



## Research Article

# Role of Early Bedside HIPEC as Adjuvant Treatment in Colorectal Peritoneal Metastasis

 Spiliotis John,<sup>1</sup>  Farmakis Dimitrios,<sup>1</sup>  Metaxas Theodoros,<sup>1</sup>  Spiliotis Nikolaos - Jasonas,<sup>2</sup>  Saroyan Hayarpi,<sup>1</sup>  
 Gianniri Mairi,<sup>2</sup>  Vaikos Dimitrios,<sup>1</sup>  Margari Harris,<sup>2</sup>  Karachalios Dimitrios<sup>1</sup>

<sup>1</sup>European Interbalkan Medical Center, Thessaloniki, Greece

<sup>2</sup>Athens medical Center Marousi, Athens, Greece

### Abstract

**Objectives:** Peritoneal metastasis (PM) is a poor prognostic factor for all malignancies and remains difficult to treat with systemic chemotherapy because of poor peritoneal vascularization, resulting in limited drug delivery and penetration into tissues. Our study aims to investigate the efficacy and safety of different locoregional treatment protocols with hyperthermic intraperitoneal chemotherapy (HIPEC), Early Peritoneal Chemotherapy (EPIC), Pressurized Intraperitoneal Chemotherapy (PIPAC) in the management of advanced colorectal cancer with metachronous PM.

**Methods:** A total of 42 patients were divided into three groups, as follows. Group A: After neoadjuvant systemic chemotherapy, 15 patients received cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) and then adjuvant systemic chemotherapy. Group B: After neoadjuvant systemic chemotherapy, 12 patients received CRS + HIPEC + early postoperative intraperitoneal chemotherapy for 5 postoperative days and then adjuvant systemic chemotherapy. Group C: After neoadjuvant chemotherapy, 15 patients received CRS + HIPEC and then an adjuvant bedside HIPEC on the 10th postoperative day combined with postoperative adjuvant chemotherapy.

**Results:** Patients in group A had a median overall survival (OS) of 33 months; however, log-rank tests showed that survival distributions of the three groups were not statistically significant different for both OS and disease-free survival.

**Conclusion:** In conclusion, CRS plus HIPEC remains an alternative to locoregional treatment in well-selected patients with PM in combination with systemic neoadjuvant and adjuvant chemotherapy.

**Keywords:** Hyperthermic Intraperitoneal Chemotherapy (HIPEC), Cytoreductive Surgery (CRS), Peritoneal Metastasis (PM), Colorectal Cancer (CRC), adjuvant treatment

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Colorectal cancer (CRC) remains one of the most common forms of cancer and is the second cause of cancer-related mortality in Western countries. The main cause of death is always the consequence of metastatic spread to distant sites, such as the liver and lungs, and patients with peritoneal metastasis (PM) have the worst prognosis.<sup>[1, 2]</sup>

The true incidence of PM is therefore unclear but it was reported to be as high as 4080% in an autopsy series. However,

PM is underdiagnosed as detection with routine imaging methods is difficult because of its small size.<sup>[3, 4]</sup>

The development of PM is often associated with rapidly recurrent bowel obstruction, the formation of malignant ascites, pain, and malnutrition. If left untreated, the median overall survival (OS) of these patients is less than 5 months.<sup>[5]</sup>

In this paper, we present a retrospective analysis of different groups of patients with different types of regional

**Address for correspondence:** Spiliotis John, MD. European Interbalkan Medical Center, Thessaloniki, Greece

**Phone:** +306942 40 40 14 **E-mail:** jspil@hotmail.gr

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treatments, such as hyperthermic intraoperative chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC) and second bedside HIPEC, during the first 10 days after initial cytoreductive surgery (CRS) and HIPEC.

## Methods

This study aims to investigate the efficacy and safety of a novel bedside adjuvant HIPEC early after CRS + HIPEC (on the 10<sup>th</sup> postoperative day) in the treatment of advanced CRC.

### Patient Recruitment

From 2010, patients with PM from CRC were studied retrospectively and divided into the following three groups:

Group A: After neoadjuvant systemic chemotherapy (four cycles of FOLFOX), 15 patients with PM and mean Peritoneal Cancer Index (PCI) = 7.8 (range 4–11) received CRS plus HIPEC (mitomycin 15 mg/m<sup>2</sup> for 60 min at 42.8 °C) and then adjuvant systemic chemotherapy in addition to four cycles of FOLFOX.

Group B: After four cycles of neoadjuvant chemotherapy, 12 patients with PM and mean PCI = 7.5 (range 4–10) received CRS plus HIPEC (as did group A) and EPIC with 5-fluorouracil for the first 5 postoperative days and then adjuvant systemic chemotherapy with four cycles of FOLFOX.

Group C: After neoadjuvant chemotherapy as above, 15 patients with PM and mean PCI = 7.6 (range 3–11) received CRS plus HIPEC (mitomycin 15 mg/m<sup>2</sup> for 60 min at 42.8 °C). All patients in group C received a second cycle of bedside HIPEC with platinum 30 mg/m<sup>2</sup> for a 24-hour period, at a flow rate of 180–200 ml/min of Normal Saline (N/S) (range 2000–3500 ml). Before the bedside HIPEC procedure, patients were routinely given antiemetic drugs, intravenous saline, and dextrose 5% to prevent renal dysfunction.

The end point of our study was disease-free survival and OS. The secondary end points were the incidence of morbidity and mortality between the three groups.

### Statistical Analysis

Time-to-event outcomes were analyzed using the Kaplan–Meier estimator, and 7-year probabilities were presented according to the independent variables. The log-rank test was used to assess the effect of the evaluated variables on progression-free survival (PFS) and OS.

PFS was defined as the time from the initial treatment to the time of recurrence or progression of the disease or the time of last contact. OS was defined as the same starting time as PFS to the time of patient death or the time that the

patients were still alive at the end of the study.

Analyses were performed based on the type of treatment for the colon (group A: neoadj + CRS + HIPEC + syst.chem; group B: neoadj + CRS + HIPEC + EPIC + syst.chem; group C: neoadj + CRS + HIPEC-A + HIPEC-B), patient age group ( $\leq 55$  and  $> 55$  years), sex group (male and female), and complication group (small–medium and serious–dangerous). Continuous data are reported as the mean ( $\pm$  standard deviation) and median (range). Categorical data are reported as the number (percentage). Patient groups were compared by using the chi-squared test (categorical data) and Kruskal–Wallis test (continuous data). A p-value  $< 0.05$  was considered statistically significant. All statistical data were analyzed using SPSS version 25.

## Results

Of the 42 patients included in the analyses, the most common age was in sixth decade of life, with a median age of 58.5 years, ranging from 37 to 71 years (the mean age was  $57.5 \pm 8.4$  years). Twenty-eight patients (66.7%) were older than 55 years. The majority of patients were male (52.4%). Fifteen patients developed complications (seven small, five medium, and three serious). Participants were randomly assigned to three different interventions: 15 (35.7%) had intervention type A, 12 (28.6%) had intervention type B, and 15 (35.7%) had intervention type C. Patient characteristics are shown in Table 1. The mean length of follow-up was  $36.3 \pm 14.7$  months, and the median follow-up duration was 31.5 months, ranging from 14 to 76 months. Sixteen patients (38.1%) had died by the end of follow-up, whereas 26 (61.9%) were the censored cases. Six patients (38.1%) in intervention group A, six (50%) in intervention group B, and four (26.7%) in intervention group C had died by the end of follow-up. The censored cases were nine (60%) in intervention group A, six (50%) in intervention group B, and 11 (73.3%) in intervention group C. Seven female patients (35%) and nine male patients (40.9%) had died by the end of follow-up.

The censored cases were 13 female patients (65%) and 13 male patients (59.1%). Six patients (38.1%) in the age group  $\leq 55$  years and six (50%) in the age group  $> 55$  years had died by the end of follow-up. The censored cases were eight (57.1%) in the age group  $\leq 55$  years and 18 (64.3%) in the age group  $> 55$  years. Seven patients (58.3%) with small–medium complications and one (33.3%) with serious–dangerous complications had died by the end of follow-up. The censored cases were five (57.1%) in the group with small–medium complications and 18 (64.3%) in the group of serious–dangerous complications.

**Table 1.** Patient and tumor characteristics

	Group A	Group B	Group C	Total	p
Sex					
Female	7	6	7	20	0.981
Male	8	6	8	22	
Complication					
No complication	11	8	8	27	0.855
Small	2	1	4	7	
Medium	1	2	2	5	
Serious	1	1	1	3	
Dangerous	0	0	0	0	
age >55					
≤55	5	4	5	14	1.000
>55	10	8	10	28	
Age					
Mean	57.9	56.2	58.1	57.5	0.890
Standard Deviation	9.4	8.2	8.0	8.4	
Median	59.0	57.5	59.0	58.5	
Minimum	37.0	39.0	47.0	37.0	
Maximum	71.0	67.0	70.0	71.0	

## OS

Patients who underwent therapy A had a median OS of 33 months (95% confidence interval [CI] 29.1–36.9). For groups B and C, the median survival time could not be calculated because there was no time point at which the survival function took a value <50%. A log-rank test was conducted to determine if there were differences in the survival distribution for the different types of interventions. The survival distributions for the three interventions were not statistically significantly different;  $\chi^2(2) = 2.464$ ,  $p=0.292$ .

Female patients in group A had a median OS of 54 months. For males, the median survival time could not be calculated because there was no time point at which the survival function took a value <50%. A log-rank test was conducted to determine if there were differences in the survival distribution for the sex groups. The survival distributions for the sex groups were not statistically significantly different;  $\chi^2(1) = 0.297$ ,  $p=0.586$ .

Patients aged ≤55 years in group A had a median OS of 39 months (95% CI 28–50) and patients aged >55 years had a median OS of 54 months. A log-rank test was conducted to determine if there were differences in the survival distribution for the age groups. The survival distributions for the age groups were not statistically significantly different;  $\chi^2(1) = 0.348$ ,  $p=0.556$ .

Patients in group A with small–medium complications had a median OS of 39 months (95% CI 28–50) and those with serious–dangerous complications had a medium OS of 30

months. A log-rank test was conducted to determine if there were differences in the survival distribution for the complication groups. The survival distributions for the complication groups were not statistically significantly different;  $\chi^2(1) = 0.005$ ,  $p=0.946$ .

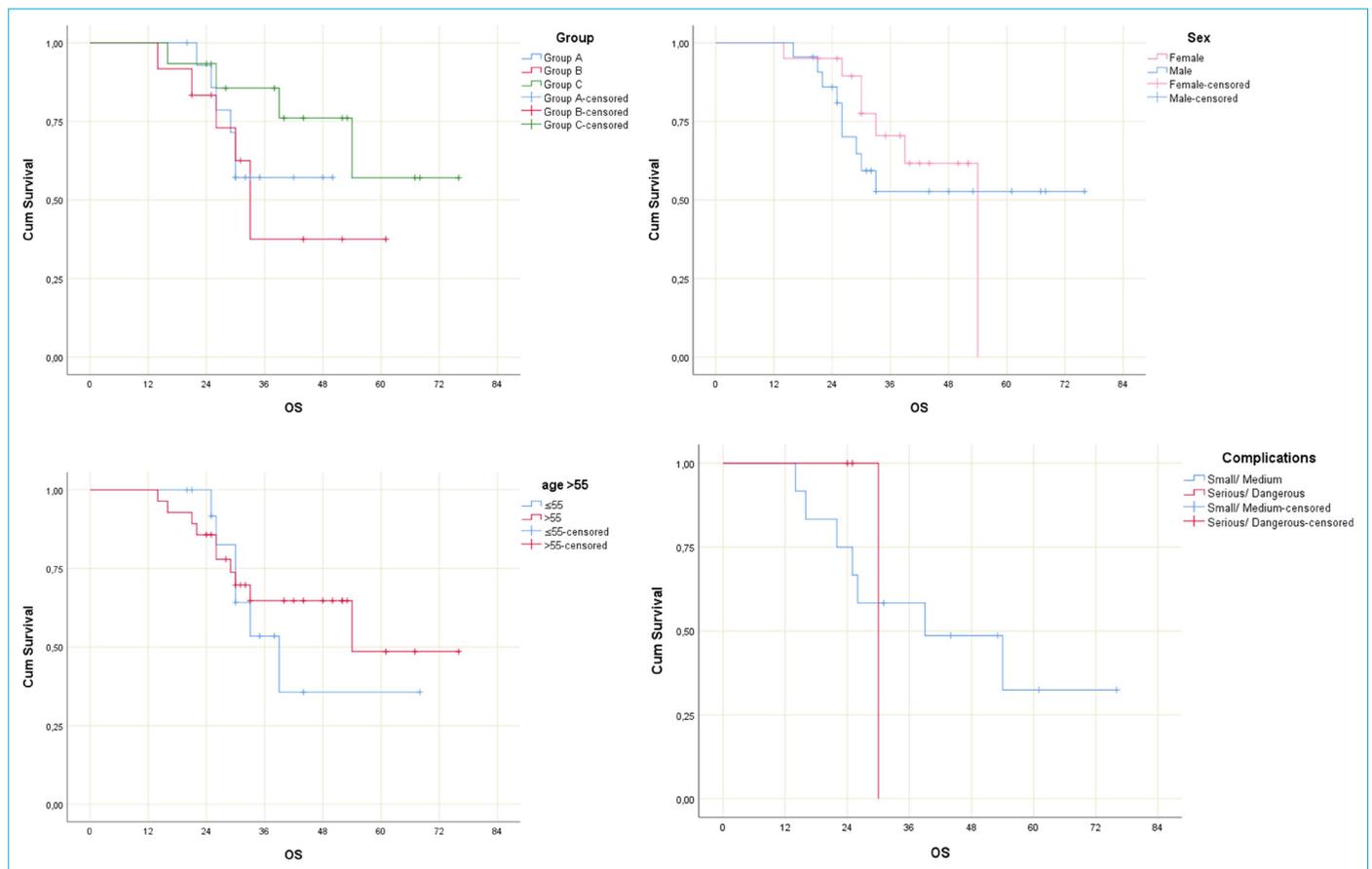
Survival curves showing factors affecting the OS are shown in Figure 1.

## PFS

Patients who underwent therapy A had a median PFS of 21 months (95% CI 29.1–36.9). For groups A and C, the median survival time could not be calculated because there was no time point at which the survival function took a value <50%. A log-rank test was conducted to determine if there were differences in the survival distribution for the different types of interventions. The survival distributions for the three interventions were not statistically significantly different;  $\chi^2(2) = 1.888$ ,  $p=0.389$ .

For males and females, the median PFS time could not be calculated because there was no time point at which the survival function took a value <50%. A log-rank test was conducted to determine if there were differences in the survival distribution for the sex groups. The survival distributions for the sex groups were not statistically significantly different;  $\chi^2(1) = 0.357$ ,  $p=0.550$ .

For both age groups, the median PFS time could not be calculated because there was no time point at which the survival function took a value <50%. A log-rank test was



**Figure 1.** Survival curves showing factors affecting the overall survival.

conducted to determine if there were differences in the survival distribution for the age groups. The survival distributions for the age groups were not statistically significantly different;  $\chi^2(1) = 0.455$ ,  $p=0.500$ .

Patients with small–medium complications had a median PFS of 18 months (95% CI 0–52) and patients with serious–dangerous complications had a median PFS of 14 months. A log-rank test was conducted to determine if there were differences in the survival distribution for the complication groups. The survival distributions for the complication groups were not statistically significantly different;  $\chi^2(1) = 0.059$ ,  $p=0.808$ .

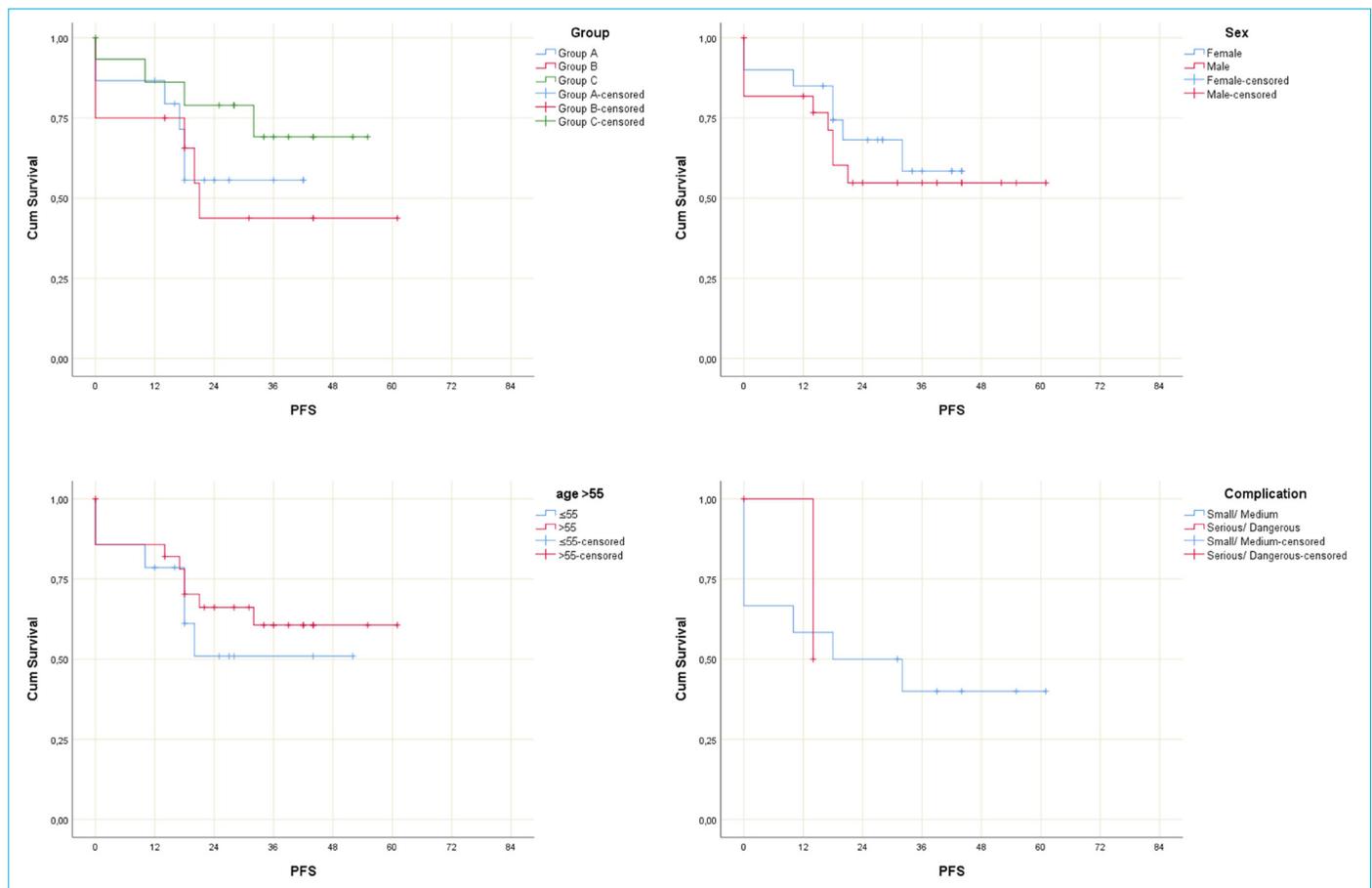
Survival curves showing factors affecting the OS are shown in Figure 2.

## Discussion

CRC is one of the most common forms of cancer and the second leading cause of cancer-related mortality in the Western world. Death from CRC is virtually always the consequence of metastatic spread to distant sites in the body, such as the liver, peritoneal cavity, and lungs. Patients with metastases in the peritoneal cavity (PM) have the worst prognosis.<sup>[1, 2]</sup>

In general, PM is underdiagnosed as detection with routine imaging protocols is difficult, because of its small size and limited contrast resolution in soft tissues.<sup>[3, 4]</sup> The true incidence of PM is therefore unclear, although it was reported to be as high as 40–80% in an autopsy series (5, 6) (Table 1). The development of PM in patients with CRC is often associated with a rapidly declining performance status, involving recurrent bowel obstruction, the formation of malignant ascites, visceral pain, and malnutrition (Table 1).<sup>[7]</sup> In most cases, this precludes surgery and systemic therapy, leaving only palliative care to ensure the best possible quality of life. When left untreated, the median OS of this patient group is ~5 months.<sup>[8]</sup> The benefit of systemic chemotherapy is dramatically reduced in the subgroup of CRC patients with PM<sup>[2, 9]</sup>, and their poor visualization complicates the assessment of their response to treatment. In the past decade, this has resulted in the active exclusion of patients with PM from clinical trials.<sup>[10]</sup> Taken together, CRC with PM is a common and highly aggressive but underdiagnosed and under-studied disease entity.

The evolutionary history of metastases is a topic of intense research in many types of cancer.<sup>[11–13]</sup> Models of tumor evolution describe the processes that lead to the generation



**Figure 2.** Survival curves showing factors affecting the progression-free survival.

of metastasis-competent clones in primary tumors, the timing of their dissemination, and the factors determining successful outgrowth at distant sites.

Furthermore, the PM-seeding entities are clusters of tumor cells that bud off from the primary tumor.<sup>[14]</sup> Cancer-associated fibroblasts within the peritoneal microenvironment may play an important role in the process of peritoneal seeding of cancer cells.<sup>[15]</sup>

Specific histological subtypes—in particular, mucinous adenocarcinoma and signet ring cell carcinoma—show a remarkable preference for metastasizing to the peritoneum. Even within the peritoneum, the requirements for success-

ful site-specific adaptation may be different depending on the site within the peritoneum, such as omental fat, diaphragm, and the surface of intra-abdominal organs. Processes governing site-specific adaptation (through whatever evolutionary mechanism) and (epi)genetic diversity within and between PM are likely to be highly relevant for the potential success of intraperitoneal therapies. The metabolic adaptation of PM to the fatty acid-rich microenvironment of the abdomen may create a targetable, generic, PM-specific vulnerability.<sup>[16]</sup>

Often, the intraperitoneal seeding is a progressive phenomenon which call “tumor cell entrapment” phenomenon.<sup>[17]</sup> In this case, microscopic not visible cells are en-

**Table 2.** Adverse events in the B groups

	Group A (n=15)	Group B (n=12)	Group C (n=15)
Nausea/Vomitins	-	1	1
Diarrhea	-	1	2
Thrombocytes	2	1	1
Renal toxicity	1	-	1
Liver dysf.	-	-	-

**Table 3.** Complications

	Group A (n=15)	Group B (n=12)	Group C (n=15)
Infection	2	1	4
Fistula	0	1	1
Pleural effusions	0	1	2
Delayed bowel moments	1	1	3

trapped in the wound-healing areas and with the presence of “trophic” factors due to healing are “recurrent” early at the microscopic level.

For all these reasons, the model of early locoregional intraperitoneal chemotherapy after surgery is an interesting idea. Many studies, especially on EPIC, are proposed in the postoperative period, with controversial results.

Our study tries to evaluate retrospectively the role of the second HIPEC on the 10<sup>th</sup> postoperative day after the initial procedure (CRS + HIPEC) and compares this approach with EPIC and the conventional approach. The role of HIPEC in the management of PM from CRC needs resolving, in addition to the increased temperature and the type of drugs used and the type of drugs used.

From the trials exploring the benefits of HIPEC, many questions arise concerning the drug, the temperature and the duration of the procedure. Future directions with clinical trials are underway to evaluate unanswered questions in the management of CRC PM.

One notable trial, CAIRO6, seeks to evaluate perioperative systemic chemotherapy and CRS-HIPEC compared to CRS-HIPEC alone in patients with upfront resectable PM. In the phase II portion of that study, the perioperative chemotherapy regimen appeared safe, although there were similar proportions of macroscopically complete CRS between study arms, perhaps suggesting a lack of benefit of preoperative therapy.<sup>[18]</sup> The results of the phase III portion are eagerly awaited.<sup>[19]</sup>

In addition, the GECOP-MMC trial is a phase IV randomized trial evaluating CRS alone compared to CRS-HIPEC with 90 min of Mitomycin-C (MMC).<sup>[20]</sup> Importantly, this trial will be limited to patients with a PCI 20 who undergo complete cytoreduction, and the primary outcome is 3-year peritoneal recurrence-free survival. A similar study was discussed at the Advanced Cancer Therapies 2022 Annual Meeting by the authors of PRODIGE 7. Together, these trials promise to advance our knowledge on the optimal role and sequence for both systemic therapy and CRS-HIPEC in patients with CRC PM.

What appears clear is that a more complete understanding of tumor biology is needed to better comprehend these conflicting data. Beyond pathological determinants of poor tumor biology, novel biomarkers, such as plasma circulating tumor DNA (ctDNA), promise to improve our detection of and treatment for CRC PM.<sup>[21]</sup> Preoperative ctDNA offers a potential avenue to improve selection, as the detection of ctDNA has been associated with reduced disease-free survival, potentially indicating undiagnosed systemic disease or an increased potential for metastatic spread.<sup>[22]</sup> Furthermore, postoperative ctDNA has been as-

sociated with decreased PFS.<sup>[23]</sup> Improved platforms such as these will inform future clinical trials, helping to select the most efficacious regimens to individualize cancer care for this complex patient population.

## Conclusion

In conclusion, colorectal PM is a clinical problem commonly encountered in practice, which requires evaluation and management at specialized centers by experienced doctors. The most important factor is the proper management selection. Our study shows that adjuvant bedside HIPEC 1 week after the initial CRS plus HIPEC is an ineffective strategy to reduce PM or recurrence and improve survival in patients with PM from CRC.

The important role of HIPEC was reevaluated after the PRODIGE 7 study, and we established the benefit and improve of survival in Low PCI patients and mitomycin as intraperitoneal drug administration.<sup>[24]</sup>

Recently, in the ESSO congress 2022, the T4 HIPEC trial in high-risk patients demonstrated improved survival. It is time to develop future randomized multicentric phase III trials to resolve criticisms and respond to potential survival benefits of HIPEC for CRC PM.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – J.S.; Design – J.S., D.F., D.K., N-J.S.; Supervision – J.S.; Materials – J.S., H.M., M.G.; Data collection &/or processing – J.S., D.V., T.M.; Analysis and/or interpretation – J.S., H.M., M.G.; Literature search – H.S., J-N.S.; Writing – H.S.; Critical review – J.S.

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