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INSIGHT FROM THE EXPERTS

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: Where do we stand?

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Plain Language Summary:

- Patients with colorectal cancer that has spread to the lining of the abdomen (peritoneum) benefit from surgery to remove all the cancer.
- The addition of certain types of intra-abdominal chemotherapy during surgery improves survival for select patients.

Colorectal cancer (CRC) peritoneal metastases (PMs) occur in approximately 8%–25% of patients, with a much higher prevalence found in patients with mucinous tumors or signet ring histology.[1,2] Unlike other metastatic sites, PMs often lead to death by local progression resulting in malignant bowel obstruction. Unfortunately, treatment with systemic chemotherapy alone for patients with isolated PM is associated with a median survival of 16 months, which is significantly lower than that for other metastatic sites, even in well-selected patients.[3] Locoregional therapies are therefore extremely appealing in the management of these patients.

Cytoreductive surgery (CRS) is a curative-intent, locoregional modality for patients with PM. Cytoreduction is distinct from (palliative) tumor debulking in terms of the targeted aim. The goal of CRS is to obtain a "complete" cytoreduction, which is considered the resection of all grossly visible peritoneal disease (a completeness of cytoreduction [CC] score of 0) or the removal of all disease greater than 2.5 mm (a CC score of 1). As such, candidates for CRS must be diligently screened because high tumor burdens, extensive mesenteric involvement, malignant bowel obstructions, and/or malignant ascites often preclude eligibility.

Long-term survival is possible in almost 17% of patients with appropriately aggressive surgery; however, ideal patient selection requires a low burden of disease and the feasibility of complete cytoreduction.[4] The addition of intraperitoneal chemotherapy to CRS is an area of active investigation. Although the ability to deliver high-dose regional chemotherapy directly to the site of diffuse disease is theoretically sound, recent large randomized trials (PRODIGE 7, PROPHYLOCHIP, and COLOPEC) have demonstrated that the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin to CRS does not improve survival in the metastatic, occult–metastatic, or prophylactic settings.[4–6] The purpose of this commentary is to examine current controversies in the management of PM from CRC, specifically around the use of intraperitoneal chemotherapy.

What is the current standard of care for resectable PM?

Patients with PM should be evaluated by a multidisciplinary team at a high-volume center. Patients with low-volume (Peritoneal Cancer Index [PCI] scores < 19–25) and isolated peritoneal disease amenable to complete cytoreduction (a CC score of 0 or R0) are optimal candidates for CRS, especially if they are presenting with metachronous metastasis after a long disease-free interval (>1 year). In the large, multicenter, randomized controlled trial PRODIGE 7,

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survival for patients undergoing CRS was 41 months, which is significantly longer than that reported by prior studies of systemic chemotherapy alone.[3,4,7–10]

The true benefit of systemic chemotherapy in patients with resectable PM is currently being investigated. Unfortunately, prior investigations establishing systemic chemotherapy as the standard of care for unresectable, metastatic CRC often have not included patients with isolated PM because of an inability to accurately detect peritoneal disease noninvasively.[11] Recent evidence from JCOG0603[12] (when supplemented with European Organisation for Research and Treatment of Cancer 40983 trial data)[13] has brought into question the survival benefit of perioperative systemic chemotherapy for patients with resectable hepatic metastases. Although perioperative systemic chemotherapy for resectable PM appears to be safe according to preliminary results from the CAIRO-6 trial, it remains to be seen if there is an associated survival benefit because these outcomes have not yet been reported.[14]

Controversy concerning the standard of care for such patients pertains to the application of intraperitoneal chemotherapies such as HIPEC; this is borne out by divergent guidelines from the National Comprehensive Cancer Network,[15] the European Society for Medical Oncology,[16] the Chicago Consensus,[17] and Peritoneal Surface Oncology Group International. This is explored further in the following discussion.

What is the evidence for intraperitoneal chemotherapy?

Early data supporting CRS–HIPEC for CRC came from a Dutch trial of patients with either synchronous or metachronous peritoneal disease without evidence of other distant metastases (Table 1).[18,19] CRS–HIPEC with mitomycin C for 90 min in combination with systemic fluorouracil and leucovorin significantly improved both progression-free survival (12.6 vs. 7.7 months; $p = .02$) and disease-specific survival (22.2 vs. 12.6 months; $p = .028$) over treatment with systemic chemotherapy alone. This trial also demonstrated the importance of obtaining an adequate cytoreduction with a median survival of 48 months and a 5-year overall survival (OS) rate of 45% in those for whom the surgical cytoreduction of all gross disease was possible (R1) versus 0% for all patients with a resection status > R1. Notably, this trial had several limitations, including a failure to assess the efficacy of contemporary first-line chemotherapy regimens, high treatment-related morbidity, and the inclusion of a small number of patients with appendiceal cancer.[17] This trial was designed to assess only the impact of CRS and HIPEC combined in comparison with systemic chemotherapy and not the relative effectiveness of either the CRS or HIPEC component in isolation. Despite these limitations, intraperitoneal mitomycin C for 90 min clearly became the standard of care for PM.

TABLE 1 Summary of major HIPEC trials in the setting of colorectal cancer

Source	Population	Comparison	HIPEC drug dosing	Simultaneous intravenous systemic chemotherapy	Outcomes
Verwaal 2008[19]	Synchronous or metachronous PM or positive cytology	CRS–HIPEC plus adjuvant systemic chemotherapy versus systemic chemotherapy alone	Mitomycin C at 17.5 mg/m^2 followed by 8.8 mg/m^2 every 30 min for 90 min Total dose limited to 70-mg maximum	None	CRS–HIPEC improved both PFS (12.6 vs. 7.7 months) and disease-specific survival (22.2 vs. 12.6 months)
COLOPEC 2019[5]	T4, N0–2, or perforated tumors without PM	Resection plus adjuvant HIPEC and systemic chemotherapy versus resection and adjuvant systemic chemotherapy	Oxaliplatin at 460 mg/m^2 for 30 min	FU at 400 mg/m^2 with leucovorin at 20 mg/m^2	No difference in OS, DFS, or PM-free survival at 18 months (80.9% and 76.2% for CRS–HIPEC and systemic chemotherapy alone, respectively)
PROPHYLOCHIP 2020[6]	Perforated tumor or synchronous, resectable PM	Systemic chemotherapy and surveillance versus planned second-look surgery with CRS–HIPEC	Oxaliplatin at 300–360 mg/m^2 with irinotecan at 200 mg/m^2 or oxaliplatin at 460 mg/m^2 alone or mitomycin C at 35 mg/m^2 for 30 min	FU at 400 mg/m^2 with leucovorin at 20 mg/m^2	No difference in 3- or 5-year OS or DFS
PRODIGE 7 2021[4]	Isolated, synchronous PM with PCI ≤ 25	CRS alone versus CRS–HIPEC	Oxaliplatin at 360 or 460 mg/m^2 for 30 min	FU at 400 mg/m^2 and folinic acid at 20 mg/m^2	No difference in OS (41.2 vs. 41.7 months), relapse-free survival (11.1 vs. 13.1 months), or PM-free survival

Abbreviations: CRS, cytoreductive surgery; DFS, disease-free survival; 5FU, 5 fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; PCI, Peritoneal Cancer Index; PFS, progression-free survival; PM, peritoneal metastasis.

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What are the data for intraperitoneal oxaliplatin (30 min, 300 mg/m^2)?

Oligometastatic disease

Following promising data from large, prospective, observational studies using oxaliplatin for 30 min in combination with fluorouracil and leucovorin, the PRODIGE 7 trial examined the role of adding intraperitoneal oxaliplatin to CRS.[4] The trial included 265 patients with synchronous PM and a PCI score ≤ 25 who were randomized to either CRS–HIPEC with oxaliplatin or CRS alone. Both groups were heavily treated with standard neoadjuvant and adjuvant systemic chemotherapy for a total of 6 months. The addition of HIPEC to CRS did not prolong OS (41.2 vs. 41.7 months; $p = .99$) or relapse-free survival (11.1 vs. 13.1 months; $p = .43$). Peritoneal-free survival was also similar for the two treatment arms, and this suggests that oxaliplatin may be ineffective as a local therapy. Alternatively, HIPEC was administered for only 30 min, which may have been insufficient to produce an appropriate response. The addition of HIPEC to CRS did not appear to increase rates of early postoperative complications; however, patients receiving HIPEC did have more complications between 31 and 60 days postoperatively (15% vs. 26%) and had a significantly longer median time to the initiation of their next cycle of chemotherapy (56 vs. 67 days).

Although there was no difference in OS between the CRS–HIPEC and CRS-only groups, there was a significantly lower risk of death (hazard ratio, 0.44; 95% confidence interval, 0.21–0.90) among patients with intermediate PCI scores (11–15) receiving CRS–HIPEC in a subgroup analysis. This may reflect the biology of peritoneal disease and the existence of a sweet spot where intraperitoneal oxaliplatin may have a role.

The main criticisms of this negative trial are the high crossover rate, the short duration of HIPEC perfusion, and the use of intraperitoneal oxaliplatin in patients with extensive prior systemic exposure to oxaliplatin leading up to CRS–HIPEC, which may have induced drug-resistant residual disease. Supporting this consideration are data suggesting that short-duration oxaliplatin might not effectively penetrate a tumor to yield oncologically significant results.[20,21] Furthermore, there was substantial heterogeneity in the use of targeted therapy (anti-VEGF or anti-EGFR) in the study population, and the dose and duration of the concurrent, systemic fluorouracil infusion have also been criticized as insufficient.[22] Finally, patient data on the RAS or BRAF mutational status were also not considered.

The impressive survival rates reported in this trial must be considered in light of all patients in both arms receiving extensive amounts of systemic therapy. Additionally, this likely represents a selected cohort of patients with PM. In practice, however, tolerability and toxicity commonly limit the amount of chemotherapy that patients receive. Data on actual intention-to-treat rates of neoadjuvant therapy completion, the subsequent ability to undergo CRS–HIPEC, and potentially recommended adjuvant therapy are limited for this patient population.[23,24]

In addition to this landmark study, we have also included selected major nonrandomized studies examining the role of CRS and HIPEC for CRC PM (Table 2).

Occult metastatic disease

Because of the propensity for high-risk patients to experience recurrence rapidly but not predictably, there has been substantial interest in delineating potential screening strategies to catch patients with early recurrences while they are more likely to be eligible for cytoreduction. One approach has been a systematic delayed CRS–HIPEC protocol, which was the subject of the PROPHYLOCHIP trial published in 2020.[6] Patients in this trial were eligible if they had a perforated primary tumor and/or synchronous and localized PM resected with the primary. The HIPEC drugs involved in this trial were oxaliplatin and irinotecan ($n = 21$), oxaliplatin alone ($n = 38$), and mitomycin C alone ($n = 8$). Compared with standard surveillance protocols, systematic second-look surgery with CRS–HIPEC did not improve 3- or 5-year disease-free survival (DFS) or OS. Notably, 26 of the 75 patients (35%) in the surveillance arm and 24 of the 75 patients (32%) in the experimental arm developed PM, and this highlights the commonality of locoregional recurrence in this population.

Prophylactic CRS–HIPEC

COLOPEC, a trial also using short-duration oxaliplatin intraperitoneally, did not demonstrate a benefit of HIPEC concurrent with, or 5–8 weeks after, resection of the primary in patients with perforated or T4 tumors without locoregional metastases in terms of OS, DFS, or PM-free survival.[5] Notably, 21% of the patients overall developed peritoneal recurrences in both the experimental arm (HIPEC with oxaliplatin followed by systemic chemotherapy) and the control group (systemic fluorouracil and oxaliplatin or capecitabine and oxaliplatin alone). This included 9% of the patients in the experimental arm who developed PM before receiving HIPEC. Additionally, 12% of the patients in the control arm who developed PM during surveillance and met the criteria for HIPEC ultimately crossed over. Despite these considerations, the results of this trial do not support the adjuvant use of HIPEC in patients with high-risk CRC without synchronous PM and suggest that short-duration intraperitoneal oxaliplatin does not improve survival.

What is the effectiveness of intraperitoneal mitomycin C versus oxaliplatin?

The American Society of Peritoneal Surface Malignancies conducted a retrospective review of 15 databases in North America and Europe between 2000 and 2012 to compare the effectiveness of HIPEC with mitomycin C versus oxaliplatin.[25] No differences in median survival

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TABLE 2 Selected nonrandomized studies examining the role of CRS and HIPEC in the treatment of patients with CRC PM

Source	Population (*n*)	Comparison (*n*)	HIPEC drug	Simultaneous intravenous systemic chemotherapy	Outcomes
Glehen 2004[8]	Synchronous or metachronous PM (506)	None	Mitomycin C (71.4%) Mitomycin C + cisplatin (12.5%) Oxaliplatin (8.4%)	None	Median OS: • Complete CRS: 32.4 months • Incomplete CRS: 8.4 months • ($p < .001$)
Elias 2009[43]	Synchronous or metachronous PM (96)	CRS–HIPEC (48) versus systemic chemotherapy alone (48)	Oxaliplatin at 460 or 460 mg/m^2 for 30 min	5FU at 400 mg/m^2 and leucovorin at 20 mg/m^2	Median OS: • CRS–HIPEC: 63 months • Chemotherapy alone: 24 months ($p < .05$)
Elias 2010[44]	Synchronous or metachronous PM (563)	None	Mitomycin C (55%) Oxaliplatin (45%)	None	Median OS: 30.1 months
Kuijpers 2013[45]	Synchronous or metachronous PM (660)	None	Mitomycin C at 35 mg/m^2	None	Median OS: 33 months
Esquivel 2014[46]	Synchronous or metachronous PM (1013)	CRS–HIPEC (705) versus systemic chemotherapy alone (308)	Mitomycin C (60.3%) Oxaliplatin (28.3%)	None	Median OS: • CRS–HIPEC: 41 months • Chemotherapy alone: 10 months ($p < .001$)
Prada-Villaverde 2014[25]	Synchronous or metachronous PM (539)	Mitomycin C versus oxaliplatin	Mitomycin C (72%) Oxaliplatin (28%)	None	Median OS: 32.6 months • Mitomycin C: 32.7 months • Oxaliplatin: 31.4 months ($p = .9$)
Alzahrani 2016[47]	Synchronous or metachronous PM (PCI $\leq$ 20) (234)	None	Oxaliplatin at 350 mg/m^2 for 30 min	5FU at 400 mg/m^2	Median OS: 28 months
Hentzen 2019[48]	Synchronous or metachronous PM (433)	Synchronous versus metachronous PM	Mitomycin C (88.5%) Oxaliplatin (9%)	None	Median OS: • Synchronous PM: 34 months • Metachronous PM: 33 months

Abbreviations: CRC, colorectal cancer; CRS, cytoreductive surgery; 5FU, 5 fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; PCI, Peritoneal Cancer Index; PM, peritoneal metastasis.

were evident for patients treated with each drug, even among the 539 patients undergoing complete CRS (32.7 and 31.4 months for mitomycin C [$n = 385$] and oxaliplatin [$n = 154$], respectively; $p = .92$). When they were stratified by burden of disease and biology, however, patients with a Peritoneal Surface Disease Severity Score (PSDSS) of I or II had a median OS of 54.3 months when they were receiving mitomycin C versus 28.2 months with oxaliplatin ($p = .012$). Conversely, the median survival for patients with more extensive disease (PSDSS stage III or IV) was greater for those receiving oxaliplatin versus mitomycin C (30.4 vs. 19.4 months), although this difference was not significant ($p = .427$). In a multivariate analysis, the use of oxaliplatin was associated with a higher risk of death than mitomycin C (hazard ratio, 1.40; 95% confidence interval, 1.01–1.94; $p = .042$) after controlling for the degree of cytoreduction, PSDSS, and patient age. This suggested that mitomycin C may be superior to oxaliplatin as an intraperitoneal agent only for patients with a low burden of disease.

A recently published analysis of the Netherlands Cancer Registry also failed to identify a survival benefit from either HIPEC drug. The median survival was 30.7 months for 177 patients treated with mitomycin C and 46.6 months for 120 patients receiving oxaliplatin, but this did not significantly differ after risk adjustments.[26] The rates

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of 1-, 2-, and 3-year survival also did not differ. Importantly, relatively few patients in either cohort received neoadjuvant systemic chemotherapy (25.4% in the mitomycin C group and 27.5% in the oxaliplatin group) per the standard of care in the Netherlands. As such, these survival results are likely less influenced by potential tumor drug resistance induced by oxaliplatin-containing neoadjuvant regimens, which has been cited as a concern with the PRODIGE 7 trial and supported in ex vivo testing.[27]

One Australian, single-center, retrospective review of patients from 1996 to 2015 suggested a significant survival benefit for patients treated with oxaliplatin (at 350 mg/m^2 for 30 min) versus mitomycin C (12.5 mg/m^2 for 90 min), especially in women, those with a PCI score of 10–15, and those with lower grade tumors (56 vs. 29 months; hazard ratio, 0.59; $p = .017$).[28] No differences in DFS were observed. Rates and total exposure to systemic neoadjuvant therapy were not reported, and early postoperative intraperitoneal chemotherapy was used in 69.8% of the patients treated with mitomycin C but in only 2% of those receiving oxaliplatin. Results from smaller retrospective reviews have been somewhat inconsistent in reported OS, but they have not demonstrated significant differences between drugs.[29,30] Systematic reviews of this question have also failed to yield satisfactory conclusions because of heterogeneity in cohorts, comparisons, and results.[31,32]

On the basis of the heterogeneity of these studies, it is scientifically difficult to conclude that intraperitoneal oxaliplatin and mitomycin C are similar, especially for patients with a low burden of disease. Hence, it is incorrect to extrapolate the results from a negative oxaliplatin trial to the efficacy of mitomycin C as an intraperitoneal agent. At best, there is one prospective, randomized trial demonstrating a benefit with mitomycin C as well as another showing a lack of benefit from oxaliplatin.[4,19] Current evidence shows that HIPEC with oxaliplatin is not effective; therefore, mitomycin C should be used as we await additional clinical trial results.

What relevant clinical trials are ongoing?

HIPECT4 is a multicenter trial examining the role of adjuvant HIPEC with mitomycin C for 60 min in patients with resected T4N0–2 CRC tumors with a primary end point of rates of locoregional control at 12 and 36 months.[33] Preliminary results presented at the 2022 annual meeting of the European Society for Medical Oncology suggest increased locoregional control for prophylactic HIPEC with mitomycin C at 30 mg/m^2. The phase 3 APEC trial (NCT02965248) will also compare the incidence of PM between patients receiving prophylactic HIPEC with oxaliplatin (or raltitrexed) and adjuvant chemotherapy for high-risk T3–4N0–3 tumors and patients receiving the standard of care. Building on this paradigm, the phase 3 PROMENADE trial (NCT02974556) will assess the oncologic benefit of limited prophylactic organ resection in addition to HIPEC (also in patients with T3–4N0–3 tumors). These patients will undergo omentectomy, appendectomy, and bilateral adnexectomy concurrently with primary tumor resection and subsequently receive HIPEC with oxaliplatin and concomitant systemic fluorouracil and leucovorin. Adjuvant systemic therapy will then be with CAPOX or FOLFOX. This approach is hypothesized to proactively address any occult micrometastatic disease in the peritoneum and decrease rates of peritoneal recurrence at 3 years.

What is the evidence for pressurized intraperitoneal aerosol chemotherapy?

New approaches to intraperitoneal chemotherapeutic delivery are emerging as viable alternative to HIPEC.[34] Pressurized intraperitoneal aerosol chemotherapy involves insufflation of the abdomen with CO_2 at 12 mm Hg and the injection of an aerosol containing drugs under pressure for approximately 30 min with subsequent evacuation. Common regimens involve either oxaliplatin monotherapy or a combination of cisplatin and doxorubicin and have shown safety and feasibility.[35,36] Among the reported data so far, 50%–88% of patients with PM have demonstrated a response to therapy. Response rates for patients with PM from CRC range from 71% to 86% with a median survival of 15–16 months as third-line therapy.[35] Iterative pressurized intraperitoneal aerosol chemotherapy has also been successfully used to convert initially unresectable disease to the point of being amenable to CRS–HIPEC for multiple histologies, including CRC.[36–38]

Is perioperative systemic chemotherapy effective?

Although it is considered standard of care, prospective, randomized data are surprisingly sparse for the effectiveness of perioperative chemotherapy for patients undergoing CRS–HIPEC.[39–41] CAIRO-6 is an actively accruing multicenter trial in the Netherlands seeking to address the impact of contemporary perioperative systemic chemotherapy on patients undergoing CRS–HIPEC for isolated, resectable CRC PM versus CRS–HIPEC alone.[42] Patients will receive neoadjuvant and adjuvant FOLFOX, neoadjuvant and adjuvant CAPOX, or neoadjuvant FOLFIRI and adjuvant fluoropyrimidine monotherapy. All patients will also receive neoadjuvant bevacizumab. The primary outcome of the study will be 3-year OS with secondary outcomes of progression-free survival, DFS, health-related quality of life scores, surgical outcomes, and, importantly, health care costs within the Dutch system. Notably, treating physicians will be allowed to choose either oxaliplatin or mitomycin C for HIPEC. It remains to be seen (1) what proportion of patients will be treated with each drug and (2) whether those receiving perioperative FOLFOX or CAPOX and HIPEC with oxaliplatin will have higher rates of local peritoneal recurrence, as potentially suggested by the results of PRODIGE 7.

In conclusion, in our opinion, patients with PM from CRC require evaluation and treatment at expert institutions with experience in peritoneal surface disease. The standard of care for patients with low-volume, resectable PM is CRS. Perioperative systemic chemotherapy for resectable metastases is safe, but its effectiveness has

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yet to be determined. The application of intraperitoneal therapy (i.e., HIPEC) with mitomycin C during CRS is appropriate according to current evidence; however, HIPEC with short-duration oxaliplatin is likely not beneficial in the metastatic, prophylactic, or adjuvant setting. Future clinical trials will delineate the benefits, or lack thereof, of existing and/or novel intraperitoneal agents and techniques of delivery.

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CONFLICTS OF INTEREST

Kiran K. Turaga reports acting as a consultant for Merck. The other authors made no disclosures.

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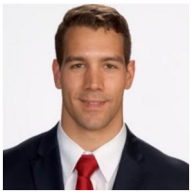

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