed in KQ 2b are not elaborated upon further because none of them described PM-specific results for response to systemic therapies (Table S5). Three studies aligned with the above hypothesis by highlighting lower ctDNA mutant allele frequencies in patients with peritoneal-only metastases compared to nonperitoneal (e.g., liver) metastases.[102–104] The inconclusive evidence regarding the utility of ctDNA in monitoring PM precludes any strong recommendations; thus, utilization should be based on provider discretion.[105,106]

## CRC with the metachronous PM pathway (Figure 2; Table 1)

Because of the commonalities between the metachronous and synchronous CRC-PM pathways, the aim of the following text focuses on distinct aspects of the metachronous pathway. Where there are commonalities between the synchronous and metachronous pathways, the text recommendations for the synchronous blocks apply to the metachronous blocks as well. Consensus percentages for rounds 1 and 2 for the metachronous pathway are outlined in Tables 3 and 4. We defined metachronous metastases by a disease-free interval (i.e., the duration between diagnosis of the primary tumor and PM) of at least 6 months. Other definitions have been used in the literature, including a shorter disease-free interval of at least 3 months or the detection of PM during relapse after resection of the primary tumor.[107]

A risk stratification schematic was developed on the basis of clinical and pathological features, dichotomized into low- or high-risk features (block 3). High-risk features are a disease-free interval of less than 1 year, positive lymph nodes, a high-grade primary tumor, signet ring histology, a high PCI (a strict cutoff is not defined), and a right-sided primary cancer. The peritoneal surface disease severity score can be considered for additional risk stratification.[108,109] For patients without high-risk disease features, systemic therapy may be initiated and candidacy for CRS ± IPCT may be ascertained after a diagnostic laparoscopy, as outlined in blocks 4–6. For patients with any high-risk disease features, systemic therapy should be offered for 3–6 months. Further treatment should be guided on the basis of disease response as assessed by repeat cross-sectional imaging, tumor marker assessment, and diagnostic laparoscopy, as outlined in blocks 7 and 8. Recommendations for the management of recurrence (block 9) and surveillance (block 10) are consistent with the synchronous pathway, the latter not being subjected to consensus voting again in the metachronous pathway. Notably, patients with metachronous CRC-PM may experience earlier recurrence after CRS ± IPCT compared to those with synchronous CRC-PM.[110]

## Patient and caregiver perspectives

COLONTOWN is an online community of more than 100 private social media groups for patients with CRC and their caregivers. Four members of the COLONTOWN community, two patients with CRC-PM and two caregivers of patients with CRC-PM, provided their perspectives on managing this disease. They emphasized the importance of (1) clinical trial enrollment, (2) balancing survival and quality-of-life goals, (3) nurse navigators, (4) supporting mental health, and (5) obtaining input from PSM experts.

The patients and caregivers reported limited options when it comes to finding a clinical trial that offers a lasting impact, let alone a cure, but they noted that current trials do provide patients with reprieve from chemotherapy. One caregiver said, "I would like to see more support for patients and caregivers researching clinical trials." The other caregiver recounted that her husband has completed two clinical trials with plans to start a third. The patient has had significantly fewer side effects from these trials compared to from his chemotherapy. One patient stated, "The more we can be involved in clinical trials, the more hope there is that we will find a cure." There are limited treatment options for patients with CRC-PM, and these respondents have highlighted the need for more clinical trials in CRC-PM.

## DISCUSSION

Herein, we report updated results of a modified Delphi consensus on the clinical management of patients with synchronous and metachronous CRC-PM. Our current consensus group was expanded to include

**TABLE 4** Key question 2a: In patients with CRC-PM, does plasma-based liquid biopsy offer better sensitivity, specificity, and lead-time therapy compared with standard surveillance modalities in detecting recurrence after CRS?

| Study | Population | Index test | Index test timing | Sample size, No. | PM, % | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Preoperative ctDNA | Postoperative ctDNA | Sites of recurrence | ctDNA versus CEA |
| Beagan 2020[68] (The Netherlands) | CRC-PM ± limited LM | Tumor-informed cfDNA | Preop and ≥1 postop, then every 3 months for 2 years | 30 (24 CRS-HIPEC) | 100 | Detectable in 33% of pts (8 of 24) A/w inferior RFS versus undetectable ctDNA: HR, 3.5 (95% CI, 1.1–10.4) | Available for 19 pts: Sn, 38% of pts (5 of 13) and Sp, 100% of pts (6 of 6) for recurrence | Lower Sn of ctDNA for locoregional versus systemic recurrence (1 of 8 vs. 4 of 5) | NR |
| [a]Baumgartner 2018[94] (USA) | PM (multiple primaries) | Tumor-agnostic ctDNA (Guardant) | Between 1 and 2 weeks preop, no postop | 80 (11 CRC) | 100 | Detectable in 39% of pts (31 of 80) [b]High ctDNA A/w inferior PFS: HR, 2.4 (95% CI, 1.02–5.45) | NR | NR | NR |
| [a]Baumgartner 2020[95] (USA) | PM (multiple primaries) | Tumor-agnostic ctDNA (Guardant) | 1–2 weeks preop and 2–5 weeks postop | 71 (16 CRC) | 100 | Detectable in 39% of overall pts (28 of 71), 62.3% of pts (10 of 16) with CRC [b]High ctDNA A/w inferior PFS: HR, 3.0 (95% CI, 1.6–6.0) | Detectable in 52% of overall pts (38), 63% of pts (10 of 16) with CRC [b]High ctDNA A/w inferior PFS: HR, 2.2 (95% CI, 1.1–4.2) | NR | NR |
| [a]Dhiman 2023[96] (USA) | CRC and high-grade AC with PM | Tumor-informed ctDNA (Signatera) | Every 3 months for 1 year postop | 33 (13 CRC) | 100 | NR | Rising ctDNA A/w inferior DFS versus undetectable ctDNA: HR, 3.7 (95% CI, 1.1–12.7) Rising ctDNA Sn, 85.0% of pts (17 of 20) and Sp, 84.6% of pts (11 of 13) for recurrence | Systemic recurrence A/w higher ctDNA levels versus peritoneal-only recurrence (199.3 vs. 0.9 MTM/mL) | ctDNA more Sn than CEA (85% vs. 50%) for recurrence |
| Hofste 2023[97] (The Netherlands) | Metastatic CRC (multiple sites) | Tumor-informed ctDNA | Preop on day of surgery and 1 week postop | 53 | 11.30 | Detectable in 81% of pts (43 of 53) | Available for 16 pts: detectable in 25% of pts (4 of 16) | LM A/w higher preop ctDNA detection rate (84% vs. 33%) and ctDNA levels (125.3 vs. 3.3 MTM/mL) compared to PM | Preop ctDNA levels correlated with tumor burden; CEA levels did not |
| Lopez-Rojo 2020[98] (Spain) | *KRAS*-mutated CRC and AC with PM/risk for PM | ddPCR for *KRAS* mutations in ctDNA | Preop and 48 h postop | 11 (7 CRC^) | 55 | Detectable in 71% of pts (5 of 7) with CRC: Sn, 80% of pts (4 of 5) and Sp, 50% of pts (1 of 2) for recurrence | Available for 5 pts with CRC, detectable in 80% of pts (4 of 5): Sn, 100% of pts (4 of 4) and Sp, 100% of pts (1 of 1) for recurrence | NR | NR |

(Continues)

**TABLE 4** (Continued)

| Study | Population | Index test | Index test timing | Sample size, No. | PM, % | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Preoperative ctDNA | Postoperative ctDNA | Sites of recurrence | ctDNA versus CEA |
| Loupakis 2021[99] (Italy) | Metastatic CRC (multiple sites) | Tumor-informed ctDNA (Signatera) | Within 4 weeks postop and at progression or last follow-up | 112 | 14.20 | NR | ctDNA detection (MRD) in 54% of pts (61 of 112): Sn, 72% of pts (59 of 82) and Sp, 93% of pts (28 of 30) for recurrence MRD A/w inferior DFS: HR, 5.8 (95% CI, 3.3–10.0) | NR | MRD A/w inferior DFS, CEA not associated: HR, 1.5 (95% CI, 0.8–2.7) |

Abbreviations: A/w, associated with; CEA, carcinoembryonic antigen; cfDNA, cell-free DNA; CI, confidence interval; CRC, colorectal cancer; CRS, cytoreductive surgery; ctDNA, circulating tumor DNA; ddPCR, digital droplet polymerase chain reaction; DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; LM, liver metastases; MRD, minimal or molecular residual disease; MTM, mean tumor molecules; NR, not reported; PFS, progression-free survival; PM, peritoneal metastases; postop, postoperatively; preop, preoperatively; pts, patients; RFS, recurrence-free survival; Sn, sensitivity; Sp, specificity.

[a]Baumgartner 2018, Baumgartner 2020, and Dhiman 2023 do not report CRC-specific outcomes; ^HIPEC indication in seven patients with CRC: carcinomatosis (4) and second look for high-risk CRC (3).

[b]High ctDNA levels: maximum somatic variant allele fraction of ≥0.25%.

surgical oncologists, medical oncologists, radiologists, pathologists, and patient advocates. Consensus was achieved in all seven question blocks after two rounds of review. Four blocks with <90% consensus in the synchronous pathway and three in the metachronous pathway underwent revisions after the first modified Delphi round, with subsequent improvements in the levels of agreement. The primary area of disagreement in the synchronous pathway was regarding upfront CRS ± IPCT, which was deemphasized and highlighted as an option in carefully selected patients alone. Other areas of conflict were the utility of IPCT in addition to CRS, management in the setting of progression while on systemic therapy, and the role of ctDNA testing. These were addressed by recommending consideration for the relevant therapeutic and surveillance approaches on the basis of shared decision-making between patients and a multidisciplinary team.

Major limitations of this expert consensus merit discussion. First, the available evidence for our rapid reviews were of low quality and scarce, which precluded more advanced statistical techniques, such as meta-analysis, to synthesize evidence from the included studies. Therefore, the consensus methodology was used to provide guidance regarding matters of equipoise. Second, the expert panel consisted primarily of surgical oncologists. We anticipated this bias during the inception of this study, and involved leaders in medical oncology, radiation oncology, palliative care, and other disciplines early on to review feedback from the first Delphi round and outline principles of systemic therapy. Last, the Delphi consensus entailed voting on blocks rather than individual itemized recommendations, which aligned with the original Chicago consensus framework. Although this approach helped mitigate survey fatigue, it may have compromised the granularity of the feedback received.

## National perspectives

The NCCN colon cancer guidelines recommend systemic therapy for colon cancer with nonobstructing synchronous PM. For obstructing or near-obstructing disease, the NCCN recommends surgical management of the obstruction (i.e., resection, ostomy, bypass, or stenting) followed by systemic therapy. This aligns with our pathway regarding malignant gastrointestinal obstruction.[39,88] However, the NCCN does not make any recommendations on the value of CRS ± IPCT, which contrasts substantially with our group.

The 2022 American Society of Clinical Oncology (ASCO) guidelines for the treatment of metastatic CRC recommend CRS along with systemic therapy for CRC-PM. In line with our consensus, the ASCO guidelines emphasize the importance of a multidisciplinary tumor board in the management of peritoneal disease, and state that CRS should only be performed at PSM centers. Whereas our consortium does not consider extraperitoneal disease to be an absolute contraindication to CRS, the ASCO guidelines do. The ASCO guidelines also recommend against oxaliplatin-based IPCT, and reference PRODIGE 7 as justification for this statement. Whereas our consensus discourages oxaliplatin-based IPCT, specifically of short duration, a conditional recommendation for mitomycin-based IPCT was made.[72] The ASCO guidelines do not propose an alternative IPCT regimen.[111]

Similar to our consensus, the 2022 ASCRS clinical practice guidelines for colon cancer make a strong recommendation for CRS ± IPCT for patients with resectable peritoneal disease. Our consensus and the ASCRS clinical practice guidelines also highlight a potential role for PET-CT in staging metastatic colon cancer.[112]

## International perspective

The recently published 2022 PSOGI "Consensus on HIPEC Regimens for Peritoneal Malignancies: Colorectal Cancer" was an international consensus of 70 expert panelists who responded to 10 clinical questions regarding IPCT regimens for CRC-PM. In line with our consensus, the PSOGI consensus gave a conditional recommendation for HIPEC for patients with CRC-PM, and recommended against short-duration and high-dose oxaliplatin. Both also recommended consideration of repeat CRS and IPCT for peritoneal recurrence at greater than 1 year after the index CRS.[113]

The 2023 European Society for Medical Oncology (ESMO) clinical practice guidelines for metastatic CRC recommend complete CRS, and state that IPCT should only be offered in the setting of a clinical trial. They highlight the need for ongoing trials with other HIPEC regimens. Guidelines from the PSOGI, ASCO, ESMO, and our group stress the importance of multidisciplinary tumor boards and appropriate referral to PSM centers for CRC-PM.[111,113,114]

Guidelines from the Japanese Society for Cancer of the Colon and Rectum (JSCCR) refer to the "P" classification system, a scoring system for quantifying peritoneal disease like the PCI; P0 represents no PM, P1 refers to PM adjacent to the primary tumor without distant PM, P2 refers to few distant PM, and P3 involves numerous distant PM. The JSCCR recommends CRS for P1 and P2 disease if the resection is not significantly invasive, similar to our recommendations. The JSCCR does not comment on IPCT, recommends systemic therapy for peritoneal recurrence, and does not identify a role for repeat CRS.[115]

A 2019 binational survey of Australasian colorectal surgeons differed critically from our recommendations in questioning the value of CRS ± IPCT and referral to PSM centers for patients with CRC-PM.[116] It is important to highlight differences in the structuring questions between this survey and our consensus, with the former lumping CRS and HIPEC together, whereas ours offered flexibility in considering CRS with or without IPCT. Notably, the survey, a 2018 international PSOGI consensus, and our consensus consider Krukenberg tumors as PM and not an absolute contraindication to CRS.[116,117]

## CONCLUSION

This study reported on a modified Delphi consensus for the management of CRC-PM. By building on the 2018 Chicago consensus guidelines, pathways for synchronous and metachronous CRC-PM were updated on the basis of the results of this expert consensus. Three systematic rapid reviews highlighted the optimal systemic therapy for patients with CRC-PM undergoing CRS ± IPCT and the limited evidence regarding the utility of ctDNA for surveillance. These questions and other matters of equipoise, such as the role of IPCT in addition to CRS, warrant further investigation as part of the multimodal treatment of CRC-PM.

### AUTHOR CONTRIBUTIONS

**Kurt S. Schultz**: Conceptualization; data analysis; data interpretation; writing—review and editing. **Varun V. Bansal**: Conceptualization; data analysis; data interpretation; writing—review and editing. **Michael M. Wach**: Data interpretation; methodology; writing—review and editing. **Neal Bhutiani**: Data interpretation; methodology; writing—review and editing. **Frederick A. Godley IV**: Data interpretation; methodology; writing—review and editing. **Jaeyun (Jane) Wang**: Data analysis; data review; writing—review and editing. **Muhammad Talha Waheed**: Data analysis; data review; writing—review and editing. **Joanna T. Buchheit**: Data analysis; data review; writing—review and editing. **Emily Papai**: Data analysis; data review; writing—review and editing. **Susan Campbell**: Data analysis; data review; writing—review and editing. **Lauren E. Schleimer**: Data analysis; data review; writing—review and editing. **David G. Su**: Data analysis; data review; writing—review and editing. **Kiran K. Turaga**: Conceptualization; methodology; data analysis; writing—review and editing; supervision; funding acquisition; project administration. **Craig G. Gunderson**: Data analysis; data review; methodology; supervision; validation. **Michael G. White**: Validation; writing—review and editing. **Abhineet Uppal**: Validation; writing—review and editing. **Kanwal P. S. Raghav**: Validation; writing—review and editing. **Daniel M. Labow**: Validation; writing—review and editing. **Umut Sarpel**: Validation; writing—review and editing. **Ardaman P. Shergill**: Validation; writing—review and editing. **John Paul Shen**: Validation; writing–review and editing. **Cathy Eng**: Validation; writing—review and editing. **Michael B. Foote**: Validation; writing—review and editing. **Joel M. Baumgartner**: Conceptualization; data interpretation; validation; writing—review and editing.

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## CONFLICT OF INTEREST STATEMENT

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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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