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ORIGINAL ARTICLE – COLORECTAL CANCER

Increased Survival of Patients with Synchronous Colorectal Peritoneal Metastases Receiving Preoperative Chemotherapy Before Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Background. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) can result in long-term survival for selected patients with colorectal peritoneal metastases (PM). Most patients are additionally treated with systemic chemotherapy, but timing (adjuvant vs. preoperative) varies between treatment centers. This study aimed to compare short- and long-term outcomes for patients with synchronous colorectal PM undergoing CRS + HIPEC who received preoperative or adjuvant chemotherapy.

Methods. This study enrolled patients with synchronous colorectal PM who underwent macroscopically complete or near complete CRS + HIPEC. Data were collected from a prospective database containing all patients between 2007 and 2014. Perioperative outcome and survival were compared between patients who underwent adjuvant chemotherapy (adjuvant strategy [AS]) and those who had preoperative chemotherapy followed by adjuvant systemic chemotherapy if possible (preoperative strategy [PS]).

Results. The study enrolled 91 patients, 25 (28 %) of whom received preoperative chemotherapy. The peritoneal cancer index (PCI) score was lower and the operation length shorter for the patients receiving preoperative chemotherapy (both $p = 0.02$). The complication rates were comparable between the two groups. The median survival after diagnosis was 38.6 months in the AS group, whereas median survival was not reached in the PS group ($p < 0.01$). The 3-year overall survival rates were 50 and 89 %, respectively. After correction for other significant prognostic factors, preoperative chemotherapy was independently associated with improved survival (HR 0.23; 95 % confidence interval, 0.07–0.75; $p = 0.01$).

Conclusion. Treatment with preoperative chemotherapy was associated with improved long-term survival after CRS + HIPEC compared with adjuvant chemotherapy. Ideally, a randomized controlled trial should be performed to investigate the optimal timing of systemic chemotherapy for colorectal PM patients.

At least 10 % of patients with colorectal cancer experience metastasis to the peritoneum (PM), a condition commonly termed "peritoneal carcinomatosis."[1] Patients with this ominous condition have a median survival of only a few months if untreated, and long-term survival cannot be achieved with systemic treatment alone.[2,3] However, for well-selected patients with limited colorectal PM, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) can result in 5 year-survival rates up to 40 %.[4]

In the only available randomized controlled trial investigating CRS + HIPEC, the HIPEC-procedure was followed by adjuvant systemic chemotherapy, and this strategy demonstrated prolonged survival compared with palliative chemotherapy alone.[5] Therefore, the majority of the

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CRS + HIPEC protocols worldwide include adjuvant systemic chemotherapy.[6–8]

In contrast to the adjuvant strategy in the randomized trial, various centers around the world have now adopted a preoperative strategy in which systemic chemotherapy is given before CRS + HIPEC.[9–11] The potential benefits of preoperative chemotherapy include tumor downstaging, patient selection, and elimination of undetectable systemic disease. Such a strategy has already proved to be successful in the treatment of rectal, gastric, and esophageal cancers, as well as in primary unresectable colorectal liver metastases.[12–15]

The timing of systemic chemotherapy in relation to CRS + HIPEC has never been prospectively studied, so it currently is unknown which strategy is the most effective. The current study aimed to compare both short- and long-term outcomes for patients with synchronous colorectal PM who received either adjuvant or preoperative systemic chemotherapy combined with CRS + HIPEC at our institution.

METHODS

Patients

The study included all patients with synchronous colorectal PM who underwent macroscopically complete (*R*1) or near macroscopically complete (*R*2a) CRS + HIPEC in the Catharina Hospital Eindhoven between April 2007 and December 2014. Patients who received preoperative chemoradiation and patients who had a primary tumor with signet ring cell histology were excluded. All relevant patient characteristics including details on systemic treatment, postoperative outcome, and survival were retrospectively extracted from a prospective database. Perioperative outcome and survival were compared between patients who received adjuvant chemotherapy (adjuvant strategy [AS]) and those who had preoperative chemotherapy (preoperative strategy [PS]).

CRS + HIPEC Procedure

The CRS + HIPEC treatment was performed by a specialized surgical team using the open-colloseum technique as described previously.[16] Peritoneal tumor load was determined with the peritoneal cancer index (PCI) score.[17] Patients were considered suitable for CRS + HIPEC if they had a resectable primary tumor, a PCI score lower than 20, and no unresectable liver or lung metastases. The procedure was terminated if such a large portion of the small intestine was affected that proper resection would have resulted in short-bowel syndrome.

The result of cytoreductive surgery was scored with the *R* score as follows: *R*1 (no macroscopic residual tumor), *R*2a (macroscopic residual tumor $\leq$2.5 mm), and *R*2b (macroscopic residual tumor >2.5 mm).

Postoperative complications were staged according to the Clavien-Dindo classification of surgical complications,[18] with a Clavien-Dindo grade of 3 or higher indicating a complication requiring a surgical, endoscopic, or radiologic intervention or admission to intensive care.

Statistical Analysis

Baseline characteristics were compared between the groups using the χ^2 square test or Fisher's exact test according to sample size. In case of continuous variables, between-group comparisons were made using the Student's *t* test or the Mann–Whitney *U* test, depending on the distribution. Continuous variables are shown as mean ± standard deviation or median (range), depending on the distribution. Survival was determined from the date of primary tumor diagnosis to the date of death or the date of the last follow-up visit according to the Kaplan–Meier method. Survival was compared with the log-rank test.

To determine the prognostic value of preoperative chemotherapy treatment, uni- and multivariate Cox regression analyses were performed. All tests were performed in a two-sided manner, and a *p* value lower than 0.05 was regarded as statistically significant. All statistical analyses were performed with IBM SPSS Statistics software version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient and Tumor Characteristics

In this study, 91 patients with synchronous colorectal PM underwent CRS + HIPEC. According to the standard of care in the Netherlands, 66 patients (73 %) underwent CRS + HIPEC with intent to treat with adjuvant systemic chemotherapy afterward. This strategy succeeded for 59 (89 %) of these patients.

For 25 patients (28 %), a preoperative strategy was chosen. As can be expected, the median interval from diagnosis of the primary tumor to CRS + HIPEC was significantly longer in the PS group (5.6 months; range 2.2–8.2 vs. 2.1 months; range 0.5–32.6 months; $p < 0.01$). No other significant differences between the two groups regarding patient and tumor characteristics could be identified (Table 1).

Preoperative Systemic Chemotherapy

The main reasons for choosing a preoperative strategy were downstaging of peritoneal tumor load in case of

TABLE 1 Patient and tumor characteristics of patients undergoing CRS + HIPEC for synchronous peritoneal metastases of colorectal origin

	Preoperative strategy ($n = 25$)		Adjuvant strategy ($n = 66$)		p value
	n	%	n	%	
Gender					
Male	15	(60.0)	33	(50.0)	0.39
Female	10	(40.0)	33	(50.0)	
Mean age (years)	62.3 ± 10.8		62.2 ± 8.2		0.94
ASA score					
1	1	(4.0)	14	(21.2)	0.12
2	21	(84.0)	46	(69.7)	
3	3	(12.5)	6	(9.1)	
Primary tumor location					
Colon	21	(84.0)	60	(90.9)	0.45
Rectum	4	(16.0)	6	(9.1)	
Tumor differentiation					
Good	2	(8.0)	2	(3.0)	0.71
Moderate	16	(64.0)	40	(60.6)	
Poor	5	(20.0)	18	(27.3)	
Unknown	2	(8.0)	6	(9.1)	
Mucinous adenocarcinoma	9	(36.0)	14	(21.2)	0.15
T stage					
≤3	9	(36.0)	25	(37.9)	0.87
4	16	(64.0)	41	(62.1)	
N status					
0	6	(24.0)	13	(19.7)	0.65
1 or 2	19	(76.0)	53	(80.3)	
Median interval between diagnosis and CRS + HIPEC: months (range)[a]	5.6 (2.2–8.2)		2.1 (0.5–32.6)		<0.01

CRS + HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, *ASA* American Society of Anesthesiologists

[a] Mann–Whitney *U*

extensive PM at the time of diagnosis ($n = 8$), locally advanced primary tumor ($n = 9$), and presence of synchronous liver metastases ($n = 5$). Other reasons were poor general condition after primary surgery ($n = 2$) and a long waiting time until CRS + HIPEC could be performed ($n = 1$).

For 96 % of the PS patients, the chemotherapeutic regimen consisted of 5-fluorouracil/leucovorin/oxaliplatin (either FOLFOX or CAPOX). Seven patients (28 %) also received a biologic treatment (bevacizumab) in addition to chemotherapy (Table 2). The mean number of chemotherapy cycles administered was 4.3 ± 1.8.

At the end of chemotherapeutic treatment, restaging was performed by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scan if indicated. The majority of patients (72 %) could be classified as responders to preoperative chemotherapy because their primary tumor (and distant metastases if present) showed evident regression on imaging. Furthermore, two patients (8 %) showed stable disease, and the response of five patients to preoperative chemotherapy (20 %) was unknown. None of the patients whose response to chemotherapy was known experienced progressive disease after preoperative systemic treatment.

Surgical Outcome and Postoperative Course

The AS group had a significantly higher median PCI score (8; range 1–25 vs. 6; range 1–15; $p = 0.02$) and a significantly longer mean operation time (361 ± 80 vs. 317 ± 81 min; $p = 0.02$; Table 3). Severe postoperative complications (Clavien-Dindo grade ≥3) occurred for 11 patients (17 %) in the AS group compared with six patients (24 %) in the PS group ($p = 0.55$). Some patients in both groups required a reoperation (8 vs. 16 %; $p = 0.25$). The median hospital stay was 11 days (range 5–79 days) in the AS group compared with 10 days (range 4–45) days in the

TABLE 2 Details of preoperative systemic chemotherapy before CRS + HIPEC

	n	%
Reason of preoperative chemotherapy		
Logistical reason	1	(4.0)
Extensive peritoneal metastases	8	(32.0)
Locally advanced disease	9	(36.0)
Liver metastases	5	(20.0)
Poor general condition	2	(8.0)
Preoperative chemotherapy regimen		
Capecitabine	1	(4.0)
CAPOX	15	(60.0)
CAPOX/bevacizumab	7	(28.0)
FOLFOX	2	(8.0)
Mean no. of cycles	4.3 ± 1.8	
Response to preoperative chemotherapy		
Response	18	(72.0)
No response/stable disease	2	(8.0)
Progressive disease	0	
Unknown	5	(20.0)

CRS + HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, *CAPOX* capecitabine/oxaliplatin, *FOLFOX* 5-fluorouracil/leucovorin/oxaliplatin

PS group ($p = 0.98$). In the AS group, 7 patients (11 %) did not receive adjuvant chemotherapy, mainly due to postoperative complications. In the PS group, 21 patients (84 %) received adjuvant systemic treatment in addition to the preoperative treatment. The median number of adjuvant chemotherapy cycles administered was 8 (range 2–12) in the AS group and 4 (range 1–6) in the PS group.

Survival Analysis

The median follow-up time was 28 months (range 2.2–88.5 months) in the AS group and 33.7 months (range 7.1–66.6 months) in the PS group. Kaplan–Meier curves are depicted in Fig. 1. The median survival time was 38.6 months (95 % confidence interval [CI] 26.1–51.2 months) in the AS group, whereas median survival was not reached in the PS group ($p < 0.01$). The 3-year overall survival rate was 50 % in the AS group and 89 % in the PS group. Death occurred for 39 patients (59 %) in the AS group compared with 3 patients (12 %) in the PS group ($p < 0.01$).

The univariate analysis identified the following prognostic indicators for survival: preoperative chemotherapy (hazard ratio [HR], 0.21; 95 % CI 0.06–0.67; $p < 0.01$), T4 tumor stage (HR 2.64; 95 % CI 1.28–5.43; $p = 0.01$), lymph node involvement (HR 3.46; 95 % CI 1.23–9.73; $p = 0.02$), and PCI score (HR 1.14 per additional point; 95 % CI 1.07–1.20; $p < 0.01$; Table 4). After correction for these variables with multivariate analysis, preoperative chemotherapy remained a strong prognostic factor for improved overall survival (HR 0.23; 95 % CI 0.07–0.75; $p = 0.01$).

DISCUSSION

In adjunction to CRS + HIPEC, perioperative systemic chemotherapy is considered an important component in the treatment of colorectal PM patients because several studies have suggested a survival benefit for patients receiving additional systemic treatment.[2,6,8] However, the optimal timing of chemotherapy, either adjuvant or preoperative, currently is unknown and was the subject of the current study. Interestingly, the administration of preoperative chemotherapy before CRS + HIPEC was associated with a survival benefit and a 3-year overall survival rate of nearly 90 %. This was significantly longer than the survival of patients receiving the standard of care in the Netherlands, which is immediate CRS + HIPEC followed by adjuvant chemotherapy. Even after multivariate correction for important prognostic factors, preoperative chemotherapy was associated with improved overall survival. These results are even more interesting because the preoperative group consisted of patients initially rejected for CRS + HIPEC because of poor prognostic factors such as a locally advanced primary tumor, extensive PM, synchronous systemic metastases, or poor general condition.

This finding may have several explanations. First, preoperative systemic treatment clarifies the biologic behavior of the disease and its sensitivity to chemotherapy. This treatment may prevent the use of CRS + HIPEC for patients with an aggressive tumor biology who are not responding to preoperative treatment or patients who experience metastases during treatment. This strategy results in improved patient selection and prohibits futile and potentially harmful surgical treatment for patients with refractory disease, but it might also result in a selection bias.[19] This certainly may have played an important role in the current study, which reflects daily clinical practice. Because Catharina Hospital Eindhoven is a tertiary referring center, peritoneal cancer patients are discussed with us on a regular basis, usually by phone or e-mail consultation. Besides the 25 patients in this study who apparently were successfully advised to undergo preoperative chemotherapy, other patients may have progressed during systemic treatment with a less favorable outcome. These patients were not included in the current study because data for them was not available. To overcome this problem in part, patients who did not have a macroscopically complete resection also were included in this study. Nevertheless, to

TABLE 3 Surgical outcome for patients undergoing CRS + HIPEC for synchronous peritoneal metastases of colorectal origin

	Preoperative strategy ($n = 25$)		Adjuvant strategy ($n = 66$)		p value
	n	%	n	%	
Median PCI score (range)[a]	6 (1–15)		8 (1–25)		0.02
R score					
*R*1	24	(96.0)	64	(97.0)	1.00
*R*2a	1	(4.0)	2	(3.0)	
Operative parameters					
Median blood loss: ml (range)[a]	1000 (250–3300)		625 (100–6600)		0.32
Mean operation length (min)	317 ± 81		361 ± 80		0.02
Enterostomy after procedure	11	(44.0)	38	(57.6)	0.25
Patients with severe postoperative complications (Clavien–Dindo grade ≥3)	6	(24.0)	11	(16.7)	0.55
Postoperative complications					
Gastrointestinal leakage	3	(12.0)	2	(3.0)	0.13
Bleeding	0		1	(1.5)	1.00
Abscess	3	(12.0)	1	(1.5)	0.06
Urinary tract infection	0		5	(7.6)	0.32
Pneumonia	1	(4.0)	5	(7.6)	1.00
Wound infection	6	(24.0)	9	(13.6)	0.34
Ileus	7	(28.0)	11	(16.7)	0.25
Wound dehiscence	1	(4.0)	1	(1.5)	0.48
Fistula	0		4	(6.1)	0.57
Other infection	0		4	(6.1)	0.57
Patients with reoperation	4	(16.0)	5	(7.6)	0.25
30-Day in-hospital mortality	0		1	(1.5)	1.00
Median hospital stay: days (range)[a]	10 (4–45)		11 (5–79)		0.98

CRS + HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, *PCI* peritoneal cancer index, *Clavien-Dindo* Clavien-Dindo classification of surgical complications

[a] Mann–Whitney *U*

investigate the optimal timing of systemic chemotherapy, a prospective study with intention-to-treat analysis certainly is warranted to understand the role of selection.

Second, preoperative chemotherapy can be effective in the downstaging of both local and peritoneal tumor load, thereby improving prognosis. In the current study, the majority of the patients treated with preoperative chemotherapy indeed showed evident tumor regression on imaging before CRS + HIPEC. Additionally, the PCI score at the time of CRS + HIPEC was significantly lower, and achievement of complete cytoreduction required less time in the PS group. Both the PCI score and completeness of cytoreduction are important prognostic factors for survival among PM patients undergoing CRS + HIPEC.[5,8] A preoperative strategy has been proved successful for other tumors as well. For example, for patients with initially unresectable colorectal liver metastases, preoperative chemotherapy may downsize hepatic tumor load to make these patients suitable for surgery.[15] Furthermore, for

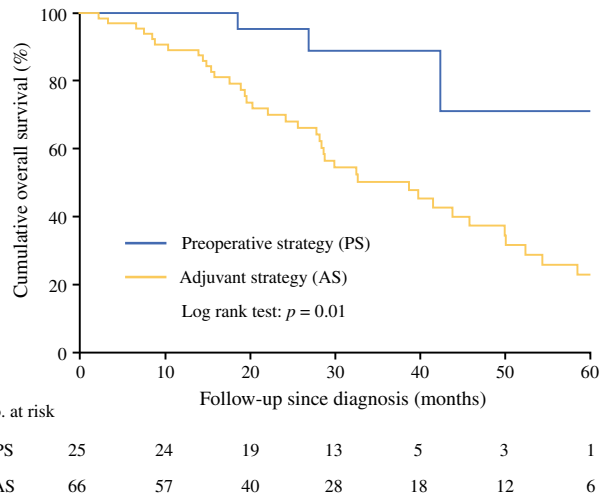

FIG. 1 Log-rank survival analysis comparing survival of patients in the adjuvant strategy (AS) and preoperative strategy (PS) groups calculated from the date of primary tumor diagnosis

TABLE 4 Uni- and multivariate Cox regression analysis of factors influencing overall survival of patients undergoing CRS + HIPEC for synchronous peritoneal metastases of colorectal origin

Variable	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Preoperative chemotherapy				
No	1.00		1.00	
Yes	0.21 (0.06–0.67)	<0.01	0.23 (0.07–0.75)	0.01
Gender				
Male	1.00			
Female	1.10 (0.60–2.01)	0.77		
Age[a]	1.01 (0.98–1.05)	0.49		
Primary tumor location				
Rectum	1.00			
Colon	1.08 (0.42–2.75)	0.88		
Tumor differentiation				
Good	1.00			
Moderate	3.64 (0.49–27.01)	0.21		
Poor	3.47 (0.45–27.04)	0.24		
Unknown	2.64 (0.29–23.71)	0.39		
Mucinous adenocarcinoma				
No	1.00			
Yes	1.61 (0.80–3.25)	0.18		
T stage				
≤3	1.00		1.00	
4	2.64 (1.28–5.43)	0.01	2.12 (1.01–4.48)	0.05
N stage				
0	1.00		1.00	
1 or 2	3.46 (1.23–9.73)	0.02	2.46 (0.86–7.01)	0.09
Interval between diagnosis and CRS + HIPEC[b]	0.96 (0.88–1.05)	0.36		
PCI score[c]	1.14 (1.07–1.20)	<0.01	1.08 (1.02–1.15)	0.01

CRS + HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, *HR* hazard ratio, *CI* confidence interval, *PCI* peritoneal cancer index

[a] Hazard ratio per additional year

[b] Hazard ratio per additional month

[c] Hazard ratio per additional PCI point

patients with appendiceal PM (PMCA), preoperative chemotherapy seemed to be effective in reducing the PCI score.[20] Also, in gastric cancer, preoperative treatment currently is the strategy of choice when possible.[12] For patients with locally advanced rectal cancer, preoperative chemoradiation is associated with more sphincter-preserving procedures and better locoregional control than adjuvant chemoradiation.[21] Furthermore, for patients with resectable esophageal cancer, preoperative chemoradiation before surgery is associated with improvement of both local control and survival.[13]

Third, a preoperative strategy may ensure the administration of systemic chemotherapy for PM patients treated with CRS + HIPEC because it is known that severe postoperative complications occur for approximately 25 % of the patients.[22] For an important part of these patients, adjuvant systemic treatment often is delayed or even impossible, which might explain the association between complications and impaired long-term survival.[23–25] Indeed, 11 % of our patients could not be treated with adjuvant chemotherapy. Preoperative treatment partly overcomes this problem.

Other retrospective cohort studies also have investigated the effect that timing of systemic chemotherapy has on patients treated with CRS + HIPEC. Passot et al.[26] found a significant univariate increase in overall survival among patients receiving preoperative systemic chemotherapy. However, this positive prognostic effect was not found in a

multivariate analysis. In a French multicenter study, preoperative chemotherapy was even associated with a decreased survival after CRS + HIPEC in both uni- and multivariate analyses.[6] Another study reported improved survival for patients treated with preoperative systemic chemotherapy but only when this was combined with bevacizumab.[27] Given these contradictory results, the issue of timing of systemic chemotherapy is not settled to date, again highlighting the need for further research.

The use of preoperative chemotherapy also might have a few drawbacks. Due to regression of peritoneal tumor deposits after preoperative chemotherapy, gross tumor implants may no longer be visible during surgery. Theoretically, this can result in difficulties achieving a complete cytoreduction. Furthermore, it might be feared that preoperative chemotherapy will result in more postoperative complications. In the current study, no such effect was observed, which is consistent with the results of previous studies.[25,27] Nevertheless, the PS group seemed to show a nonsignificant trend toward an increased risk of infectious complications such as gastrointestinal leakage, wound infection, and abscess formation. Further research with a larger study cohort should determine whether preoperative chemotherapy actually is associated with an increased risk of infectious complications. However, the vascular endothelial growth factor (VEGF) inhibitor bevacizumab should be included in a preoperative strategy with caution because it has been associated with an increased risk of intraabdominal complications after CRS + HIPEC.[28,29] Nevertheless, the small number of patients ($n = 7$) treated with preoperative chemotherapy containing bevacizumab in the current cohort did not show an increase in postoperative complications (data not shown).

Besides the evident selection bias addressed earlier, several other limitations of the current study should be taken into account. Although data were gathered prospectively, this study had a retrospective design. Moreover, a relatively small number of patients were included in the study, particularly in the group that received preoperative systemic chemotherapy. Furthermore, the survival advantage observed in the PS group might be partly attributable to the different intervals from diagnosis of the primary tumor until CRS + HIPEC in the two groups. Because of this potential bias, survival also was calculated from the date of CRS + HIPEC, and survival remained significantly longer in the PS group (data not shown).

CONCLUSION

Systemic chemotherapy combined with CRS + HIPEC is thought to play an important role in the treatment of patients with synchronous colorectal PM, but optimal timing of chemotherapy is unknown and varies among treatment centers. Despite unfavorable prognostic factors, treatment with preoperative chemotherapy was associated with improved long-term survival after CRS + HIPEC in the current study. Ideally, a randomized controlled trial should be performed to investigate the optimal timing of systemic chemotherapy for colorectal PM patients undergoing CRS + HIPEC. Such a study may further improve the survival of these patients.

DISCLOSURE There are no conflicts of interest.

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