Original Article

Oxaliplatin-based hyperthermic intraperitoneal chemotherapy with single drug versus multiple drug treatment for colorectal cancer with peritoneal metastases: an observational cohort study

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Background: Long-term survival for selected patients with peritoneal metastases (PM) from colorectal cancer (CRC) is possible when treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The objective of this study was to compare three different oxaliplatin-based (OX)-HIPEC regimens. Primary end-point was disease-free survival (DFS), and secondary endpoints, morbidity and overall survival (OS).

Methods: This is a retrospective study of all patients with colorectal PM treated with CRS and HIPEC between 2004 and 2015 from the prospectively maintained Uppsala HIPEC database. One hundred and thirty-three patients were identified. Three HIPEC regimens were included: OX-HIPEC, OX-HIPEC + post-operative intraperitoneal chemotherapy (EPIC) with 5-fluorouracil (5-FU), and oxaliplatin-irinotecan-based (OXIRI)-HIPEC. Multivariable Cox regression for DFS was performed.

Results: Sixty-one patients received OX-HIPEC, 24 patients received OX-HIPEC + 5-FU EPIC, and 48 patients received OXIRI-HIPEC. The DFS for the OX-HIPEC group was 10.5 months, OX-HIPEC + EPIC 11.9 months, and OXIRI-HIPEC 13.4 months (OX-HIPEC *vs.* OXIRI HIPEC, P=0.049). The morbidity and OS did not differ between the groups. In the multivariable analysis, low peritoneal cancer index (PCI), absence of liver metastases, low completeness of cytoreduction (CC) score, and multiple drug (EPIC or OXIRI) HIPEC regimen were independent prognostic factors for DFS.

Conclusions: This study showed improved DFS with an intensification of HIPEC by adding irinotecan or EPIC compared to oxaliplatin alone without an increase in morbidity or mortality.

Keywords: Colorectal cancer (CRC); peritoneal metastases (PM); cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); oxaliplatin

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Introduction

For a long period of time colorectal cancer (CRC) with peritoneal metastases (PM) was considered a palliative situation with a median survival of 5–7 months (1). In the past, these patients received palliative chemotherapy. Cytoreductive surgery (CRS) is a relatively new development in the surgical treatment of advanced gastrointestinal cancer. In brief, the general consensus is that CRS should only be used in patients without hematogenic, extra-abdominal or retro-peritoneal lymph node metastases, with the exception of 1–3 liver metastases (2). The median survival for patients in whom complete

cytoreduction is achieved is around 30 months (3-5). A recent comprehensive meta-analysis by Huang *et al.* (6), conclude that CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) improve median OS in patients with CRC with PM.

The HIPEC method is heterogenous, and the treatment lacks standardization. The recent results from the PRODIGE-7 study, published as an abstract only, suggest that the addition of oxaliplatin-based (OX)-HIPEC does not influence overall survival (OS) (7). Consequently, it would be of interest to evaluate if an intensification of HIPEC by adding EPIC or irinotecan to OX-HIPEC could influence the outcome. The aim of the present study was to examine the impact of three different HIPEC regimens on disease-free survival (DFS), OS, and morbidity and mortality. The three different regimens that are studied are OX-HIPEC, OX-HIPEC + post-operative intraperitoneal chemotherapy (EPIC) with 5-fluorouracil (5-FU), and oxaliplatin-irinotecan-based (OXIRI)-HIPEC + EPIC with 5-FU, and OXIRI-HIPEC. We present the study in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (8) (available at http://dx.doi.org/10.21037/jgo-20-494).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the regional Ethical Review Board, DnR 2013/203. Given the retrospective design of the study, the Ethical Board did not consider a written informed consent to be necessary.

Study design

This study used data from a prospectively maintained HIPEC database at Uppsala University Hospital. All patients with colorectal PM who underwent CRS and OX-HIPEC ± EPIC or OXIRI-HIPEC from 1st January 2004 to 31st December 2015, were included (*Figure 1*). Prior to treatment, all patients were discussed in a multi-disciplinary meeting to ensure that they were eligible for CRS and HIPEC. The eligibility criteria were a histologically confirmed diagnosis of CRC and PM, no distant metastasis, WHO performance ≤2, and normal renal, liver and hematopoietic functions. The presence of one to three liver metastases was not considered a contraindication, as long as they were easily resectable simultaneously as CRS.

Clinicopathological data were obtained from patient records and the Uppsala University Hospital HIPEC database. Variables that were collected included gender, age, prior surgical score (PSS), peritoneal cancer index (PCI), completeness of cytoreduction (CC) score, and type of HIPEC treatment (OX-HIPEC, OX-HIPEC + EPIC, and OXIRI-HIPEC), location of primary tumor (colon or rectum), and node positive primary. Furthermore, in hospital, and 90-day mortality and morbidity, as well as the use of adjuvant chemotherapy, and histopathology were collected from the patient records.

Surgical procedure

At laparotomy the resection of PM followed the principles of Sugarbaker (9). The PCI was calculated, which ranges from 1 to 39. This is a semi-quantitative measure of the tumor burden, obtained by calculating the lesion size scores [0–3] in the 13 regions of the abdomen (10). The CC score was calculated (11), where CC-0 corresponds to no visible tumor tissue left in the abdomen. CC-1 indicates residual tumor nodules <2.5 mm in diameter, and CC-2 means there are remaining nodules between 2.5 and 25 mm, and CC-3 means remaining nodules >25 mm. If the PM was considered too extensive, so as to preclude a complete macroscopic resection the procedure was aborted and CRS not performed. These patients were not included in this study.

Chemotherapy agents

At the start of the Uppsala HIPEC program, OX-HIPEC was given together with 5-FU EPIC for 5 days. After a short period, the EPIC addition was discontinued due to preliminary reports of increased morbidity, and instead combination OXIRI-HIPEC was used. This continued until a national program in Sweden was put in place around 2011, in which case all Swedish centers used single OX-HIPEC as the common standard (*Figure 2*). The HIPEC treatment was given according to the coliseum method (12), where either oxaliplatin (460 mg/m^2) was administered intraperitoneally for 30 minutes or in combination with irinotecan (400 mg/m^2 for both drugs) for 30 minutes. All three different HIPEC regimens in this study included a single bolus-dose of IV 5-FU at 400 mg/m^2 intraoperatively (sometimes dose reduced if necessary). The intra-abdominal temperature was targeted at 41–43 ℃, and controlled with three thermal probes,

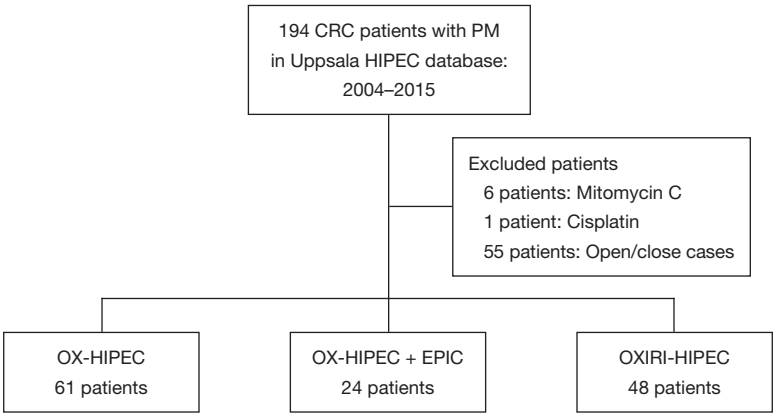


Figure 1 Flowchart of patients with CRC and PM (n=133). CRC, colorectal cancer; PM, peritoneal metastases; HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC.

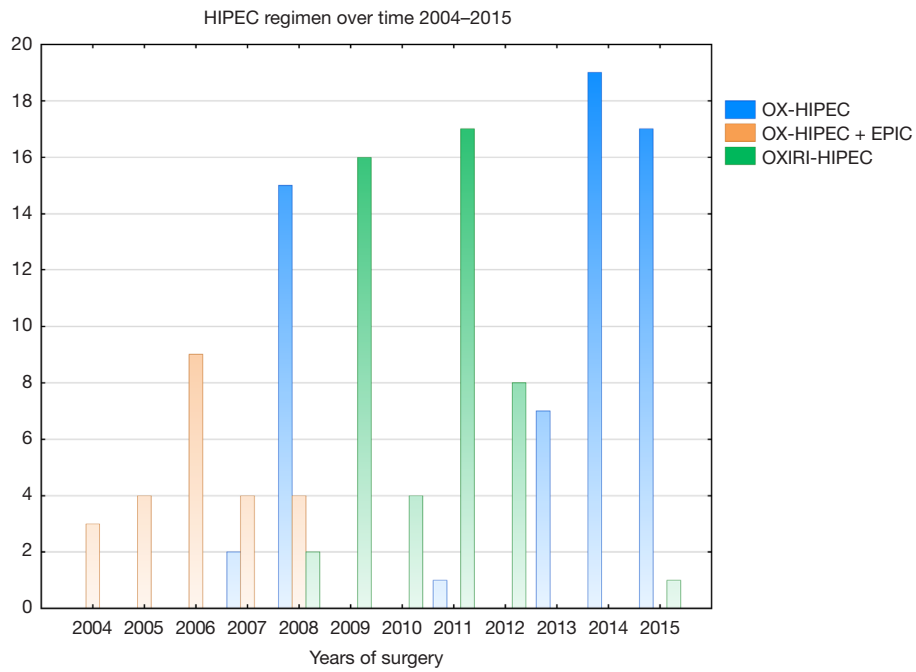


Figure 2 Description of which HIPEC regimen, that was used during the study period 2004–2015. HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC.

with a flow-rate of 1–2 L/min. Electrolyte-free glucose (50 mg/mL) was used for perfusion. The EPIC treatment was a normothermic 5-FU treatment administered daily at post-operative day 1–5 at 500–600 mg/m^2 in 250 mL of saline solution that was injected through an abdominal drainage catheter. The drains were clamped overnight and then opened for a few hours before the next administration.

Follow-up after surgery

All patients were followed-up 4 weeks post-operatively in

the outpatient clinic. Thereafter, follow-up was done, as a minimum, every 6 months for 2 years and then yearly, with contrast enhanced computed tomography (CE-CT) of the chest and abdomen. The median follow-up time was defined as median observation time for those patients who were alive at the end of the study. Information regarding recurrence was retrieved from patient medical records, and death and cause of death from the Swedish Data Registry.

Statistical analysis

DFS was defined as the time interval between date of surgery and documented recurrence or death from any cause. OS was defined as the time period between date of surgery and death from any cause. Time was censored at the last follow-up for patients that were still alive or lost to follow-up. Survival was analyzed with the Kaplan-Meier method, and compared with the log-rank test. Pearson's chi^2 test was used to compare differences in categorical variables between the three groups, and Kruskal-Wallis test was used when comparing continuous variables. A univariable and multivariable Cox proportional hazard regression model was used to assess the relationship between a predetermined set of clinicopathological variables and DFS. All analyses were carried out with Statistica 13.4.0.14 (TIBCO Software Inc., Palo Alto, CA, USA), and the level of statistical significance was defined as a two-sided $P<0.05$.

Results

Patient characteristics

This study included 133 patients (*Table 1*). Median age for the whole study population was 59 years. A majority of patients were women, 76 (57%) compared to 57 (43%) men. Sixty-one patients were treated with OX-HIPEC, 24 patients with OX-HIPEC + EPIC, and 48 patients with OXIRI-HIPEC. The primary tumor was located in the colon in 92% (n=123) of the patients and in the rectum in 8% (n=10). Liver metastases were present in 25% (n=6) of the patients in the OX-HIPEC + EPIC compared to 7% (n=4) and 13% (n=6) in the OX-HIPEC and OXIRI-HIPEC groups, respectively (P=0.06).

Synchronous colorectal PM were present in 71% of the cases in the OXIRI-HIPEC group compared to 58% and 56%, in OX-HIPEC + EPIC and OX-HIPEC groups, respectively. There was a statistical difference between the groups in terms of neoadjuvant chemotherapy (P=0.004) and node positive primary (P=0.003), but not in terms of adjuvant chemotherapy (P=0.64). Overall, the three groups showed similar demographic and patient characteristics (*Table 1*). The median follow-up time was 86 (IQR, 52–117) months.

Surgical results

Median PCI was 14 in the whole cohort. A CC-0 resection was achieved in 89% (n=118) of the patients. There was no difference in CC-scores between the groups (P=0.094). Resection of liver metastases was performed in 16% (n=35) of patients. There was a difference in operating time between the groups (P=0.004). Mean operating time in the OX-HIPEC was 456 minutes (SD: 197), compared to 542 minutes (SD: 155) in the HIPEC + EPIC, and 522 minutes (SD: 137) in the OXIRI-HIPEC.

Post-operative mortality and morbidity

In-hospital mortality occurred in 2 cases (1.5%). Post-operatively, 14 patients were re-operated due to complications (*Table 2*). There were no differences in morbidity, defined as Clavien-Dindo grade 3 or 4, between the groups (P=0.2). The overall rate of morbidity was 26% (n=35). Post-operative neutropenia occurred in 44% (n=28) of the patients in the OXIRI-HIPEC group, compared to only 1.6% (n=1) of patients in the OX-HIPEC group ($P\leq0.0001$) (*Table 2*) (13). A secondary analysis that compared single-drug HIPEC (OX-HIPEC) and multiple-drug HIPEC (OX HIPEC + EPIC or OXIRI-HIPEC) revealed no differences in Clavien-Dindo grades 3–4, or return to operation theatre post-operatively (*Table 2*). The rate of peritoneal recurrence was improved from 49% to 32% with a borderline P value (P=0.051).

Survival analyses

In the univariable analysis PCI, and a CC score 1–3 *vs.* 0, were associated with worse DFS (*Table 3*). In the multivariable Cox regression model PCI (HR: 1.03, 95% CI: 1.01–1.06), liver metastases (HR: 2.29, 95% CI: 1.25–4.19), and CC score 1–3 *vs.* 0 (HR: 5.19, 95% CI: 2.46–11.0), remained significantly associated with poor DFS. Moreover, combination drug-therapy with HIPEC + EPIC or OXIRI-HIPEC, was associated with better DFS (HR: 0.48, 95% CI: 0.25–0.92, and HR: 0.59, 95% CI: 0.37–0.94, respectively), than monotherapy (OX-HIPEC) (*Table 3*).

At 24 months 48 (36%) patients had a systemic recurrence,

Table 1 Demographics and baseline characteristics of patients with CRC with PM

Variable	OX-HIPEC, n=61	OX-HIPEC + 5-FU EPIC, n=24	OXIRI- HIPEC, n=48	Whole cohort, n=133	P value
Age [years], median [IQR]	58 [46–67]	58 [50–64]	59 [46–65]	59 [47–65]	NS
Gender, n [%]					0.057
Male	25 [41]	6 [25]	26 [54]	57 [43]	
Female	36 [59]	18 [75]	22 [46]	76 [57]	
Primary tumor, n [%]					0.75
Colon	55 [90]	23 [96]	45 [94]	123 [92]	
Rectum	6 [10]	1 [4]	3 [6]	10 [8]	
PM disease, n [%]					0.26
Synchronous	34 [56]	14 [58]	34 [71]	82 [62]	
Metachronous	27 [44]	10 [42]	14 [29]	51 [38]	
Neoadjuvant treatment, n [%]	24 [39]	16 [67]	39 [81]	79 [59]	0.0004
Node positive primary, n [%]	46 [75]	12 [50]	34 [49]	92 [69]	0.003
Missing data	1 [2]	6 [25]	2 [4]	9 [7]	
Differentiation, n [%]					0.3
Poor	18 [30]	8 [33]	11 [23]	37 [28]	
Moderate/high	40 [66]	11 [46]	34 [71]	85 [64]	
Missing data	3 [4]	5 [21]	3 [6]	11 [8]	
Signet cells, n [%]	8 [13]	3 [12]	6 [12]	17 [13]	1.00
PCI, median [IQR]	14 [9–23]	17 [11–24]	13 [7–20]	14 [7–22]	NS
Liver metastases, n [%]	4 [7]	6 [25]	6 [13]	35 [16]	0.06
Operating time, mean ± SD	456±197	542±155	522±137	495±132	0.047
CC score, n [%]					0.094
0	55 [90]	19 [79]	44 [92]	118 [89]	
1	5 [8]	1 [4]	3 [6]	9 [7]	
2	0 [0]	3 [13]	1 [2]	4 [3]	
3	1 [2]	1 [4]	0 [0]	2 [1]	
Adjuvant chemotherapy, n [%]					0.64
Yes	26 [43]	11 [46]	15 [31]	75 [56]	
No	30 [49]	13 [54]	32 [67]	52 [39]	
Missing data	5 [8]	0 [0]	1 [2]	6 [5]	

CRC, colorectal cancer; PM, peritoneal metastases; HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; 5-FU, 5-fluorouracil; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC; PCI, peritoneal cancer index; CC, completeness of cytoreduction.

Table 2 Morbidity outcomes and recurrence analysis

Variable	OX-HIPEC, n=61	OX-HIPEC + EPIC, n=24	OXIRI-HIPEC, n=48	Whole cohort, n=133	P value
Morbidity					
Return to OR postop, n [%]	6 [10]	4 [17]	4 [8]	14 [11]*	0.4
Clavien-Dindo grade 3–4, n [%]	19 [31]	7 [29]	9 [19]	35 [26]	0.2
3	15 [25]	7 [29]	7 [15]	29 [22]	
4	4 [6]	0 [0]	2 [4]	6 [4]	
In-hospital mortality, n [%]	1 [2]	1 [4]	0 [0]	2 [2]	
Any grade neutropenia, n [%]	1 [2]	6 [25]	21 [44]	28 [21]	<0.0001
Recurrences at 24 months					
Systemic recurrence	18 [30]	9 [37]	21 [44]	48 [36]	0.2
Missing data	8 [13]	7 [29]	5 [10]	20 [15]	
Peritoneal recurrences	30 [49]	7 [29]	16 [33]	53 [40]	0.08
Missing data	5 [8]	1 [4]	3 [6]	9 [7]	
Secondary analysis: single drug HIPEC *vs.* multiple drug HIPEC	Single drug HIPEC, n=61	Multiple drug HIPEC (OX EPIC and OXIRI), n=72			
Return to OR postop, n [%]	6 [10]	8 [11]		14 [11]*	0.9
Clavien-Dindo grade 3–4, n [%]	19 [31]	16 [22]		35 [26]	0.3
Peritoneal recurrences, n [%]	30 [49]	23 [32]		53 [40]	0.051

*, Reasons for re-operation (n=14): 2 bleeding, 2 anastomotic leakage, 2 sepsis unclear abdominal cause, 3 small bowel or gastric perforations, 2 wound dehiscence, 1 mesh-caused bowel obstruction, 1 unclear severe postop pain, 1 ureter perforation. HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC; OR, operating room.

and 53 (40%) patients had a peritoneal recurrence. There were no differences in systemic recurrence between the groups; however, peritoneal recurrences showed a trend toward improved recurrence rates, P=0.08 (*Table 2*). *Figure 3* shows DFS for the respective groups. In the OX-HIPEC group DFS was 10.5 months compared to 13.4 months in OXIRI-HIPEC (P=0.049). DFS was 11.9 months in the OX-HIPEC + EPIC group. In a subgroup analysis excluding CC 1–3 and liver metastases, DFS was 11.7 months in OX-HIPEC, OX-HIPEC + EPIC 23.6 months, and OXIRI-HIPEC 18.6 months (*Figure 4*).

Overall median survival in the OX-HIPEC group was 31.2 months, and in the OX-HIPEC + EPIC, and OXIRI-HIPEC groups 24 and 36.5 months, respectively (*Figure 5*). There were no statistical differences between the groups.

Discussion

Intensification of OX-HIPEC with either the addition of irinotecan during HIPEC or 5-FU EPIC treatment resulted in improved DFS, both in the Kaplan-Meier analysis with log-rank test and in the multivariable Cox regression model with hazard ratios. The subgroup analysis with CC1–3 and liver metastases excluded confirmed this conclusion further with median DFS reaching 24 months. However, as with the preliminary results from the PRODIGE-7 study, an OS difference was not achieved (7). Nonetheless, this is probably explained by the fact that the patients will receive a wide array of future treatments. Further curative intent surgeries/interventions, different number of palliative lines of treatment including possibly new trial drugs, etc., make OS comparisons difficult to do without significantly increasing the sample size.

The rationale for HIPEC

PM from CRC is associated with a poor prognosis. For a long period of time these patients were considered palliative

Table 3 Univariable and a priori multivariable Cox proportional analysis with DFS as endpoint

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.00 (0.99–1.01)	0.6	1.00 (0.99–1.02)	0.9
Gender male/female (n)	1.16 (0.85–1.60)	0.4	0.86 (0.55–1.35)	0.8
Rectum *vs.* colon	1.24 (0.73–1.21)	0.4	2.22 (0.95–5.00)	0.07
Neoadjuvant treatment	0.98 (0.70–1.35)	0.9	0.96 (0.61–1.50)	0.8
Node positive disease primary	1.10 (0.74–1.65)	0.6	0.89 (0.54–1.47)	0.6
PCI	1.05 (1.03–1.07)	<0.001	1.03 (1.01–1.06)	0.005
Liver metastases	1.32 (0.79–2.19)	0.3	2.29 (1.25–4.19)	0.008
Adjuvant chemotherapy given	1.20 (0.83–1.73)	0.3	1.24 (0.79–1.92)	0.3
CC score 1–3 *vs.* 0	4.18 (2.33–7.52)	<0.001	5.19 (2.46–11.0)	<0.001
HIPEC regimen				
OX-HIPEC	Reference			
OX-HIPEC + 5-FU EPIC	0.76 (0.44–1.31)	0.3	0.48 (0.25–0.92)	0.03
OXIRI-HIPEC	0.66 (0.43–1.01)	0.06	0.59 (0.37–0.94)	0.03

DFS, disease-free survival; CI, peritoneal cancer index; CC, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; 5-FU, 5-fluorouracil; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC.

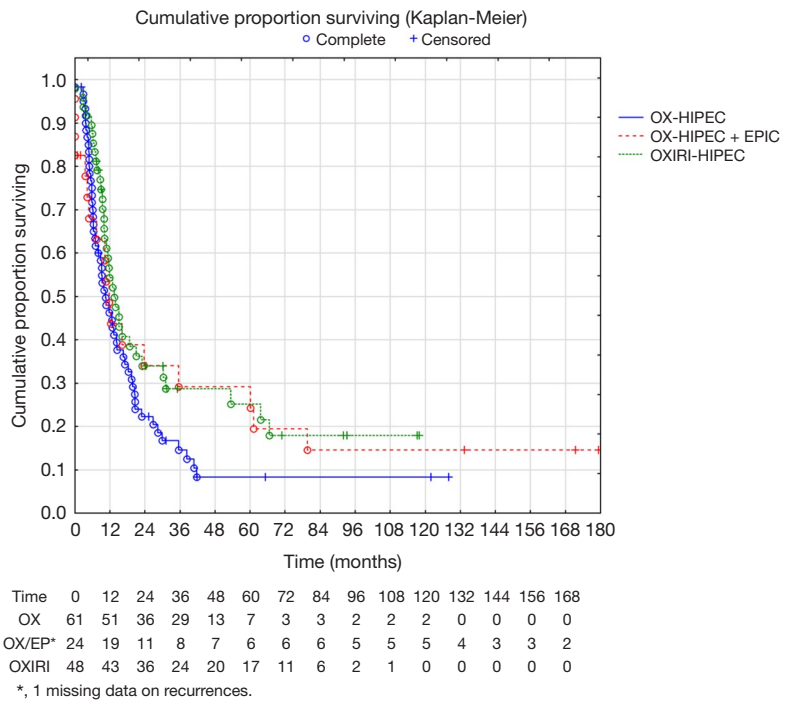
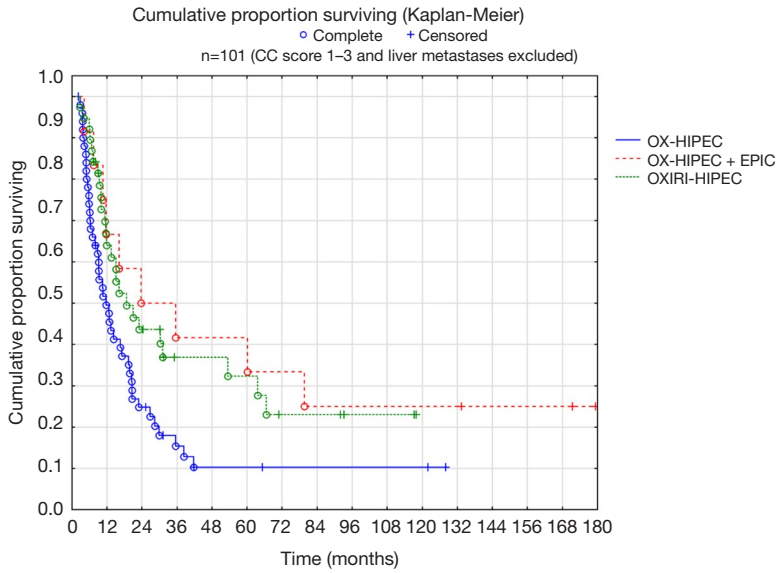
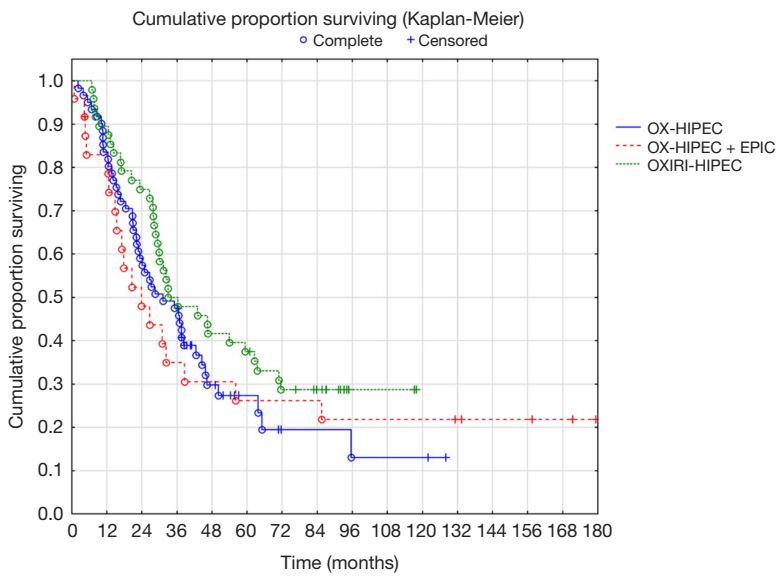


Figure 3 DFS between the three HIPEC regimens. OX-HIPEC *vs.* OX-HIPEC + EPIC P=0.33, OX-HIPEC *vs.* OXIRI-HIPEC P=0.049 (total n=133). DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC.



Time	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168
OX	51	24	12	6	3	3	2	2	2	2	2	0	0	0	0
OX/EP	12	8	6	5	5	5	4	3	3	3	3	3	2	2	2
OXIRI	38	22	15	8	8	7	4	4	2	2	0	0	0	0	0

Figure 4 DFS between the three HIPEC regimens, excluding CC1–3 and liver metastases. OX-HIPEC *vs.* OX-HIPEC + EPIC P=0.029, OX-HIPEC *vs.* OXIRI-HIPEC P=0.017 (total n=101). DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; CC, completeness of cytoreduction; OX-HIPEC, oxaliplatin-based HIPEC; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC.



Time	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168
OX	61	51	36	29	13	7	3	3	2	2	2	0	0	0	0
OX/EP	24	19	11	8	7	6	6	6	5	5	5	4	3	3	2
OXIRI	48	43	36	24	20	17	11	6	2	1	0	0	0	0	0

Figure 5 OS between the three HIPEC regimens. OX-HIPEC *vs.* OX-HIPEC + EPIC P=0.9, OX-HIPEC *vs.* OXIRI-HIPEC P=0.16 (total n=133). OS, overall survival; HIPEC, hyperthermic intraperitoneal chemotherapy; OX-HIPEC, oxaliplatin-based HIPEC; EPIC, post-operative intraperitoneal chemotherapy; OXIRI-HIPEC, oxaliplatin-irinotecan-based HIPEC.

with a median OS of 5–7 months (1). Advancements in chemotherapy, and molecular-targeted drugs, such as cetuximab and bevacizumab, may potentially extend median OS in these patients to nearly a year (14). Nevertheless, the prognosis is grim. In the last decades, CRS and HIPEC show promising results in patients in whom a complete macroscopic resection is achieved. Several studies have compared CRS and intraperitoneal chemotherapy, such as HIPEC and EPIC, with systemic chemotherapy in patients with CRC and PM (15-21).

A recent meta-analysis that included 76 studies, that assessed the therapeutic efficacy of CRS and HIPEC in patients with CRC and PM, concluded that HIPEC conferred significantly better survival in selected patients with CRC and PM (6). Unfortunately, the number of randomized control trials is limited, and there still remains a controversy regarding the role of HIPEC in patients with CRC and PM (17). Few previous studies have compared the long-term results of CRS and OX-HIPEC or OX-HIPEC + EPIC and OXIRI-HIPEC in patients with CRC and PM (22).

Baseline characteristics

This retrospective study, that included 133 patients compared OX-HIPEC with OX-HIPEC + EPIC and OXIRI-HIPEC in patients with CRC and PM. Primary end-point was DFS, and secondary end-points morbidity and OS. All three treatment groups show similar baseline characteristics (*Table 1*). There are no differences with regards to age, gender, PCI, location of primary tumor, presence of liver metastases (although trend to more liver metastases in the intensified treatment groups, P=0.06) or whether PM is metachronous or synchronous. Of note, is that there was a higher proportion of node-positive primary in the OX-HIPEC group compared to OXIRI-HIPEC. Furthermore, neo-adjuvant chemotherapy was more commonly given in the OXIRI-HIPEC group compared with the other HIPEC regimens. A CC score-0 was similar across the three groups, and achieved in 89% of the cases in the whole cohort.

DFS, OS and complications

In contrast to Quenet *et al.* (22), DFS was better in patients that received intensified treatment with OXIRI-HIPEC compared to OX-HIPEC. DFS was 13.4 months compared to 10.5 months (P=0.049), and median OS was 35.6 months compared to 31.2 months (P=0.16). Five-year OS rate was 11% in OX-HIPEC, 25% in OX-HIPEC + EPIC, and 35% in OXIRI-HIPEC.

The multivariable Cox regression model showed that CC-score 1–3 *vs.* 0 was strongly associated with worse DFS (HR: 5.19, 95% CI: 2.46–11.0). PCI and liver metastases were also identified in the multivariable analysis as associated with worse DFS. Additionally, intensification of HIPEC with either OX-HIPEC + EPIC or OXIRI-HIPEC was associated with better DFS (*Table 2*). Morbidity according to Clavien-Dindo grades 3–4 were similar across the three treatment regimens. Neutropenia was significantly more common in the OXIRI-HIPEC group compared to OX-HIPEC and OX-HIPEC + EPIC (P≤0.0001). There were no differences in mortality between the three HIPEC treatments (*Table 3*).

A limitation of the present study is its retrospective non-randomized design. The proper impact of HIPEC on survival may therefore be difficult to assess due to selection biases. Even though these three regimens essentially represent three time periods, patient selection has been refined over the years. However, it is interesting to note that the most recent time period has been that of single-oxaliplatin use (the current national standard in Sweden) and OX-HIPEC with EPIC was used during the initial phase of the HIPEC program with the OXIRI HIPEC period in between. As such, it was unexpected that the multiple drug regimens would do so well in this comparison considering their early use.

Another potential limitation of this paper is the possibility of lead-time bias. That is, that the difference in DFS between the OXIRI-HIPEC and OX-HIPEC groups is merely a reflection of when and how often the scanning was performed. This is unlikely, however, given that all patients were followed-up similarly, according to national guidelines, with pre-specified time intervals between the imaging.

A common argument against HIPEC is that standard adjuvant systemic chemotherapy may have offered similar survival benefits for these highly selected patients. To answer, this question a randomized control trial is required. Nevertheless, this study provides important results concerning increased rates of DFS with intensified HIPEC treatments that can provide suggestions for future clinical trials. In Sweden, one such phase I/III trial program has recently been approved for funding by the Swedish Research Council. This program will dose-titrate a 1-day early EPIC with 5-FU and then move into a randomized

trial where oxaliplatin HIPEC will be compared to oxaliplatin/irinotecan HIPEC + 1-day 5-FU EPIC for patients with CRC and PM disease (23).

Conclusions

An intensification of HIPEC by adding either irinotecan to oxaliplatin (OXIRI-HIPEC) or adding 5-FU EPIC resulted in better DFS compared to OX-HIPEC alone without an increased Clavien-Dindo morbidity or in-hospital mortality.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the regional Ethical Review Board, DnR 2013/203. Because of the retrospective nature of the study, the Ethical Board did not consider a written informed consent to be necessary.

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