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Colorectal Peritoneal Metastases Treated by Perioperative Systemic Chemotherapy and Cytoreductive Surgery With or Without Mitomycin C-Based HIPEC: A Comparative Study Using the Peritoneal Surface Disease Severity Score (PSDSS)

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ABSTRACT

Background. The Prodige-7 trial has questioned the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal metastases from colorectal cancer (CRC-PM).

Patients and Methods. We compared a prospectively collected group of 48 patients undergoing oxaliplatin/irinotecan-based perioperative systemic chemotherapy (s-CT) with targeted agents, and cytoreductive surgery (CRS) (no-HIPEC group) with 48 controls undergoing the same perioperative s-CT and CRS/HIPEC (HIPEC group). Patients were matched (1:1) according to the Peritoneal Surface Disease Severity Score, completeness of cytoreduction, history of extraperitoneal disease (EPD), and Peritoneal Cancer Index.

Results. The groups were comparable, except for a higher number of patients in the HIPEC group with World Health Organization performance status 0, pN2 stage primary tumor, and treated with preoperative s-CT. Forty-one patients in the no-HIPEC group and 43 patients in the HIPEC group had optimal comprehensive treatment ($P = 0.759$), defined as complete cytoreduction of PM and margin-negative EPD resection. Median follow-up was 31.6 months in the no-HIPEC group and 39.9 months in the HIPEC group. Median overall survival was 39.3 months in the no-HIPEC group and 34.8 months in the HIPEC group ($P = 0.702$). In the two groups, severe morbidity occurred in 14 (29.2%) and 13 (27.1%) patients, respectively ($P = 1.000$), with no operative deaths. On multivariate analysis, left-sided primary and curative treatment independently correlated with better survival while HIPEC did not (hazard ratio 0.73; 95% confidence interval 0.47–1.15; $P = 0.178$).

Conclusions. Our results confirmed that, in selected patients, perioperative s-CT and surgical treatment of CRC-PM resulted in unexpectedly high survival rates. Mitomycin C-based HIPEC did not increase morbidity but did not impact prognosis.

Colorectal cancer (CRC) is the third most common tumor worldwide, and peritoneal metastases (PM) are a leading cause of cancer-related death, after liver and, probably, lung metastases.[1,2] CRC-PM is often diagnosed at an advanced stage, due to lack of symptoms and current limitations of imaging studies to detect small-volume peritoneal disease. Also, it is reported that modern systemic chemotherapy (s-CT) and targeted agents do not show the same benefit in CRC-PM as in nonperitoneal metastases.[3–5] Surgical resection of PM has traditionally been regarded as an intrinsically incomplete procedure. More recently, aggressive cytoreductive surgery (CRS) has increasingly been accepted as a curative-intent approach, based on the standardization of peritonectomy procedures and awareness of PM as a locoregional disease stage. To control the microscopic residual tumor, CRS is commonly associated with systemic and intraperitoneal chemotherapy, mostly in

the form of hyperthermic intraperitoneal chemotherapy (HIPEC).[3] It has been reported that this comprehensive strategy results in survival improvements over historical controls, as well as a successful randomized trial.[6–9]

The adjunctive contribution of HIPEC over complete CRS has been demonstrated in animal models and, in humans, in gastric and ovarian PM.[10–12] On the contrary, the recent randomized trial Prodige-7 failed to demonstrate a survival difference between patients with CRC-PM treated by CRS and s-CT with or without oxaliplatin-based HIPEC.[13] Possible explanations for this lack of benefit are the surprisingly high survival rates in controls receiving no HIPEC and oxaliplatin efficacy issues.[14]

In 2013, we started to use perioperative s-CT and CRS (with no HIPEC) to treat patients with CRC-PM who either refused or were borderline candidates for HIPEC, based on literature data.[15–19] The present study compares the characteristics, operative outcomes, and long-term survival of these patients with individually matched controls undergoing s-CT, CRS, and mitomycin C-based HIPEC in our center during the same period. Patients were matched using the Peritoneal Surface Disease Severity Score (PSDSS), which was recently reported to be an independent prognostic predictor for CRC-PM.[20–22]

PATIENTS AND METHODS

Data for the present analysis were retrieved from a prospective database. All patients were treated according to protocols approved by the Institutional Ethics Committee in accordance with the principles of Helsinki Declaration, and signed informed consent forms.

Perioperative s-CT and Cytoreductive Surgery (No-HIPEC Group)

Between January 2012 and December 2018, 64 patients with pathologically confirmed CRC-PM were enrolled in a comprehensive protocol involving perioperative s-CT and complete CRS, according to the following criteria: age $\leq$ 75 years, WHO performance score $\leq$ 2, no significant comorbidities, preoperative imaging showing slight to moderate peritoneal involvement amenable to potentially complete CRS, and no disease progression under s-CT.[23] Indications to resect EPD were individually tailored, based on low volume of EPD and objective response or stabilization after s-CT, as reported elsewhere.[24] Patients intraoperatively deemed not amenable to significant cytoreduction and/or not able to complete the assigned s-CT were included in this study on an intention-to-treat basis.

All patients underwent intensive clinical–radiological work-up including clinical history, physical examination, colonoscopy, thoracic–abdominal–pelvic contrast-enhanced computed tomography (CT) scan, serum markers [carcinoembryonic antigen (CEA), cancer antigen (CA) 19.9], and fluorodeoxyglucose positron emission tomography. Each patient was discussed at multidisciplinary meetings.

Operative Treatment

Indications for perioperative s-CT were given according to international guidelines, based on clinical condition and response to previous therapies.[25] The choice between preoperative s-CT, postoperative s-CT, or both, was left to medical oncology staff. Cytoreductive surgery was aimed at removing all visible tumor, by means of peritonectomy procedures and visceral resections, as needed.[26] Colon resections for primary tumors were performed according to the oncologic principles of adequate lymphadenectomy.

The Peritoneal Cancer Index (PCI) was used intraoperatively to score peritoneal involvement. In the PCI, lesion size is rated from 0 to 3 (no tumor, $\leq$ 5 mm, > 5–50 mm, or > 50 mm) in 13 abdominal–pelvic regions, resulting in a numeric score (PCI 0–39).[27] The completeness of the cytoreduction (CCR) of peritoneal disease was classified as macroscopically complete (CCR-0), nearly complete with residual disease $\leq$ 2.5 mm in any region (CCR-1), or grossly incomplete with residual disease > 2.5 mm (CCR-2).[27] Surgical treatment was considered optimal if CCR-0/1 was achieved, and EPD was resected with negative margins, either simultaneously with PM or by staged procedures.

Tumors were staged according to the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) classification, 7th edition. The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 were used to score complications occurring within the first 60 postoperative days.[28] All patients underwent postoperative follow-up, consisting of physical examination, thoracic–abdominal CT scan, and marker measurements performed 3-monthly during the first 2 years and 6-monthly thereafter.

Perioperative S-CT and Cytoreductive Surgery with HIPEC (HIPEC Group)

Seventy-six patients underwent CRS/HIPEC during the same period. Preoperative work-up, perioperative s-CT, CRS procedures, and postoperative follow-up were performed as in the no-HIPEC group. Closed-abdomen HIPEC was performed for 60 min at 42.5 °C with mitomycin C

(3.3 mg/m²/L) plus cisplatin (25 mL/m²/L), or mitomycin C alone (35 mg/m²). Perfusate volume was 4–6 L. Standard dose reductions were applied.[26]

Statistics

Patients were individually matched by PSDSS, CCR score, history of EPD, and PCI (± 3). The PSDSS has been described elsewhere.[18,19,29] Briefly, PSDSS is estimated on the basis of symptom severity (absent: 0 points; mild: 1 point; moderate: 6 points), PCI (1–10: 1 point; 11–20: 3 points; > 20: 7 points), and primary tumor histopathology (well/moderately differentiated, pN0: 1 point; well/moderately differentiated, pN1/2: 3 points; poorly differentiated: 9 points). Stages are defined as follows: I: 2–3 points; II: 4–7 points; III: 8–10 points; IV: > 10 points.[20] The investigators were unaware of patient outcomes during the matching process.

Baseline differences between groups were assessed by Student t test, Chi squared test, or Fisher's exact test, as appropriate. The primary study end-point was overall survival, calculated by the Kaplan–Meier method from surgery to death or last follow-up date. Differences in survival distribution were assessed by two-tailed log-rank test. Continuous variables were categorized into two classes by using their mean value as cutoff. To exclude any residual selection bias, multivariate analysis of factors with univariate P value < 0.1 was performed using the Cox proportional hazard model. All patients in both the HIPEC and no-HIPEC groups were included in the multivariate analysis. HIPEC was forced into the model as the main variable of interest. P values < 0.05 were considered significant. All statistical analyses were conducted using SPSS, version 20.0.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Forty-eight patients from the HIPEC group could be individually matched with 48 patients from the no-HIPEC group. Forty-four patients were excluded due to an imbalance in PSDSS stage ($n = 36$), CCR score ($n = 2$), history of EPD ($n = 1$), and PCI ($n = 5$). The main characteristics of the 96 patients included in the present analysis are presented in Table 1.

All patients in the no-HIPEC group were initially considered for CRS/HIPEC but underwent CRC alone for the following reasons: age and/or morbidities contraindicating HIPEC ($n = 5$), patient refusal ($n = 3$), limited PM treated synchronously with primary tumor ($n = 9$), concomitant PM and pelvic/retroperitoneal/abdominal wall recurrences

deemed as suboptimal target for HIPEC ($n = 14$), late referral at the completion of s-CT, and not compatible with our waiting-list length ($n = 17$).

Perioperative s-CT was given to all 48 patients in the HIPEC group and to 45 patients in the no-HIPEC group ($P = 0.242$), with no difference in the proportion of patients treated with oxaliplatin/irinotecan-containing regimens ($P = 0.268$) or anti-epidermal growth factor receptor (EGFR)/vascular endothelial growth factor (VEGF) agents ($P = 0.650$) (data not shown). A higher number of patients in the HIPEC group had preoperative s-CT (42 vs. 26; $P = 0.001$), WHO score 0 ($P = 0.030$), and pN2 primary stage ($P = 0.038$). Conversely, there was no significant difference between groups regarding the proportion of patients with KRAS ($P = 0.829$), NRAS ($P = 0.616$), or BRAF ($P = 0.112$) mutations, or microsatellite instability ($P = 0.141$) (data not shown).

Operative Treatment

CCR-0, CCR-1, and CCR-2 cytoreduction was achieved in 33, 12, and 3 patients in each group, respectively. Among those who had CCR-2 cytoreduction, one patient in the HIPEC group underwent open-and-close laparotomy, and one patient in the no-HIPEC group was thought to benefit from additional s-CT and delayed surgical treatment, even though he was intraoperatively deemed as potentially amenable to complete cytoreduction. Unfortunately, disease progression occurred during s-CT, and this patient was not operated again.

Twelve patients in each group had history of EPD, as they were either referred to our center with both EPD and PM, or treated for EPD before the onset of PM. EPD was resected simultaneously with PM in eight patients in the HIPEC group, namely liver ($n = 7$) and distant node ($n = 1$) metastases, and six patients of the no-HIPEC group, namely liver ($n = 4$), distant nodes ($n = 1$), and lung metastasis, by staged procedure ($n = 1$). The difference was not significant ($P = 0.773$).

Five and seven patients in the HIPEC and no-HIPEC group, respectively, did not undergo optimal surgical treatment ($P = 0.759$). In the HIPEC group, lung metastases were not resected in three patients, due to progression while waiting for staged surgery ($n = 2$) or and incomplete CRS ($n = 1$). Additional two patients had CCR-2 cytoreduction. In the no-HIPEC group, lung metastases were not resected in four patients, due to progression while waiting for staged surgery ($n = 3$) or incomplete CRS ($n = 1$). Two patients had CCR-2 cytoreduction, and one patient is currently waiting for staged lung metastasectomy after complete resection of liver and peritoneal metastases.

Operative outcomes are presented in Table 2. HIPEC group was associated with a higher number of

TABLE 1 Patient characteristics

Variable	Category	No HIPEC (n = 48)	HIPEC (n = 48)	P value
Sex	Male	21	19	0.836
	Female	27	29	
Age, years	Median (IQR)	55.4 (47.9–64.4)	56.7 (45.8–63.1)	0.615
WHO performance score	0	35	44	0.030
	1	13	4	
Primary site	Right	20	18	0.835
	Left	28	30	
Primary tumor stage	2–3	25	24	1.000
	4a/b	23	24	
Primary node stage[a]	0	14	8	0.038
	1a/b/c	26	20	
	2a/b	7	17	
Primary metastasis stage	0	29	22	0.357
	1a	2	3	
	1b	17	23	
Grading[b]	1–2	30	31	0.648
	3	15	12	
Histology type	Intestinal	33	31	0.829
	Mucinous	15	15	
	SRC	–	2	
PM synchronous with primary	Yes	16	23	0.212
	No	32	25	
Interval PM diagnosis/surgery, months	Median (IQR)	9.1 (1.7–22.7)	10.8 (6.2–15.6)	0.329
History of EPD	Yes	12	12	1.000
PCI	Median (IQR)	5 (3–7)	5 (3–9)	0.227
Peritoneal residual disease	No visible	32	32	1.000
	≤ 2.5 mm	13	13	
	> 2.5 mm	3	3	
PSDSS stage	I	7	7	1.000
	II	26	26	
	III	8	8	
	IV	7	7	
CEA[c]	> 5 ng/ml	33	26	0.287
	≤ 5 ng/ml	15	20	
CA19.9[d]	> 37 U/ml	23	15	0.287
	≤ 37 U/ml	25	28	

IQR interquartile range, *WHO* World Health Organization, *PM* peritoneal metastases, *PCI* Peritoneal Cancer Index, *HIPEC* hyperthermic intraperitoneal chemotherapy, *EPD* extraperitoneal disease, *PSDSS* Peritoneal Surface Disease Severity Score

[a]Data not available for three patients in the HIPEC group and one patient in the no-HIPEC group

[b]Data not available for five patients in the HIPEC group and three patients in the no-HIPEC group

[c]Data not available for two patients in the HIPEC group

[d]Data not available for five patients in the HIPEC group

cytoreductive surgical procedures (P = 0.001), longer operative time (P = 0.001), longer hospital stay (P = 0.001), and larger amount of plasma transfusions (P = 0.001). Severe (grade 3–4) operative complications occurred in 14 patients in the no-HIPEC group (29.2%) and 13 patients in the HIPEC group (27.1%). The difference was not significant (P = 1.000), nor was that for systemic toxicity (P = 0.495) or reoperation rate (P = 0.552).

TABLE 2 Operative outcomes

Variable	Category	No HIPEC (n = 48)	HIPEC (n = 48)	P value
Surgical procedures	Median (IQR)	3 (2–4)	5 (4–6.5)	0.001
Bowel anastomoses	Median (IQR)	1 (0–1)	1 (0–1)	0.595
Protective ostomies	Done	13	10	0.633
HIPEC schedule	MMC	–	24	–
	MMC and CDDP	–	23	
	No HIPEC	48	1	
Blood red cells, units	Median (IQR)	0 (0–0)	0 (0–2)	0.131
	Mean (SD)	0.47 (1.18)	0.87 (1.31)	
Fresh frozen plasma, mL	Median (IQR)	0 (0–0)	0 (0–0)	0.003
	Mean (SD)	13 (89)	209 (409)	
Operative time	Median (IQR)	233 (131–370)	540 (455–569)	0.001
Overall grade 3–5 adverse events[a]		14	13	1.000
Grade 3–5 systemic toxicity[a]		–	2	0.495
Grade 3–5 surgical morbidity[a]		14	12	0.819
Reoperation		5	8	0.552
Hospital stay	Median (IQR)	11 (7–17.7)	17 (14.2–23.7)	0.001

IQR interquartile range, *HIPEC* hyperthermic intraperitoneal chemotherapy, *MMC* mitomycin C, *CDDP* cisplatin

[a]According to the National Cancer Institute Common Terminology Criteria (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

Systemic toxicity occurred only in two patients in the HIPEC group, who experienced transitory grade 3/4 renal impairment. No operative death occurred.

Survival

Median reverse Kaplan–Meier follow-up was 31.6 months in the no-HIPEC group and 39.9 months in the HIPEC group. Median overall survival was 39.3 months in the no-HIPEC group and 34.8 months in the HIPEC group. Five-year survival rates were 21.6%, and 33.9%, respectively (Fig. 1). The difference was not significant ($P = 0.702$). The results of the univariate and multivariate analyses are presented in Table 3. To avoid collinearity effects, optimal versus suboptimal treatment and PSDSS stage were included in the Cox model, but CCR and PCI were excluded, as they concur with the determination of the former variables. Left-sided primary and optimal treatment independently correlated with better survival. HIPEC was not recognized as an independent prognostic predictor (hazard ratio 0.73; 95% confidence interval 0.47–1.15; $P = 0.178$).

DISCUSSION

To the best of the authors' knowledge, this is the only comparative nonrandomized series in literature assessing the added value of mitomycin C-based HIPEC in colorectal
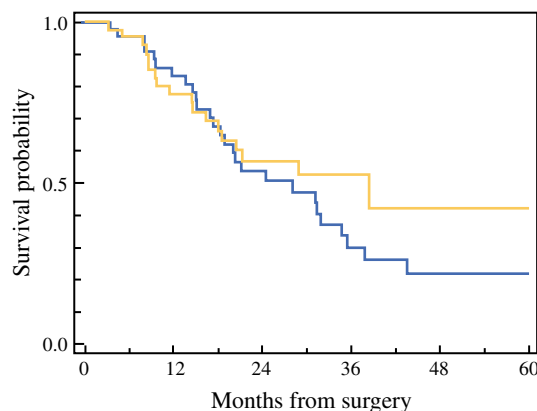
FIG. 1 Overall survival in two matched series of 48 patients treated with perioperative systemic chemotherapy and cytoreductive surgery (continuous line) and 48 patients treated with perioperative systemic chemotherapy, cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy (HIPEC) (dashed lighter line). The difference was not significant ($P = 0.701$)

peritoneal metastases treated by perioperative systemic chemotherapy and cytoreductive surgery. The approach of s-CT and CRS resulted in median survival of 39.3 months, independently confirming the unexpected survival of 41.2 months obtained in the non-HIPEC arm of the recent Prodige-7 trial.[13] As with oxaliplatin-based HIPEC in the randomized French trial, no survival advantage was associated with mitomycin C-based HIPEC in our retrospective matched analysis.

TABLE 3 Univariate and multivariate survival analysis

Variables	Categories	Median survival (months)	5-Year survival (%)	P value (log rank)	HR	95% CI	P value (Cox)
Sex	Male	31.1	17.9	0.058	1.30	0.83–2.04	0.243
	Female	39.3	44.9				
Age	≤ 57 years	35.6	31.0	0.589			
	> 57 years	38.4	32.9				
WHO performance score	0	38.4	34.1	0.097	1.71	0.91–3.22	0.097
	1	18.1	00.0				
Primary site	Right	25.0	08.8	0.004	0.55	0.36–0.86	0.008
	Left	43.7	49.1				
Primary T stage	pT2/3	43.7	39.1	0.498			
	pT4a/b	31.1	24.7				
Primary N stage*	pN0	38.4	49.8	0.555			
	pN1/2	35.6	30.1				
Primary TNM stage	I–III	38.4	44.0	0.645			
	IV	37.9	28.5				
PM synchronous with primary	Yes	34.8	27.8	0.895			
	No	38.8	44.7				
History of EPD	No	38.4	36.0	0.066	1.37	0.79–2.36	0.259
	Yes	18.9	23.5				
Grading**	1–2	NR	56.4	0.016	1.12	0.69–1.80	0.649[§]
	3	21.3	00.0				
Histological type	Intestinal	38.8	43.9	0.212			
	Mucinous/SRC	31.2	19.5				
Peritoneal residual disease	No visible	39.3	43.9	Ref.			
	≤ 2.5 mm	28.8	19.4	0.040			
	> 2.5 mm	15.1	00.0	0.016			
PCI	0–6	NR	57.6	0.001			
	> 6	18.3	00.0				
Treatment	Optimal	38.4	34.9	0.075	2.07	1.08–3.95	0.028
	Suboptimal	18.3	00.0				
HIPEC	Done	39.3	21.6	0.702	0.73	0.47–1.15	0.178
	Not done	34.8	33.9				
Complications	Yes	38.4	34.1	0.397			
	No	35.6	30.3				
PSDSS	1	NR	80.0	Ref.	1.03	0.88–1.21	0.678
	2	37.9	47.8	0.049			
	3	35.6	00.0	0.006			
	4	15.1	00.0	0.001			
Preoperative s-CT	Yes	35.6	27.1	0.343			
	No	37.9	35.9				

HR hazard ratio, *CI* confidence interval, *WHO* World Health Organization, *PM* peritoneal metastases, *EPD* extraperitoneal disease, *SRC* signet ring cell, *CCR* completeness of cytoreduction, *PCI* Peritoneal Cancer Index, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PSDSS* Peritoneal Surface Disease Severity Score, *s-CT* systemic chemotherapy

*Data available in 92 patients

**Data available in 88 patients

[§]In separate model including only 88 patients with available data

The Prodige-7 trial questioned the role of HIPEC in the clinical management of CRC-PM.[14] As underestimation of expected survival in controls receiving no HIPEC is one of the possible explanations for the results of the French trial, independent confirmation and critical assessment of outcomes in patients treated by s-CT and CRS are essential to rationalize clinical decision-making and design future trials. The strong and independent correlation with prognosis seen in the present series highlights the impact of quality of surgery. Taken together, both our study and the Prodige-7 trial support the leading role of surgery in patients' outcome and strongly suggest that complete CRS and perioperative s-CT represent the paradigm against which different therapeutic options should be tested.

Besides the overestimation of the effect size in the study design, it has been speculated that uncertain efficacy of oxaliplatin-based HIPEC might explain the lack of benefit found in the Prodige-7 trial. Although oxaliplatin is one of the drugs of choice for metastatic CRC, factors such as insufficient exposure time (30 min), adverse effects of carrier solution (5% dextrose), and potential drawbacks of hyperthermia could be related to both the lack of survival advantage and the increased 60-day treatment-related toxicity in the HIPEC arm.[14] In our series, mitomycin C with or without cisplatin was administered for 60 min in isotonic solution but was not associated with a significant survival difference, analogously to oxaliplatin in the French trial. This seems to be in line with current literature reporting the lack of a standardized method for delivering HIPEC, with high heterogeneity among centers, and no or little impact of different technical features on the efficacy of the procedure.[3,30]

Mitomycin C is currently not used in CRC systemic therapy but, like oxaliplatin, is largely used in HIPEC procedures.[3] In this setting, mitomycin C has never been directly tested against oxaliplatin, and the only retrospective comparative studies have provided conflicting results. Mitomycin C was found to be equivalent to oxaliplatin in a Dutch series, inferior to oxaliplatin in an Australian series, and superior to oxaliplatin in a large international study, but only in PSDSS stage I and II patients undergoing complete cytoreduction.[22,31,32]

In the present series, mitomycin C-based HIPEC was not associated with higher severe complication rates, unlike oxaliplatin-based HIPEC in the Prodige-7 trial.[13] Most interestingly, the operative morbidity in our HIPEC group (27.1%) compared favorably with the HIPEC arm of the French trial (40.6%). Concerning patients not receiving HIPEC, operative morbidity was similar between the studies (29.2% vs. 31.1%). These findings would suggest a better toxicity profile of mitomycin C. In fact, oxaliplatin

has been reported to be associated with a high risk for complications, especially postoperative bleeding, but retrospective comparative data are not conclusive.[33,34]

The number of cytoreductive surgical procedures, operative time, hospital stay, and plasma transfusion were significantly higher in our HIPEC group. As disease extent (and consequently the need for more extensive surgery) was not different between the groups, this may be related to HIPEC administration. In fact, we routinely performed lesser and greater omentectomies in HIPEC group to improve perfusate circulation. Also, the need for optimal hemodynamic stabilization during HIPEC presumably resulted in more liberal delivery of blood products. Finally, HIPEC may have impacted the time for patient recovery.

A strength of the present study is the highly standardized protocol with minimal treatment-related bias applied to all of our patients, and the use of modern, highly effective s-CT with oxaliplatin or irinotecan and targeted agents. The limited literature data available on CRC-PM treated by s-CT, CRS, and no HIPEC are summarized in Table 4. Early studies reported median survival of 22–25 months,[15–19] but their clinical relevance is limited due to the use of outdated 5-fluorouracil-based s-CT,[15,18,19] or the inclusion of only small-volume synchronous PM resected at the time of primary surgery,[17–19] which may represent a different prognostic setting than the general CRC-PM population.[35] More recently, Desolnaux obtained survival results comparable to our series, but patients were retrospectively included according to predetermined selection criteria (CCR-0, at least 12 cycles of s-CT) rather than on an intention-to-treat basis as in our study.[29]

We acknowledge several limitations of the present study, including its retrospective design and the relatively small sample size, which may have resulted in insufficient statistical power. Using PSDSS to match patients did not prevent the imbalance between groups regarding performance status, primary tumor nodal involvement, and the proportion of patients receiving preoperative s-CT, although these factors were not recognized as independent prognostic predictors on multivariate analysis. The comparison between the HIPEC and non-HIPEC groups has to be taken with caution because the non-HIPEC group combined potential favorable prognostic factors (such as limited synchronous PM) with unfavorable prognostic factors (such as advanced age, borderline conditions, or concomitant recurrences extensively infiltrating the retroperitoneum, or pelvic–abdominal walls). Only patients who refused HIPEC or were excluded due to logistic reasons, such as late referral after completion of preoperative s-CT, may be comparable with those in the HIPEC group.

TABLE 4 Literature series of perioperative systemic chemotherapy, cytoreductive surgery, and no HIPEC

Author[ref.]	Pts (n)	CCR 0/1 (%)	Median PCI	EPD (%)	Median survival (months)	Systemic CT	Selection criteria
Elias[15]	19	100	15–25*	5.3	25.0	5-FU	Low PCI; CCR-0/1 no PRO during preop. s-CT
Scaringi[16]	27	81.5	NS	0	15.0	NS	NS
Mulsow[17]	31	100	NS	22.6	22.0	5-FU or oxl/iri-based	CCR-0/1; only synchr. PM
Kobayashi[18]	20	100	NS	5.0	24.0	5-FU	CCR-0/1; only synchr. PM
Kobayashi[19]	484	100	NS	20.7	25.0	5-FU	CCR-0/1; only synchr. PM
Desolneux[29]	50	100	8	52.0	32.4	Oxl/iri-based ± beva/cetux	CCR-0; ≥ 12 cycles of s-CT
Prodige-7[13]	132	100	9	0	41.2	Oxl/iri-based ± beva/cetux	PCI ≤ 25; CCR-0/1
Present series	48	93.7	5	25.0	39.3	Oxl/iri-based ± beva/cetux	Low PCI; potential CCR-0/1; no PRO during preop. s-CT

s-CT systemic chemotherapy, *PCI* Peritoneal Cancer Index, *CCR 0/1* completeness of cytoreduction 0 or 1 (no visible or ≤ 2.5 mm residual disease), *PRO* disease progression, *PM* peritoneal metastasis, *5-FU* 5-fluorouracil, *oxl* oxaliplatin, *iri* irinotecan, *beva* bevacizumab, *cetux* cetuximab, *NS* not stated

*Extent of peritoneal involvement rated as moderate (PCI 15–25) in 10 patients and minimal in 9 patients (PCI < 15)

CONCLUSIONS

Our findings confirm that encouraging outcome results may be reached in selected patients with CRC-PM by the combination of modern perioperative s-CT and CRS. On retrospective matched analysis, mitomycin C-based HIPEC was not associated with survival advantage but did not increase treatment toxicity. Moving forward, and considering both our findings and those of the Prodige-7 trial (including a subset analysis suggesting possible benefit from HIPEC in moderate-extent PM), we are now administrating HIPEC within a clinical trial aimed at refining patient selection criteria. Furthermore, we are planning future investigations taking advantage of recent advances, such as PM-derived organoids, to develop individualized and more effective intraperitoneal chemotherapy strategies.[36]

REFERENCES

1. Lemmens VE, Klaver YL, Verwaal VJ, et al. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer*. 2011;128:2717–25.
2. Segelman J, Granath F, Holm T, et al. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg*. 2012;99:699–705.
3. Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015: a systematic review. *Crit Rev Oncol Hematol*. 2016;100:209–22.
4. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol*. 2012;30:263–7.
5. Klaver YL, Simkens LH, Lemmens VE, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. *Eur J Surg Oncol*. 2012;38:617–23.
6. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol*. 2009;27:681–85.
7. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol*. 2010;28:63–8.
8. Sugarbaker PH, Ryan DP. Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach? *Lancet Oncol*. 2012;13:e362–9.
9. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol*. 2003;21:3737–43.
10. Gremonprez F, Willaert W, Ceelen W. Intraperitoneal chemotherapy (IPC) for peritoneal carcinomatosis: review of animal models. *J Surg Oncol*. 2014;109:110–6.
11. Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol*. 2011;18:1575–81.

12. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med.* 2018;378:230–40.

13. http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.18_suppl.LBA3503?af=R.

14. Ceelen W. HIPEC with oxaliplatin for colorectal peritoneal metastasis: The end of the road? *Eur J Surg Oncol.* 2019;45:400–2.

15. Elias D, Delperro JR, Sideris L, et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol.* 2004;11:518–21.

16. Scaringi S, Leo F, Canonico G, Batignani G, Ficari F, Tonelli F. The role of cytoreductive surgery alone for the treatment of peritoneal carcinomatosis of colorectal origin: a retrospective analysis with regard to multimodal treatments. *Hepatogastroenterology.* 2009;56:650–5.

17. Mulsow J, Merkel S, Agaimy A, Hohenberger W. Outcomes following surgery for colorectal cancer with synchronous peritoneal metastases. *Br J Surg.* 2011;98:1785–91.

18. Kobayashi H, Enomoto M, Higushi T, et al. Validation and clinical use of the Japanese classification of colorectal carcinomatosis: benefit of surgical cytoreduction, even without intraperitoneal chemotherapy. *Dig Surg.* 2010;27:473–80.

19. Kobayashi H, Kotak, K., Sugihara, K, et al. Outcomes of surgery without HIPEC for synchronous peritoneal metastasis from colorectal cancer: data from a multi-center registry. *Int J Clin Oncol.* 2014;19:98–105.

20. Pelz O, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a Peritoneal Surface Disease Severity Score in patients with colon cancer and peritoneal dissemination. *J Surg Oncol.* 2009;99:9–15.

21. Chua TC, Morris DL, Saxena A, et al. Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study. *Ann Surg Oncol.* 2011;18:1560-7.

22. Prada-Villaverde A, Esquivel J, Lowy AM, et al. The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol.* 2014;110:779–85.

23. Baratti D, Kusamura S, Iusco D, et al. Postoperative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: a two-center study of 101 patients. *Dis Colon Rectum.* 2014;57:858–68.

24. Baratti D, Kusamura S, Iusco D, et al. Should a history of extra-peritoneal disease be a contraindication to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal cancer peritoneal metastases? *Dis Colon Rectum.* 2018;61:1026–34.

25. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* 2016;27:1386–422.

26. Deraco M, Baratti D, Kusamura S, Laterza B, Balestra MR. Surgical technique of parietal and visceral peritonectomy for peritoneal surface malignancies. *J Surg Oncol.* 2009;100:321–8.

27. Jaquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res.* 1996;15:49–58.

28. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

29. Désolneux G, Mazière C, Vara J, et al. Cytoreductive surgery of colorectal peritoneal metastases: outcomes aftercomplete cytoreductive surgery and systemic chemotherapy only. *PLoS One.* 2015;10, e0122816.

30. Bushati M, Rovers KP, Sommariva A, et al. The current practice of cytoreductive surgery and HIPEC for colorectal peritoneal metastases: results of a worldwide web-based survey of the Peritoneal Surface Oncology Group International (PSOGI). *Eur J Surg Oncol.* 2018;44:1942–48.

31. Hompes D, D'Hoore A, Wolthuis A, et al. The use of oxaliplatin or mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. *J Surg Oncol.* 2014;109:527–32.

32. Leung V, Huo YR, Liauw W, Morris DL. Oxaliplatin versus mitomycin C for HIPEC in colorectal cancer peritoneal carcinomatosis. *Eur J Surg Oncol.* 2017;43:144–9.

33. Votanopoulos K, Ihemelandu C, Shen P, Stewart J, Russell G, Levine EA. A comparison of hematologic toxicity profiles after heated intraperitoneal chemotherapy with oxaliplatin and mitomycin C. *J Surg Res.* 2013;179:e133–9.

34. van Eden WJ, Kok NFM, Woensdregt K, Huitema ADR, Boot H, Aalbers AGJ. Safety of intraperitoneal Mitomycin C versus intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis of colorectal cancer undergoing cytoreductive surgery and HIPEC. *Eur J Surg Oncol.* 2018;44:220–7.

35. Baratti D, Kusamura S, Iusco D, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of primary curative surgery in patients with colorectal cancer at high risk for metachronous peritoneal metastases. *Ann Surg Oncol.* 2017;24:167–75.

36. Ubink I, Bolhaqueiro ACF, Elias SG, et al. Organoids from colorectal peritoneal metastases as a platform for improving hyperthermic intraperitoneal chemotherapy. *Br J Surg.* [Epub ahead of print].