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The Treatment of Peritoneal Carcinomatosis of Colorectal Cancer with Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) with Oxaliplatin: A Belgian Multicentre Prospective Phase II Clinical Study

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ABSTRACT

Background. Up to 25% of patients with metastatic colorectal cancer (CRC) present with peritoneal carcinomatosis (PC) as the only site of metastases. Complete cytoreductive surgery (CCRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) aims for locoregional disease control and long-term survival. Oxaliplatin is effective for treating advanced CRC. This study assesses the safety and efficacy of CCRS with HIPEC with oxaliplatin for patients with PC of CRC.

Methods. A Belgian prospective multicenter registry was performed to monitor perioperative morbidity and assess mortality, disease-free survival (DFS), and overall survival (OS).

Results. Forty-eight consecutive patients underwent CCRS (R0/1) with HIPEC (male/female ratio 17/31, median age 60 years, range 24–76 years). Median PC index was 11 (range 1–22). Median operation time was 460 (range 125–840) min, with a median blood loss of 475 (range 2–6,000) ml. Thirty-day mortality was 0%. Complication rate (any grade) was 52.1%. Anastomotic leakage occurred in 10.4% of patients, bleeding in 6.3%, and bowel perforation in 2.1%. Median hospital stay was 20 (range 5–65) days. At median follow-up of 22.7 (range 3.2–55.7) months, OS was 97.9% [95% confidence interval (CI) 86.1–99.7] at 1 year and 88.7% (95% CI 73.6–95.4) at 2 years. DFS at 1 year was 65.8% (95% CI 52.3–76.2) and 45.5% (95% CI 34.3–55.9) at 2 years. Median time until recurrence was 19.8 months (95% CI 12–upper limit not defined). Only after dichotomizing PC index was a significant difference in OS found between low and high PC index.

Conclusions. CCRS followed by HIPEC with oxaliplatin for PC from CRC can be implemented with acceptable morbidity. Long-term DFS and OS can be achieved in selected patients.

Approximately 10% of colorectal cancer (CRC) patients present with peritoneal carcinomatosis (PC) at the time of diagnosis, and 25% of patients develop PC at recurrence.[1–4] Until recently, PC was considered a terminal condition, to be palliated with systemic chemotherapy. Most frequently, PC is part of generalized metastatic disease (e.g., liver, lung), but in about 25–35% of cases, PC is the only site of recurrent disease.[1,5–7] Therefore, it may be

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TABLE 1 OS after CCRS with HIPEC

Study	Journal and year	Intraperitoneal chemotherapy	Total no. of patients	N syst. M+	R0–1	R2a (≤2.5 mm)	R2b (>2.5 mm)	Median OS (month)	OS		
									1 year	3 years	5 years
Verwaa[1]	*Ann Surg Oncol*, 2005	MMC	117	0%	50.4%	37.6%	12%	21.8	75%	28%	19%
Verwaal[34]	*Ann Surg Oncol*, 2008	MMC	54	0%	41%	41%	18%	22.2	–	–	R1: 45% R2: 5%
Franko[35]	*Cancer*, 2010	MMC	67	Yes (%?)	91%	9.0%		34.7	–	–	–
Elias[22]	*J Clin Oncol*, 2009	Oxaliplatin	48	0%	100%	0%	0%	62.7	–	–	51%
Elias[19]	*Ann Surg*, 2010	MMC or oxaliplatin	440	15.9%	100%	0%	0%	–	–	–	33%
Elias[20]	*J Clin Oncol*, 2010	MMC or oxaliplatin	523	15%	85%	10%	5%	–	81%	41%	27%

the first step in dissemination and should not necessarily be interpreted as generalized disease.[5,8] Such a locoregional tumor extension warrants a locoregional treatment approach. Thus, the background for the concept of complete cytoreductive surgery (CCRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) was developed to obtain locoregional disease control and long-term survival for PC (Table 1).

Because oxaliplatin proved to be effective for treating advanced CRC, Pestieau and Sugarbaker performed pharmacokinetic studies on the intraperitoneal use of oxaliplatin.[9,10] Their experimental studies showed that the exposure of peritoneal surfaces to oxaliplatin was significantly increased with intraperitoneal administration, compared to intravenous administration ($P < 0.0001$). The area under the receiver-operating characteristic curve (AUC) ratio (AUC peritoneal fluid/AUC plasma) was 16(±5):1 for intraperitoneal delivery as opposed to 1:5(±2) for intravenous delivery ($P = 0.0059$).[10] Mahteme and Pahlman showed a low systemic exposure of oxaliplatin and a half-life of 29.5 min in the perfusate.[11] Elias and Bonnay found high peritoneal and tumor oxaliplatin concentrations, and on the basis of dose-escalation studies, they recommended a dose of 460 mg/m^2 oxaliplatin in 2 l/m^2 of 5% dextrose for HIPEC at a temperature of 42–44°C over 30 min.[12]

The aim of this multicenter prospective observational clinical study was to assess the safety and efficacy of CCRS followed by HIPEC with oxaliplatin for patients with PC of CRC in different Belgian centers.

MATERIALS AND METHODS

A Belgian prospective multicenter protocol and registry was started in January 2004, and in August 2008, an analysis was performed for perioperative morbidity and mortality, as well as for disease-free survival (DFS) and overall survival (OS). Nine centers involved in the management of peritoneal disease by CCRS with HIPEC collaborated on the development of the study protocol. The principal investigator, all cooperating centers, and the centers' respective medical ethics committees approved the final version of the protocol. Eventually, 6 surgical centers included consecutive patients with PC from CRC. Patients with intra-abdominal mesotheliomas or pseudomyxomas were excluded from the trial, as were patients in whom there was evidence of extra-abdominal disease or liver metastases. Patients who received chemotherapy or radiotherapy in the course of 4 weeks before surgery were also excluded from the trial.

The diagnosis of PC of CRC and the assessment of its resectability were achieved through computed tomography, positron emission tomography–computed tomography, and/or laparoscopic evaluation.

Extent of Disease at Surgery

The extent of disease was described by the peritoneal cancer index (PCI) according to Jacquet and Sugarbaker, assessing the number of abdominal regions involved and scoring their maximum lesion size.[13] As prescribed by protocol, only patients with a PCI score of <25 were included in the trial.

Complete Cytoreductive Surgery

Extensive debulking with peritonectomy and, when needed, multiorgan resection was performed as described by Sugarbaker.[14] The aim was to obtain a macroscopically CCRS (R0/1)—that is, no macroscopically visual residual tumor was left at the end of the surgical resection. Only

patients in whom a complete debulking (CC-0) could be reached went on to the HIPEC procedure.

HIPEC Protocol

At the end of the surgical debulking procedure, about 1 h before starting the actual HIPEC procedure, systemic folinic acid (20 mg/m^2) and 5-fluorouracil (5-FU; 400 mg/m^2) were administered. In the meantime, after complete cytoreduction was achieved, arrangements were made for the actual HIPEC procedure. First, the abdominal cavity was rinsed with saline, and the coliseum for the open HIPEC technique was built up. Hyperthermic circulation was started with 2 l/m^2 of a glucose 5% solution until a steady state of about 41–42°C was reached. Oxaliplatin at a dose of 460 mg/m^2 was then added and circulated for 30 min.

Before construction of the necessary anastomoses and closure of the abdomen, the abdominal cavity was extensively rinsed with 3 l of saline solution.

Statistical Analysis

Cox regressions and log rank tests were used to evaluate the relation between a set of variables and OS and DFS, respectively. Hazard ratios and 95% confidence intervals (CI) are reported. DFS is defined as the time until recurrence. All patients who died experienced recurrence of disease. Considered variables are patient related (age and sex), primary tumor related (carcinoembryonic antigen, grade of differentiation, mucinous type, synchronous occurrence of PC, node involvement of the primary tumor), extent of disease related (number of abdominal regions involved in the PC, maximal diameter of the PC lesions, PCI score), surgical procedure related (blood loss, need of transfusion, duration of the surgical procedure, small bowel resection, occurrence of a diaphragmatic tear), and pre- and postoperative intra-abdominal and extra-abdominal complications related. Restricted cubic splines are used in the Cox model to allow a nonlinear relation between PCI score and (log) hazard ratio.[15] Because of the low number of events (5 deaths, 21 recurrences), no stratified tests or multivariable Cox models were considered. For OS, an exact log rank test (conditional on risk set) was used to verify the robustness of the result.[16] An optimal cut point for PCI is defined as the dichotomization maximizing the likelihood in the Cox regression model. A 95% CI for the cut point is constructed on the basis of the likelihood function. Fisher exact tests, Mann–Whitney *U*-tests, and Spearman correlations are used to explore relations with the occurrence of intra-abdominal complications and with length of hospital stay.

All analyses were performed by SAS software, version 9.2 for Windows (SAS, Cary, NC, USA).

RESULTS

Patient and Tumor Characteristics

Between January 2004 and August 2008, a total of 48 consecutive patients with PC from CRC were included in the trial, 17 of whom were male and 31 female (Table 2). Median age at surgery was 60 (range 24–76) years. In this series, in 72.9% of patients, the primary tumor had already been previously resected. In 75% of patients, PC was already present at the time of primary tumor presentation. Most primary tumors were as localized in the ascending and rectosigmoid colon and had a moderate to poor differentiation. A total of 39.6% of tumors were of mucinous cell type.

Extent of Disease

Median PCI score was 11 (range 1–22); with a median of 6 abdominal regions (range 1–11) involved and a median lesion size score of 3 (range 1–3).

CCRS and HIPEC

To obtain a macroscopically CCRS (CC-0), a median of 2 (range 2–6) organs needed to be resected, with anterior resection in 45.8%, total colectomy in 8.3%, and small

TABLE 2 Characteristics of 48 patients

Characteristic	Value
Sex, *n*	
Male	17
Female	31
Primary tumor, *n* (%)	
Previously resected	35 (72.9%)
PC present at primary tumor	36 (75%)
Localization, *n*	
Appendix	9
Caeca-ascending colon	12
Transverse colon	2
Descending colon	5
Rectosigmoid	20
Differentiation, *n*	
Well	7
Moderate	26
Poor	12
Not specified	3
Mucinous cell type, *n* (%)	19 (39.6%)

bowel resection in 12.5% of cases. A median of 1 anastomosis (range 0–6) was performed per patient. Almost one-third were low anastomoses, and 82.1% were performed after HIPEC. In 16 patients, construction of a diversion was needed (Table 3).

Median operation time was 460 (range 125–840) min, with a median blood loss of 475 (range 2–6,000) ml. HIPEC posed few procedural problems. The 30-day mortality was 0%. Complication rate (any grade) was 52.1%, with 18 intra- and 17 extra-abdominal complications. All extra-abdominal complications were World Health Organization grade 1 or 2, except for one grade 4 pneumonia. For the intra-abdominal complications, anastomotic leakage occurred in 10.4% of patients (all National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 4) and bleeding in 6.3% (all NCI-CTC grade 4). One bowel perforation (2.1%) (NCI-CTC grade 4), one abscess (2.1%) (NCI-CTC grade 4), and one rectovaginal fistula (NCI-CTC grade 2) were reported. Thus, reoperation was needed in 10 patients (20.8%). In 22.9% of patients, prolonged ileus was registered, for which no reintervention was needed. Median hospital stay was 20 (range 5–65) days (Table 4). Univariate analysis showed that the occurrence of intra-abdominal complications significantly affected hospital stay ($P = 0.002$), but no risk factors for occurrence of postoperative complications could be found.

Finally, it should be mentioned that 30 patients (62.5%) began 5-FU/leucovorin-based adjuvant chemotherapy combined with oxaliplatin or irinotecan within 8–12 weeks after CCRS with HIPEC.

OS and DFS

At a median follow-up of 22.7 (range 3.2–55.7) months, OS was 97.9% (95% CI 86.1–99.7) at 1 year and 88.7% (95% CI 73.6–95.4) at 2 years (Fig. 1a). DFS at 1 year was 65.8% (95% CI 52.3–76.2) and 45.5% (95% CI 34.3–55.9) at 2 years (Fig. 1b). The median time until recurrence was 19.8 months (95% CI 12–upper limit not defined).

There was no evidence for a relation between PCI score and OS ($P = 0.14$ assuming the relation to be linear, $P = 0.051$ when allowing a nonlinear relation). Only after dichotomizing the PCI score was a significant difference in OS found between patients with low and high PCI. The optimal cut point is 18, which is estimated with a high degree of uncertainty (95% CI 10–21). This result still corresponds with the dichotomization proposed by Elias and Blot.[17] They made a distinction between patients with PCI $\leq$15 and patients with PCI >15, which yields a significant difference ($P = 0.013$) in the current study (Fig. 2a).

Besides the dichotomized PCI score, resection of small bowel ($P = 0.004$), the occurrence of postoperative extra-abdominal complications ($P = 0.0005$), and a lesion size of >5 cm ($P = 0.043$) are significantly correlated with OS (Table 5). The same results were reached with the exact tests (data not shown).

There was no evidence for a relation between PCI score and DFS (P =0.16 assuming the relation to be linear, $P = 0.12$ when allowing a nonlinear relation).

TABLE 3 Surgical procedures performed during CCRS with HIPEC in 48 patients with PC from CRC

Characteristic	Value
No. of organs resected, median (range)	2 (2–6)
Anterior resection	22/48 (45.8%)
Total colectomy	4/48 (8.3%)
Segmentary small bowel resection	6/48 (12.5%)
Anastomoses	
No., median (range)	1 (0–6)
Low localization	13/48 (27.1%)
Timing after HIPEC	32/48 (82.1%)
Diversion	16 (33.3%)
Ileostomy	11 (22.9%)
Colostomy	5 (10.4%)

TABLE 4 Pre- and postoperative data of CCRS with HIPEC in 48 patients with PC from CRC

Characteristic	Value
Operative time, min, median (range)	460 (125–840)
Blood loss, ml, median (range)	475 (2–6,000)
Postoperative mortality	0
Postoperative complications[a]	
IAC ($n = 18$)	
Prolonged ileus[b]	11 (22.9%)
Anastomotic leakage	5 (10.4%)
Bleeding	3 (6.3%)
Bowel perforation	1 (2.1%)
RV fistula	1 (2.1%)
Abscess	1 (2.1%)
EAC ($n = 16$)	
Pulmonary	6 (12.5%)
Cardiac	1 (2.1%)
Renal–urologic	6 (12.5%)
Hematologic	1 (2.1%)
Other	6 (12.5%)
Reoperations	10 (20.8%)
Hospital stay, d, median (range)	20 (5–65)

IAC intra-abdominal complications, *EAC* extra-abdominal complications

[a] Present in 52.1% of patients

[b] Food intolerance, 9 (range 2–56) days

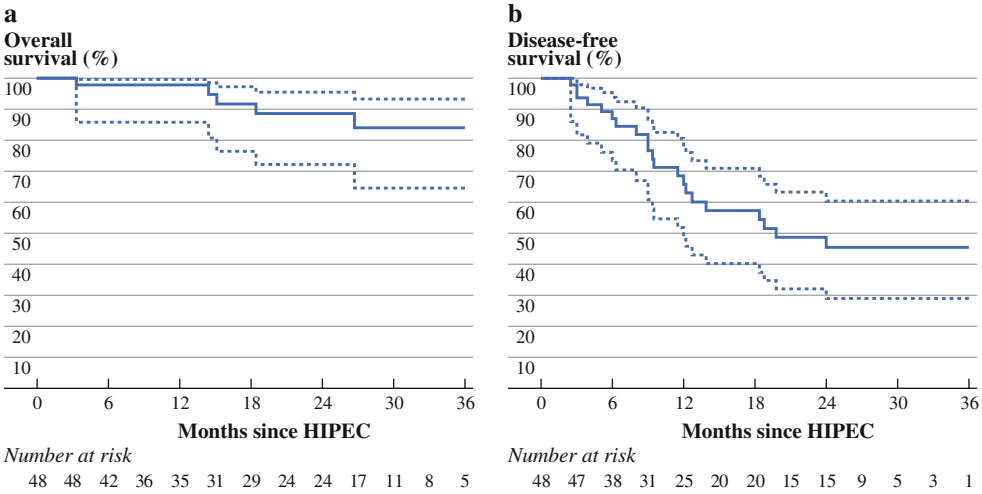

FIG. 1 **a** OS after CCRS with HIPEC (in months). *Dashed lines* represent the pointwise 95% CI. **b** DFS after CCRS with HIPEC (in months). *Dashed lines* represent the pointwise 95% CI

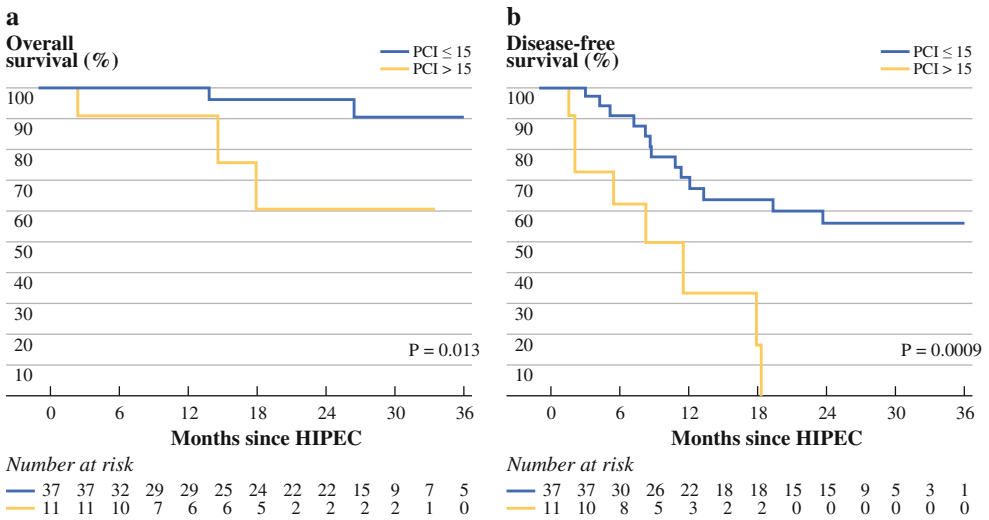

FIG. 2 **a** Influence of PCI score on OS. **b** Influence of PCI score on DFS

The optimal cut point coincides with the cut point proposed by Elias and Blot (i.e., PCI ≤15 vs. PCI >15) and yields a significant difference between both groups ($P = 0.0009$) (Fig. 2b).[17] The 95% CI for the cut point is 15–17. Besides the dichotomized PCI score, transfusion ($P = 0.018$) was significantly correlated with DFS (Table 5). For the resection of small bowel at debulking, a trend was observed ($P = 0.067$).

DISCUSSION

The primary aim of this prospective observational multicentre trial was to assess the safety and efficacy of HIPEC with oxaliplatin. Many of the larger series in literature report on the overall safety and efficacy of CCRS with HIPEC, including patients who underwent HIPEC with oxaliplatin and patients who received HIPEC with mitomycin C (MMC) in the same publication.[18–21] This might complicate the interpretation and comparison of results. The number of articles reporting only on CCRS followed by HIPEC with oxaliplatin is limited, and often, these articles include relatively small numbers of patients.[12,22,23]

In this Belgian multicenter trial, there was no 30-day mortality. The overall complication rate was 52.1%, with anastomotic leakage in 10.4% of patients, bleeding in 6.3%, and prolonged ileus in 22.9%. Surgical reintervention was needed in 20.8% of cases. The median hospital stay was 20 (range 5–65) days. These results concur with literature. Elias and colleagues reported grade 3–5 serious adverse events in up to 50% of patients who underwent CCRS, resulting in CC-0 resection, followed by HIPEC with oxaliplatin.[12,23] Larger series on CCRS with HIPEC with oxaliplatin or MMC reported mortality rates of <1–6%, grade 3–5 serious adverse events rates of 31–66%, and reintervention in 11–30% of cases.[1,18–20] The rate of

TABLE 5 Univariate results for OS and DFS

Characteristic	OS				DFS			
		95% CI				95% CI		
	HR	LL	UL	P^a	HR	LL	UL	P^a
Male vs. female	1.049	0.175	6.288	0.96	1.365	0.574	3.245	0.48
Age at HIPEC (years)	0.965	0.897	1.040	0.35	0.998	0.960	1.037	0.91
Mucinous (yes)	3.528	0.584	21.305	0.14	0.870	0.350	2.159	0.76
Synchronous (yes)	0.630	0.104	3.793	0.61	1.159	0.423	3.176	0.77
Well-differentiated primary tumor (yes)	1.831	0.203	16.491	0.58	0.598	0.139	2.581	0.49
Node-positive primary tumor	2.478	0.274	22.41	0.40	1.356	0.487	3.771	0.56
Maximum lesion score >1	0.135	0.014	1.320	0.043	0.807	0.108	6.053	0.83
Small bowel resection (yes)	[b]			0.004	4.217	0.789	22.54	0.067
Diaphragmatic tear (yes)	1.764	0.197	15.81	0.61	1.253	0.368	4.267	0.72
Transfusion (yes)	1.211	0.109	13.45	0.88	3.906	1.180	12.93	0.018
Postoperative IAC (yes)	0.414	0.046	3.707	0.42	1.067	0.442	2.577	0.89
Postoperative EAC (yes)	[b]			0.0005	2.004	0.840	4.782	0.11
Gastro-intestinal anastomosis (yes)	0.500	0.083	3.002	0.44	0.752	0.291	1.942	0.55
PCI score (1-unit increase)	1.138	0.953	1.359	0.16	1.062	0.975	1.156	0.17
PCI >15	7.231	1.182	44.24	0.013	4.270	1.686	10.82	0.0009
CEA (μg^{-1})	0.996	0.965	1.028	0.80	1.007	0.998	1.016	0.12
No. of regions (1-unit increase)	1.197	0.885	1.620	0.24	1.077	0.935	1.239	0.30
Duration (1-h increase)	1.164	0.826	1.642	0.39	1.041	0.885	1.225	0.63
Blood loss (100-ml increase)	0.734	0.346	1.557	0.42	1.016	0.978	1.056	0.41

HR hazard ratio, *LL* lower limit, *UL* upper limit, *CEA* carcinoembryonic antigen

[a] *P* value from Cox regression model for continuous predictors and from log rank test for factors with 2 group levels

[b] A point estimate for the HR (and the 95% CI) cannot be estimated because the smallest event time is for the single dead patient with small bowel resection, and all patients who died had postoperative EAC

anastomotic leakages is often not clearly specified. Elias and colleagues reported a gastrointestinal tract complications/fistula rate of 9–10%.[12,19,20] These high morbidity rates after CCRS with HIPEC indicate that patients undergoing such extensive surgery should be well selected regarding their general performance status and their extent of disease.

The OS found in our multicentric Belgian registry was 97.9% at 1 year and 88.7% at 2 years at a median follow-up of 22.7 (range 3.2–55.7) months (Fig. 1a). This is similar to the retrospective comparative trial of Elias et al. comparing modern systemic therapy for PC to CCRS with HIPEC with oxaliplatin, reporting a 2 year OS of 81% and a 5 year OS of 51%.[22] A systematic review by Cao et al. rated the results of this study as level 2b evidence.[24] DFS at 1 year was 65.7% and 45.4% at 2 years (Fig. 1b), which was also concurrent with a phase II trial from Elias et al. showing a DFS of almost 50% at 2 years.[25] Before the combination treatment of CCRS with HIPEC became available, no long-term survivors were reported for PC of CRC. Table 1 provides an overview of survival data reached with CCRS with HIPEC. If an R0/1 resection can be reached by CCRS, OS rates for CCRS with HIPEC are comparable to the 5 year OS rates of 35–60% reported by several large single- and multi-institutional experiences after curative liver resection for colorectal liver metastases.[26–31] This could be considered as level 1c evidence for this treatment strategy.

In this Belgian registry, a significant difference was found in OS and in DFS when the PCI score was dichotomized between patients with PCI $\leq$15 and patients with PCI >15 (Fig. 2). This concurs with earlier articles by Elias and Blot and by Glehen et al. showing that the PCI score, with an arbitrary cutoff at 15, had a significant impact on OS ($P = 0.019$), and completeness of cytoreduction was found to be the principal independent prognostic indicator ($P < 0.001$).[17,21] Besides the dichotomized PCI score, resection of small bowel ($P = 0.004$), postoperative extra-abdominal complications ($P = 0.0005$), and a lesion size of >5 cm ($P = 0.043$) are significantly correlated with OS. Because of the low number of deceased patients and the low number of patients who had some risk factors, results for OS need to be interpreted with care. For DFS, there is a significant correlation with transfusion ($P = 0.018$), and a

trend was observed for the resection of small bowel at debulking. In the largest HIPEC series reported by Elias et al., positive independent prognostic factors identified by multivariable analysis were complete debulking (R0/1 or CC-0), a low PCI score, no invaded lymph nodes, and the use of adjuvant chemotherapy.[20]

The conference on Peritoneal Surface Malignancies in Milan in 2006 attempted to reach a methodological consensus on the drugs to be used intraperitoneally for HIPEC, but did not succeed.[32] This illustrates the complexity of this topic. At present, MMC is still the most frequently used drug intraperitoneally.[24] Verwaal et al. performed the only prospective randomized phase III study comparing CCRS with HIPEC with palliative surgery with systemic chemotherapy, which provided compelling evidence that CCRS with HIPEC improves the survival in patients with PC of colorectal origin.[33,34] In this randomized trial, MMC was used as intraperitoneal drug, providing a high level of evidence (level 1b) for the efficacy of MMC.[24] A frequent criticism of this trial is that patients in the control arm received 5-FU/leucovorin. At present, median OS of 16.8–23.9 months is reported with modern chemotherapy regimens.[22,35] On the other hand, in a retrospective analysis by Hompes et al., patients with unresectable PC of CRC who received modern 5-FU-based systemic therapy combined with oxaliplatin or irinotecan either with or without bevacizumab only rarely reached a survival of 2 years. Of course, these patients all had unresectable and thus extensive PC.[36] Nevertheless, a study by Franko et al. recently confirmed the results of the randomized trial by Verwaal et al.; their analysis stated that even if contemporary chemotherapy was used in the control arm, the benefit in survival with CCRS with HIPEC is maintained.[35]

The characteristics of oxaliplatin and MMC are summarized in Table 6. Both drugs have a high molecular weight, resulting in high intraperitoneal drug concentrations during HIPEC but with limited systemic absorption and toxicity.[32,37] They have a comparable tissue penetration depth and are both potentiated by hyperthermia.[32] Both drugs are alkylating agents, thus interfering with DNA and DNA synthesis, and their function is not cell cycle dependent.[10,38,39] For MMC, the advised intraperitoneal dose is 35 mg/m^2 with a perfusion duration of 90 min, resulting in an AUC ratio (perfusate/plasma) of 10.1 ± 4.6, whereas for oxaliplatin, the advised dose is 460 mg/m^2 over only 30 min, resulting in an AUC ratio (perfusate/plasma) of 12.8 ± 2.9.[12,25,32,37] The intraperitoneal half-life is 49 min for MMC and 29.5 min for oxaliplatin.[11,38] Elias et al. described the high uptake of oxaliplatin in local tissues after HIPEC: 339 ng/mg in tumoral tissue and 392 ng/mg in the peritoneum.[12] Interestingly, besides this regional exposure with intraperitoneal

TABLE 6 MMC and oxaliplatin as intraperitoneal drugs for HIPEC

Characteristic	Intraperitoneal MMC	Intraperitoneal oxaliplatin	Reference
MW, Da	334.3	397.3	32
Tissue penetration depth	2,000 μm	1–2 mm	32
Mechanism[a]	Large MW; antitumoral AB: alkylating agent (tetrazine) + production of free radicals; not cell cycle dependent	Large MW; biotransformation, followed by interaction with DNA (alkylating), thus disturbing DNA synthesis; not cell cycle dependent	10,37,38, pharmaceutical compendium
AUC ratio (perfusate/plasma)	10.1 ± −4.6	12.8 ± −2.9	12,25,36
Advised intraperitoneal dose	35 mg/m^2	460 mg/m^2	32
Duration of perfusion	90 min for first 50% of dose, followed by 25% of dose at 30 and 60 min	30 min	32
Perfusate solution	Isotonic salt solution	Dextrose 5%	25,32,37
t1–2 in perfusate[b]	49 min	29.5 min	11,37
Potentiation by hyperthermia	Yes	Yes	32
Tissue concentration	NS; "rapid tissue concentration over prolonged time period"	High uptake in local tissues (C_{max} peritoneal = 25× C_{max} blood); tumor 339 ng/mg; peritoneum 392 ng/mg	12,38
Toxicity	Grade 2–3 toxicity 65%, severe neutropenia 28%, fistulae 17.6%	Grade 2–3 morbidity 40%; no neutropenia fistulae 10%	12,25,37,39

MW molecular weight, *AB* antibiotic

[a] Lysis of colon cancer cell lines is dose related in CRC

[b] Dependent on the intraperitoneal dosing (mono-, bi-, or triphasic) applied

administration of oxaliplatin, an early experimental pharmacokinetic study by Pestieau and Sugarbaker showed that the highest oxaliplatin concentrations were found in colon tissues.[10] MMC is accepted to have a pharmacokinetic profile resulting in rapid tissue concentration in residual tumor deposits and the peritoneum over prolonged periods of time, but it causes severe neutropenia in 28% of patients, which is not the case for oxaliplatin.[12,25,38–40] Thus, although the systemic absorption of intraperitoneal MMC is limited, the severe neutropenia points to a significant systemic accumulation. This is probably because toxicity is not only the result of the systemic absorption, but also of the metabolization of the chemotherapeutic agent. MMC is predominantly metabolized in the liver, whereas oxaliplatin is not subjected to CYP450-mediated metabolism.[38,41] Urinary excretion is the predominant route of platinum elimination, and tissue binding and renal elimination contribute equally to the clearance of ultrafilterable platinum from plasma.[41] Therefore, maintaining an adequate urinary output is crucial to prevent renal insufficiency. Finally, oxaliplatin has a proven systemic efficacy in CRC and a synergistic activity when used in combination with 5-FU.[42–45] This is, of course, the reason why in many centers HIPEC with intraperitoneal oxaliplatin is combined with the intravenous administration of 5-FU/leucovorin.

In conclusion, CCRS followed by HIPEC with oxaliplatin for PC of colorectal origin can be implemented with acceptable morbidity. Long-term DFS and OS should permit improved selection of patients who will benefit from this extensive surgical approach in view of prolonged survival with modern palliative chemo- and biological therapy.

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