Ann Surg Oncol
https://doi.org/10.1245/s10434-023-14417-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Is Systemic Chemotherapy Useful in Patients Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Colorectal Peritoneal Metastases? A Propensity-Score Analysis

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ABSTRACT

Purpose. Multimodal treatment of colorectal (CRC) peritoneal metastases (PM) includes systemic chemotherapy (SC) and surgical cytoreduction (CRS), eventually with hyperthermic intraperitoneal chemotherapy (HIPEC), in select patients. Considering lack of clear guidelines, this study was designed to analyze the role of chemotherapy and its timing in patients treated with CRS-HIPEC.

Methods. Data from 13 Italian centers with PM expertise were collected by a collaborative group of the Italian Society of Surgical Oncology (SICO). Clinicopathological variables, SC use, and timing of administration were correlated with overall survival (OS), disease-free survival (DFS), and local (peritoneal) DFS (LDFS) after propensity-score (PS) weighting to reduce confounding factors.

Results. A total of 367 patients treated with CRS-HIPEC were included in the propensity-score weighting. Of the total patients, 19.9% did not receive chemotherapy within

First Received: 28 February 2023
Accepted: 25 September 2023

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Published online: 13 October 2023

6 months of surgery, 32.4% received chemotherapy before surgery (pregroup), 28.9% after (post), and 18.8% received both pre- and post-CRS-HIPEC treatment (peri). SC was preferentially administered to younger ($p = 0.02$) and node-positive ($p = 0.010$) patients. Preoperative SC is associated with increased rate of major complications (26.9 vs. 11.3%, $p = 0.0009$). After PS weighting, there were no differences in OS, DFS, or LDFS ($p = 0.56$, 0.50, and 0.17) between chemotherapy-treated and untreated patients. Considering SC timing, the post CRS-HIPEC group had a longer DFS and LDFS than the pre-group (median DFS 15.4 vs. 9.8 m, $p = 0.003$; median LDFS 26.3 vs. 15.8 m, $p = 0.026$).

Conclusions. In patients with CRC-PM treated with CRS-HIPEC, systemic chemotherapy was not associated with overall survival benefit. The adjuvant schedule was related to prolonged disease-free intervals. Additional, randomized studies are required to clarify the role and timing of systemic chemotherapy in this patient subset.

Colorectal cancer (CRC) is the third most prevalent neoplasm worldwide, with approximately 2 million new cases each year.[1] The peritoneum is the second most common site of CRC metastasis, presenting after colorectal curative surgery or at diagnosis in 5% of cases.[2]

Peritoneal metastasis (PM) is a poor prognostic factor, and patients with PM have a shorter life expectancy (progression-free and overall survival, OS), even when compared to stage IV patients with other metastatic sites.[3,4]

In the past, CRC-PM was considered incurable, and palliative chemotherapy was the only appropriate option; however, cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) is currently being offered to selected patients. Surgical treatment combined with systemic chemotherapy improves overall survival, resulting in a median OS of 40–43 months.[5–7]

In cases of resectable CRC-PM, the need for systemic chemotherapy or optimal regimens has not been fully determined. Systemic chemotherapy has been advocated as a strategy to prevent or delay recurrence due to the high recurrence rate after CRS-HIPEC (up to 40% in the first year).[8]

Chemotherapy can be administered either as a neoadjuvant treatment before CRS, as an adjuvant treatment after surgery, or as part of a perioperative schedule both before and after surgery.[9–11] In the absence of consensus, each chemotherapy regimen has both advantages (prevention of recurrence, treatment of undiagnosed hematogenous micrometastases, and possibly improvement in patient selection) and disadvantages (potential increase in postoperative complications, delay in surgery, and side effects).[10,12] This study was designed to analyze the role of systemic chemotherapy on the survival outcomes of CRC-PM patients treated with radical surgery and HIPEC by using a multicenter database of the Italian Society of Surgical Oncology (SICO).

MATERIALS AND METHODS

Study Design and Patients

Data from 13 Italian centers with PM expertise were collected by a collaborative group of the Italian Society of Surgical Oncology (SICO). All participating centers are SICO-accredited referral centers for the surgical treatment of patients with peritoneal metastases. The present study was approved by the Ethics Committee of the Veneto Institute of Oncology, IOV Padua, as the responsible center (No. 194/2019). All enrolled patients were treated in accordance with national guidelines for CRC and were selected for CRS-HIPEC after multidisciplinary discussion. Race and ethnicity data were not recorded. Surgical, preoperative, and postoperative treatments have been reported previously.[13]

Two distinct analyses were performed by dividing patients based on the time schedule of systemic chemotherapy. The first analysis evaluated two groups: the chemotherapy (SC) group receiving treatment within 6 months of CRS-HIPEC and the no-SC group. The second analysis categorized treated patients into three groups: pre-HIPEC chemotherapy, peri-HIPEC chemotherapy, and post-HIPEC chemotherapy, using a cutoff period of 6 months from CRS-HIPEC. Patients who received the last chemotherapy treatment 6 months before CRS-HIPEC (e.g., adjuvant after primary tumor resection in the case of metachronous PM) or started treatment 6 months after CRS-HIPEC were included in the "no chemotherapy" group in the first analysis and excluded from the second.

Outcomes

Overall survival (OS), disease-free survival (DFS), and local (peritoneal), disease-free survival (LDFS) were the primary endpoints assessed. Overall survival was defined as the time from HIPEC to the date of death due to any cause; DFS was the time from HIPEC to the date of a local or distant relapse or death; and LDFS was the time from HIPEC to the date of a local relapse. The last date of observation was used to censor patients who did not develop an event during the study period.

Statistical Analysis

Baseline characteristics of treatment groups were compared by using Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables. The median follow-up time was determined by using the reverse Kaplan-Meier estimator. Due to the exploratory nature of the study,

no formal hypothesis or power sample size calculation was undertaken.

Each patient's propensity score (PS), i.e., the probability that a given subject would be assigned to a treatment condition, was estimated by using a logistic regression model that incorporated all confounding factors thought to influence both treatment assignment and outcomes. Age at treatment, gender (male, female), PCI score (≤ 15, > 15), completeness of cytoreduction score (CC0, CC1), primary tumor localization (colon, rectum, nodal status [N0, N1, N2]), KRAS/BRAF mutation (wild-type, mutation), the presence of signet ring cells (SRC), presence of major complications, and clinical center were the variables included in the PS analysis.

To reduce variability, stabilized weights were calculated for each patient by using the propensity score.[14] Survival curves were generated by using the adjusted Kaplan-Meier method with inverse probability weights.[15,16] We assigned a weight of 1/propensity score to patients who did not receive SC and a weight of 1/(1–propensity score) to those who did receive SC.[17]

Hazard ratios (HR) and 95% confidence intervals (CI) were derived from weighted Cox proportional-hazards regression models, and a robust variance "sandwich" estimator was used to account for the weighted nature of the sample. The covariate balance was calculated by using standardized differences after propensity-score weighting, and covariates were considered well-balanced if the standardized differences were less than 0.1.[17]

To evaluate the strength of these results, multivariable Cox proportional-hazards regression models with treatment and all variables included in the PS analysis were fitted on the whole unweighted cohort and the adjusted HRs were compared with those obtained from the weighted procedure.

All statistical tests were two-tailed, with p-values < 0.05 considered statistically significant. RStudio (RStudio: Integrated Development for R. RStudio Inc., Boston, MA) was used to perform statistical analyses.

RESULTS

The study group comprised 367 patients with available and complete data for propensity-score weighting; the study group was selected from 437 cases gathered in a SICO collaborative database. The median year of surgical treatment (CRS-HIPEC) was 2015 (IQR 2013–2018), and 86.6% of patients were treated at seven high-volume centers (hospitals with more than 35 cases enrolled in the present study). Mean PCI was 9.5 (SD = 6.3), less than 15 in 83.1% of cases, and complete cytoreduction (no residual tumor, CC0) was achieved in 83.9% of cases; the remaining patients had minimal residual disease (<2.5 mm, CC1).

Patient demographics are reported in Table 1. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) alone was used in 73 patients (19.9%). In patients who received chemotherapy, SC was administered pre-CRS-HIPEC in 119 (cases 32.4%), post-CRS-HIPEC in 106 cases (28.9%), and peri-CRS-HIPEC in 69 cases (18.8%) (before and after surgery within 6 months). KRAS-mutated patients were 194 (46.1%) and BRAF mutated 25 (6.8%). The oxaliplatin-irinotecan combination was administered before CRS-HIPEC in the most recent cases (the median administration year was 2017 compared with 2015 for other regimens; p 0.04).

Single therapy (5-FU) was used in 12 (4.1%) cases, whereas the vast majority (239 patients, 81.8%) received a doublet regimen (Oxaliplatin or Irinotecan-based); triplet schedule (FOLFOXIRI) was administered in 33 patients (11.3%). Immunotherapy was used in two patients (0.7%). Target therapy with anti-VEGF was used in 109 cases (63.4%) and anti-EGFR in 46 cases (26.7%). The administration of regimens was similar, except for greater utilization of oxaliplatin-based therapy in the post-CRS-HIPEC group (p 0.03). Most cases received only one SC line, whereas 23.1% of patients received two or more lines of systemic chemotherapy before CRS-HIPEC.

The median follow-up time was 38.6 months (95% confidence interval [CI]: 35.2, 49.3). During the follow-up period, 280 patients had an event (local or distant relapse or death), 159 had a local relapse, and 161 died. Unadjusted patient characteristics were compared between treatment groups (Table 2). Chemotherapy was administered more frequently to younger patients (the median age of treated patients was 59 years compared with 62 years for untreated patients; p 0.02) and to patients with a positive nodal status (the pathological nodal status of the primary tumor was N2 in 43.9% in treated patients compared with 20.5% of untreated patients; p 0.001). There were differences in SC administration between clinical centers; a classification tree with a Gini splitting index was used (see *Additional Materials*) to classify and statistically determine the use of chemotherapy by the different centers. Ten institutions grouped as "high SC centers" used chemotherapy in 85.5% of cases (272/318) within 6 months of CRS-HIPEC compared with three "low SC centers," which administered chemotherapy only in 44.9% of cases (22/49); p 0.0001. "High SC centers" included seven high-volume hospitals; there were no differences in regimens between centers. Major postoperative complications (Clavien-Dindo 3/4) occurred in 18.7% of treated patients compared with 11.0% of chemo-naïve (p not significant). Considering timing of SC, complications had a quantitative SC dose-correlation (p 0.009), because the pre-CRS-HIPEC group had the highest complication rate (26.9%), followed by the perigroup (15.9%) and the postgroup (11.3%—the same complication rate of untreated patients; Table 2). Considering only severe complications, 28.3% are due to anastomotic leakage or perforation, 22.6%

TABLE 1 Patient demographics

	Pre-HIPEC SC (N = 119)	Post_HIPEC SC (N = 106)	Peri_HIPEC SC (N = 69)	No SC (N = 73)	Total (N = 367)
Center					
High SC	112 (94.1%)	94 (88.7%)	66 (95.7%)	46 (63.0%)	318 (86.6%)
Low SC	7 (5.9%)	12 (11.3%)	3 (4.3%)	27 (37.0%)	49 (13.4%)
Age (yr, median [IQR])	59 (51, 65)	59 (47.2, 66)	59 (51, 64)	62 (55, 68)	60 (50, 66)
Gender					
Male	64 (53.8%)	44 (41.5%)	37 (53.6%)	32 (43.8%)	177 (48.2%)
Female	55 (46.2%)	62 (58.5%)	32 (46.4%)	41 (56.2%)	190 (51.8%)
PCI					
≤15	92 (77.3%)	95 (89.6%)	59 (85.5%)	59 (80.8%)	305 (83.1%)
>15	27 (22.7%)	11 (10.4%)	10 (14.5%)	14 (19.2%)	62 (16.9%)
Median (IQR)	9.0 (5.0, 15.0)	7.0 (5.0, 12.0)	9.0 (5.0, 12.0)	8.0 (4.0, 13.0)	9.0 (5.0, 13.5)
Mean (SD)	10.3 (6.5)	8.6 (5.9)	9.7 (5.7)	9.4 (6.7)	9.5 (6.3)
CC grade					
0 (no residual)	93 (78.2%)	95 (89.6%)	56 (81.2%)	64 (87.7%)	308 (83.9%)
1 (<2.5 mm)	26 (21.8%)	11 (10.4%)	13 (18.8%)	9 (12.3%)	59 (16.1%)
Primary tumor					
Colon	111 (93.3%)	83 (78.3%)	59 (85.5%)	62 (84.9%)	315 (85.8%)
Rectum	8 (6.7%)	23 (21.7%)	10 (14.5%)	11 (15.1%)	52 (14.2%)
Grading					
G1	3 (2.5%)	15 (14.2%)	3 (4.3%)	2 (2.7%)	23 (6.3%)
G2	61 (51.3%)	42 (39.6%)	33 (47.8%)	35 (47.9%)	171 (46.6%)
G3	47 (39.5%)	39 (36.8%)	30 (43.5%)	32 (43.8%)	148 (40.3%)
Missing	8 (6.7%)	10 (9.4%)	3 (4.3%)	4 (5.5%)	25 (6.8%)
KRAS or BRAF mutation					
Wild-type	51 (42.9%)	61 (57.5%)	31 (44.9%)	30 (41.1%)	173 (47.1%)
Mutated	68 (57.1%)	45 (42.5%)	38 (55.1%)	43 (58.9%)	194 (52.9%)
SRC histology					
No	119 (100.0%)	100 (94.3%)	68 (98.6%)	71 (97.3%)	358 (97.5%)
Yes	0 (0.0%)	6 (5.7%)	1 (1.4%)	2 (2.7%)	9 (2.5%)
Nodal status					
N0	36 (30.3%)	24 (22.6%)	22 (31.9%)	30 (41.1%)	112 (30.5%)
N1	38 (31.9%)	28 (26.4%)	17 (24.6%)	28 (38.4%)	111 (30.2%)
N2	45 (37.8%)	54 (50.9%)	30 (43.5%)	15 (20.5%)	144 (39.2%)
SC regimen					
Single-agent (5-FU)	2 (1.7%)	6 (5.7%)	4 (5.9%)		12 (4.1%)
Doublet	91 (77.1%)	94 (88.7%)	54 (79.4%)		239 (81.8%)
Oxaliplatin-based	41 (34.7%)	64 (60.4%)	27 (39.7%)		132 (45.2%)
Irinotecan-based	50 (42.4%)	30 (28.3%)	27 (39.7%)		107 (36.6%)
Triplet (FOLFOXIRI)	20 (16.9%)	4 (3.8%)	9 (13.2%)		33 (11.3%)
Immuno-therapy	1 (0.8%)	0 (0.0%)	1 (1.5%)		2 (0.7%)
Other	4 (3.4%)	2 (1.9%)	0 (0.0%)		6 (2.1%)
Missing	1		1		2
SC targeted therapy					
AntiVEGF	61 (67.0%)	12 (46.2%)	36 (65.5%)		109 (63.4%)
AntiEGFR	26 (28.6%)	4 (15.4%)	16 (29.1%)		46 (26.7%)
Other	4 (4.4%)	10 (38.5%)	3 (5.5%)		17 (9.9%)
Missing	28	80	14		122
Metachronous interval					
(mo, median (IQR))	24.9 (15.0, 42.1)	17.1 (11.8, 24.4)	23.4 (17.4, 29.8)	22.2 (14.8, 32.1)	21.4 (14.4, 32.4)

High/Low SC center refers to chemotherapy administration rate according to clinical practice (see text)

PCI peritoneal cancer index, *CC* completeness of cytoreduction, *SRC* signet ring cell, *SC* systemic chemotherapy, *IQR* interquartile range

TABLE 2 Propensity-score weighting

	SC (N = 294)	No SC (N = 73)	*p*	Unweighted SMD	PS weighted SMD	Pre-HIPEC SC (N = 119)	Post-HIPEC SC (N = 106)	Peri-HIPEC SC (N = 69)	*p*	Unweighted SMD	PS weighted SMD
Center											
High SC	272 (92.5%)	46 (63.0%)	***<0.001***	0.755	0.002	112 (94.1%)	94 (88.7%)	66 (95.7%)	*0.1590*	0.270	0.075
Low SC	22 (7.5%)	27 (37.0%)				7 (5.9%)	12 (11.3%)	3 (4.3%)			
Age (yr, median (IQR))	59 (50–65)	62 (55–68)	***0.0190***	0.306	0.060	59 (51, 65)	59 (48, 66)	59 (51, 64)	*0.9530*	0.078	0.030
Gender											
Male	145 (49.3%)	32 (43.8%)	*0.4010*	0.110	0.042	64 (53.8%)	44 (41.5%)	37 (53.6%)	*0.1320*	0.246	0.098
Female	149 (50.7%)	41 (56.2%)				55 (46.2%)	62 (58.5%)	32 (46.4%)			
PCI											
≤15	246 (83.7%)	59 (80.8%)	*0.5610*	0.074	0.090	92 (77.3%)	95 (89.6%)	59 (85.5%)	***0.0400***	0.339	0.106
>15	48 (16.3%)	14 (19.2%)				27 (22.7%)	11 (10.4%)	10 (14.5%)			
CC grade											
0	244 (83.0%)	64 (87.7%)	*0.3300*	0.132	0.161	93 (78.2%)	95 (89.6%)	56 (81.2%)	*0.0660*	0.306	0.105
1	50 (17.0%)	9 (12.3%)				26 (21.8%)	11 (10.4%)	13 (18.8%)			
Primary tumor											
Colon	253 (86.1%)	62 (84.9%)	*0.8050*	0.032	0.001	111 (93.3%)	83 (78.3%)	59 (85.5%)	***0.0050***	0.432	0.019
Rectum	41 (13.9%)	11 (15.1%)				8 (6.7%)	23 (21.7%)	10 (14.5%)			
KRAS or BRAF mutation											
Wild-type	143 (48.6%)	30 (41.1%)	*0.2480*	0.151	0.078	51 (42.9%)	61 (57.5%)	31 (44.9%)	*0.0690*	0.295	0.014
Mutated	151 (51.4%)	43 (58.9%)				68 (57.1%)	45 (42.5%)	38 (55.1%)			
SRC histology											
No	287 (97.6%)	71 (97.3%)	*0.8590*	0.023	0.065	119 (100.0%)	100 (94.3%)	68 (98.6%)	***0.0180***	0.375	0.206
Yes	7 (2.4%)	2 (2.7%)				0 (0.0%)	6 (5.7%)	1 (1.4%)			
Nodal status											
N0	82 (27.9%)	30 (41.1%)	***0.0010***			36 (30.3%)	24 (22.6%)	22 (31.9%)	*0.2970*		
N1	83 (28.2%)	28 (38.4%)		0.215	0.096	38 (31.9%)	28 (26.4%)	17 (24.6%)		0.163	0.100
N2	129 (43.9%)	15 (20.5%)		0.514	0.142	45 (37.8%)	54 (50.9%)	30 (43.5%)		0.265	0.089
Major complications											
No	239 (81.3%)	65 (89.0%)	*0.1160*	0.218	0.201	87 (73.1%)	94 (88.7%)	58 (84.1%)	***0.0009***	0.409	0.040
Yes	55 (18.7%)	8 (11.0%)				32 (26.9%)	12 (11.3%)	11 (15.9%)			

High/Low SC center refers to chemotherapy administration rate according to clinical practice (*see text*)

Major complications: Clavien-Dindo grade 3/4

SC systemic chemotherapy, *PCI* peritoneal cancer index, *CC* completeness of cytoreduction, *SRC* signet ring cell, *IQR* interquartile range, *SMD* standardized mean difference, *PS* propensity score

abdominal bleeding, 9.4% infections, and 39.7% other medical (cardiac or cerebral infarction, thrombosis, pancreatitis, pulmonary emblosim, bowel obstruction). Bleeding was observed in 42.1% of complicated cases in pregroup, compared with 15.8% of peri- with no cases in postgroup; leakage/perforation and infections rates are similar among SC groups.

The groups were well-balanced after propensity-score (PS) weighting was applied. Almost all covariates resulted in a standardized median difference (SMD) of <10%, with a slight residual imbalance for N2 nodal status (SMD = 0.142) and major morbidity (SMD = 0.201) in systemic chemotherapy versus no-SC treatment and signet ring cells (SMD = 0.206) in SC timing analysis (Table 2).

After PS weighting, there were no differences between the SC and no-SC groups in median overall, disease-free, and local disease-free survival (Fig. 1). The median overall survival was 38.8 months (95% CI 32.7, 47.9) in the SC group and 55.0 months in the no-SC group (95% CI 22.1, NE); *p* 0.56 (Table 3). The median disease-free survival was 12.9 months (95% CI 11.2, 14.0) in treated patients and 16.0 months (95% CI 11.0, 22.9) in untreated patients; *p* 0.50; the median local disease-free survival was 20.4 months (95% CI 15.9, 27.5) in treated patients in the SC group and 25.0 months (95% CI 16.0, NE) in untreated patients (*p* 0.17; Table 3).

The timing of chemotherapy administration did not correlate with survival in patients who received chemotherapy with propensity score adjustment, with the exception of the post-CRS-HIPEC schedule increasing both disease-free survival (15.4 months (95% CI 13.1, 18.2) compared with 9.8 months (95% CI 7.5, 11.6) for the pre-group; HR 0.6, p 0.003) and local disease-free survival (26.3 months (95% CI 16.6, 49.7) compared with 15.8 months (95% CI 11.2, 24.1) for the pre-group (HR 0.6, *p* 0.026). The median overall survival was 38.9 months (95% CI 29.9, 47.9) in the pre-CRS-HIPEC group, 43.1 months (95% CI 30.3, 57.3) in the peri-CRS-HIPEC group, and 37.9 months (95% CI 28.0, 54.3) in the post-CRS-HIPEC group (*p* 0.71 and 0.88) using the pre-group as the reference (Table 3).

DISCUSSION

Historically, patients with untreated peritoneal metastases of colorectal origin had a poor prognosis of 6-9 months or less.[3] Using modern chemotherapy and targeted agents, the prognosis for stage IV CRC can be improved to up to 20-24 months; however, patients with PM still have a significantly worse survival (16.3 months) than patients with isolated nonperitoneal sites (liver, lungs, and lymph nodes).[4] Most patients are still treated with palliative systemic chemotherapy due to poor functional status, technical contraindications (e.g., nonresectable lesions), or limited access to a cytoreductive surgery center.[3,18]

Consistent data on the surgical treatment of CRC-PM reveals that CRS+/-HIPEC provides good long-term survival (approximately 40 months) in select patients with limited disease (PCI less than 15/20) and when complete cytoreduction can be obtained.[19,20]

Patients referred to a center with PM management expertise can be treated with different chemotherapy strategies (pre- or perioperative) or upfront surgery, eventually followed by adjuvant chemotherapy (postoperative). Nevertheless, optimal chemotherapy regimens and strategies are still a topic of debate.[21] As for liver-only CRC metastatic patients, the use of perioperative chemotherapy remains controversial due to the absence of a proven survival benefit (increase in DFS with similar OS).[22,23]

Preoperative chemotherapy could reduce the burden of peritoneal disease, downstaging PCI and, therefore, allowing for higher rates of complete cytoreduction with limited surgery extension and possibly increasing survival.[10,24] In addition, preoperative SC could also be used to treat hematogenous micrometastasis, thus preventing early extraperitoneal recurrence.[25,26]

Given that CRS-HIPEC is a demanding procedure, chemotherapy before surgery also could improve patient selection by excluding fast-progressing patients. Conversely, if the response to SC is seen as a contraindication rather than a negative prognostic indicator, this may result in patient undertreatment, excluding a potentially curative approach in a progressing disease that is still resectable. Therefore, the multidisciplinary board decision process should carefully evaluate the response to chemotherapy as a surrogate for the biological behavior of the tumor.[27,28]

Preoperative SC is not without potential risks related to toxicity and worsening of functional status with reduced access to CRS-HIPEC treatment or a potential increase in the surgical complication rate (as with bleeding and anti-VEGF therapy).[12,29–31]

The scientific literature about the efficacy of neoadjuvant chemotherapy is still controversial. Three old series reported a detrimental effect of pre-operative SC on OS, whereas postoperative SC increased OS.[11,32] Four retrospective series have reported more recent data favoring preoperative use,[10,33–35] but only one case demonstrated a survival advantage in multivariate analysis.[36]

Two independent, systematic reviews were conducted in 2017, both reporting the lack of strong evidence of pre-, post-, or perioperative SC efficacy.[9,37] Rovers included 11 studies (1708 patients) on SC, suggesting a potential role for pre- and perioperative systemic therapy and questioning postoperative therapy as standard care.

Waite included 16 studies, reporting no advantage of preoperative treatment and limited evidence of improvement in

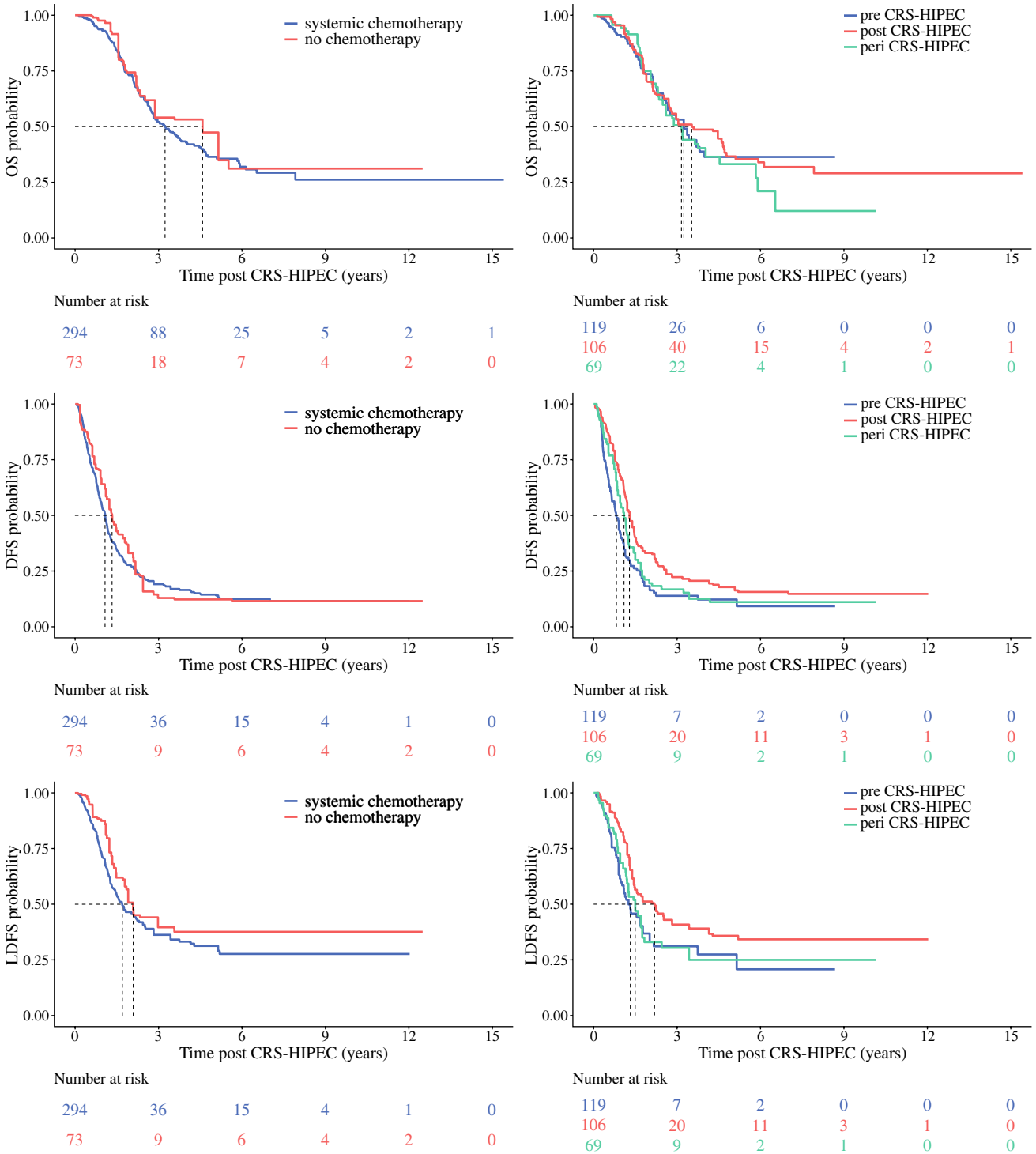

FIG. 1 Survival curves after propensity score weighting; *OS* overall survival; *DFS* disease-free survival; *LDFS* local (peritoneal) disease-free survival

OS with postoperative (weak evidence suggesting that adjuvant chemotherapy is associated with longer OS, especially after incomplete cytoreduction).

On this topic, one randomized, controlled trial (COMBATAC) evaluating perioperative FOLFOX/FOLFIRI plus Cetuximab versus CRS-HIPEC alone was closed in 2014 due to insufficient accrual of patients. With obvious limitations, the results indicate the feasibility and safety of the perioperative strategy.[30]

TABLE 3 Unadjusted and propensity score-weighted survival according to the chemotherapy regimen and timing

		Unweighted			PS weighted			Multivariable	
		Median (95% CI)	HR (95% CI)	*p*	Median (95% CI)	HR (95% CI)	*p*	HR (95% CI)	*p*
Overall survival	SC	38.4 (32.4, 47.9)	*Ref*		38.8 (32.7, 47.9)	*Ref*		*Ref*	
	No SC	55.0 (27.9, -)	0.77 (0.50, 1.20)	*0.2500*	55.0 (21.5, -)	0.85 (0.49, 1.46)	*0.5570*	0.85 (0.52, 1.40)	*0.5300*
Disease-free survival	SC	12.9 (11.2, 13.9)	*Ref*		12.9 (11.2, 14.0)	*Ref*		*Ref*	
	No SC	17.6 (13.2, 22.1)	0.75 (0.55, 1.02)	*0.0644*	16.0 (11.0, 22.9)	0.89 (0.63, 1.26)	*0.5020*	0.79 (0.56, 1.11)	*0.1710*
Local disease-free survival	SC	19.2 (15.8, 26.0)	*Ref*		20.4 (16.6, 27.5)	*Ref*		*Ref*	
	No SC	25.1 (17.7, -)	0.74 (0.49, 1.11)	*0.1420*	25.0 (17.6, -)	0.73 (0.46, 1.15)	*0.1720*	0.71 (0.45, 1.13)	*0.1480*
Overall survival	Pre-HIPEC	35.5 (27.5, 45.6)	*Ref*		38.9 (29.9, 47.9)	*Ref*		*Ref*	
	Post-HIPEC	43.1 (32.4, 57.3)	0.82 (0.55, 1.21)	*0.3220*	43.1 (30.3, 57.3)	0.92 (0.58, 1.45)	*0.7080*	0.76 (0.49, 1.19)	*0.2330*
	Peri-HIPEC	37.9 (28.0, 70.0)	0.90 (0.58, 1.40)	*0.6490*	37.9 (28.0, 54.3)	1.03 (0.65, 1.64)	*0.8840*	0.79 (0.51, 1.24)	*0.3100*
Disease-free survival	Pre-HIPEC	9.2 (6.8, 11.2)	*Ref*		9.8 (7.5, 11.6)	*Ref*		*Ref*	
	Post-HIPEC	15.7 (13.4, 20.5)	0.55 (0.41, 0.75)	*0.0001*	15.4 (13.1, 18.2)	0.60 (0.43, 0.84)	*0.0030*	0.57 (0.40, 0.79)	*0.0001*
	Peri-HIPEC	13.8 (10.1, 15.2)	0.74 (0.53, 1.04)	*0.0795*	13.1 (10.1, 15.2)	0.77 (0.54, 1.11)	*0.1680*	0.80 (0.56, 1.13)	*0.2110*
Local disease-free survival	Pre-HIPEC	15.1 (11.2, 21.1)	*Ref*		15.8 (11.2, 24.1)	*Ref*		*Ref*	
	Post-HIPEC	30.0 (19.0, 51.3)	0.54 (0.36, 0.81)	*0.0032*	26.3 (16.6, 49.7)	0.60 (0.39, 0.94)	*0.0259*	0.58 (0.37, 0.91)	*0.0190*
	Peri-HIPEC	17.2 (13.9, 21.9)	0.83 (0.54, 1.29)	*0.4115*	17.9 (13.8, 21.9)	0.87 (0.54, 1.39)	*0.5689*	0.94 (0.59, 1.48)	*0.7810*

SC systemic chemotherapy, *Pre-HIPEC* SC administration ended within 6 months of CRS-HIPEC, *Post-HIPEC* SC administration started within 6 months after CRS-HIPEC, *Peri-HIPEC* SC administration before and after CRS-HIPEC, *PS* propensity score, *SMD* standardized mean difference

Another RCT (CAIRO6) with a similar design (experimental arm: perioperative SC, control arm: CRS-HIPEC only) commenced in 2017. Preliminary results demonstrated that perioperative SC could be safely added to CRS-HIPEC with similar surgical radicality and postoperative complications. Notably, 38% of pretreated patients had a major pathological response.[38]

Cashin et al. used a large, retrospective series of 778 patients matched with propensity score-analysis and reported a survival advantage (OS and relapse-free survival) in the adjuvant setting; however, neoadjuvant SC administration resulted in comparable survival.[39]

In the absence of shared guidelines, centers adopt different approaches that reflect their organization's and clinicians' paradigms. In our series, the vast majority of patients (80.6%) had been administered chemotherapy within 6 months of CRS-HIPEC; a preoperative schedule (only pre- or perioperative administration) was preferred for 77.5% of treated patients. High-volume centers tend to treat more patients (82.9% of cases) than low-volume centers, where only 50% of patients are offered SC within 6 months of surgery (p 0.001). This may be the result of the varying perspectives of clinicians about center organizational issues (e.g., easier access to chemotherapy due to close collaboration between surgeons and oncologists, where chemotherapy is a "bridge" to surgery during the waiting list period). Neverthless, use of systemic chemotherapy in the neoadjuvant setting should be carefully evaluated considering the increased risk of major postoperative complications. There were no differences across clinical centers regarding the regimens used. The preference for the oxaliplatin-irinotecan combination in more recent cases (median administration year 2017 vs. 2015; p 0.04) may represent a shift in therapy following

the publication of the subgroup analysis from the TRIBE trial.[40]

All these disparities have been eliminated with the use of propensity score weighting, making the groups (SC vs. no-SC and pre- vs. post- vs. perioperative schedule) in the analysis comparable. The only parameters with a slight imbalance (SMD greater than 10%) are nodal status and major morbidity in SC versus no-SC and signet ring cells in SC timing analysis. This was attributed to the low prevalence of variables (e.g., 2.5% of patients have SRC), because the casual distribution of a small number of patients can lead to unbalanced standardized mean differences in PS weighting. Nevertheless, the method used can be considered reliable and robust, because unbalanced SMD variables are few with values lower than 20%; in fact, we used very restrictive criteria (SMD < 10%), even though the literature reports SMD values up to 25% as the cutoff for acceptable standardized biases.[41] In addition, multivariable Cox proportional-hazards regression models have been performed to validate the results obtained (Tables S2, S3, Supplementary Materials).

With a large and homogeneously treated sample of patients, there is no conclusive evidence of chemotherapy's advantage, which is consistent with the results on survival rates in the literature. Even after propensity score weighting to reduce the effect of known prognostic factors (such as PCI, completeness of surgery, nodal status, KRAS/BRAF mutational status, and presence of grading/signet ring cells), there is no improvement in overall, disease-free, or peritoneal disease-free survival. Furthermore, a sub-analysis on the timing of SC administration failed to demonstrate a clear preferential schedule (similar OS and LDFS for pre-, post-, and peri-; OS 38.9, 42.3, and 37.9 months and LDFS 44.8, 49.7, and 20.4 months, respectively), whereas preoperative schedule is related with increased risk of major surgical complications (26.9% vs. 11.3%, p 0.0009). We observed a higher DFS and LDFS survival in patients treated with postoperative SC (15.4 vs. 9.4 months, p 0.005; and 26.3 vs. 15.8 months, p 0.026), as reported in a recent, large, retrospective study.[39] This advantage could be explained by the fact that in the postoperative schedule, chemotherapy ended 4–6 months after surgery (and 2–3 months in the peri group); therefore, the disease-free period from the end of treatment (including SC) could be considered comparable to that of the pretreated group.

One of this study's limitations is its retrospective design with data acquired from hospital records.

Another point that can be addressed is the low proportion of patients treated with checkpoint inhibitors (0.2% vs. 14.1% of patients with microsatellite instability); specific therapy for this subset of patients could have improved survival and possibly altered the analysis. Considering this, the population of the study is quite recent; nevertheless, medical oncology is a rapidly evolving field with new prospectives and evidence emerging in the very last years (e.g., sidedness approaches and improved treatment selection), which could have changed survival outcomes.

Another limitation of this type of analysis, especially when considering overall survival, is that CRC stage IV patients receive several lines of chemotherapy during their oncological history, including systemic SC or repeated CRS at recurrence following CRS-HIPEC. Therefore, OS reflects a multimodal and iterative approach that can hide the perioperative SC administration effect; disease-free and local (peritoneal), disease-free survival may potentially be a more reliable indicator for evaluating the role of SC.

Despite these limitations, this study incorporates a large series of homogeneously treated peritoneal-only stage IV patients with CRC-PM. Subgroups of patients (SC administration and timing) used in the analysis have considerable sample sizes. Also, robust statistics were compiled by using propensity-score weighting to mitigate confounding factors.

Additional prospective or randomized studies are needed to clarify the role of systemic chemotherapy and the optimal administration or timing schedules in patients with CRC-PM who are candidates for cytoreductive surgery.

CONCLUSIONS

In CRC-PM patients who are eligible for CRS, systemic chemotherapy and perioperative timing do not appear to provide a clear survival advantage, with the exception of longer DFS and LDFS when chemotherapy is administerd after surgery. Considering study limitations, additional randomized studies are required to define the role and timing of systemic chemotherapy in this subset of patients.

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at https://doi.org/10.1245/s10434-023-14417-z.

ACKNOWLEDGMENTS The authors thank Francesca Bergamo, MD (Medical Oncology, Veneto Institute of Oncology IOV-IRCCS) for critical reviewing, advice, and suggestions.

AUTHOR CONTRIBUTIONS Conceptualization: all authors; data curation: all authors; methodology: PDB, MT, AS; writing—original draft preparation: MT, AS; review and editing: all authors. All authors have made substantial contributions to the conception of data or the analysis and interpretation of data and drafting the work or revising it critically for intellectual content. All authors have read and agreed to the published version of the manuscript.

FUNDING No funds, grants, or other support were received.

DISCLOSURES The authors have no conflicts of interest or financial ties to disclose.

ETHICS APPROVAL This study was approved by the Ethics Committee of the Veneto Institute of Oncology IOV-IRCCS (No. 194/2019).

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