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ORIGINAL ARTICLE

Retrospective Cohort Study

Comparison of hyperthermic intraperitoneal chemotherapy regimens for treatment of peritoneal-metastasized colorectal cancer

Julia Spiegelberg, Hannes Neeff, Philipp Holzner, Mira Runkel, Stefan Fichtner-Feigl, Torben Glatz

ORCID number: Julia Spiegelberg 0000-0002-1980-9104; Hannes Neeff 0000-0002-6750-3943; Philipp Holzner 0000-0001-9221-9728; Mira Runkel 0000-0002-9454-7677; Stefan Fichtner-Feigl 0000-0002-6710-562X; Torben Glatz 0000-0001-8908-0577.

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Julia Spiegelberg, Hannes Neeff, Philipp Holzner, Mira Runkel, Stefan Fichtner-Feigl, Torben Glatz, Department of General and Visceral Surgery, Medical Center – University of Freiburg, Freiburg 79106, Germany

Torben Glatz, Department of Surgery, Marien Hospital Herne, Ruhr-University Bochum, Herne 44625, Germany

Corresponding author: Torben Glatz, MD, Surgeon, Department of Surgery, Marien Hospital Herne, Ruhr-University Bochum, Hölkeskampring 40, Herne 44625, Germany. torben.glatz@uniklinik-freiburg.de

Abstract

BACKGROUND

Cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) improves patient survival in colorectal cancer (CRC) with peritoneal carcinomatosis (PC). Commonly used cytotoxic agents include mitomycin C (MMC) and oxaliplatin. Studies have reported varying results, and the evidence for the choice of the HIPEC agent and uniform procedure protocols is limited.

AIM

To evaluate therapeutic benefits and complications of CRS + MMC *vs* oxaliplatin HIPEC in patients with peritoneal metastasized CRC as well as prognostic factors.

METHODS

One hundred and two consecutive patients who had undergone CRS and HIPEC for CRC PC between 2007 and 2019 at the Medical Center of the University Freiburg regarding interdisciplinary cancer conference decision were retrospectively analysed. Oxaliplatin and MMC were used in 68 and 34 patients, respectively. Each patient's demographics and tumour characteristics, operative details, postoperative complications and survival were noted. Complications were stratified and graded using Clavien/Dindo analysis. Prognostic outcome factors were identified using univariate and multivariate analysis of survival.

RESULTS

The two groups did not differ significantly regarding baseline characteristics. We found no difference in median overall survival between MMC and oxaliplatin HIPEC. Regarding postoperative complications, patients treated with oxaliplatin

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HIPEC suffered increased complications (66.2% *vs* 35.3%; $P = 0.003$), particularly intestinal atony, intraabdominal infections and urinary tract infection, and had a prolonged intensive care unit stay compared to the MMC group (7.2 d *vs* 4.4 d; $P = 0.035$). Regarding univariate analysis of survival, we found primary tumour factors, nodal positivity and resection margins to be of prognostic value as well as peritoneal cancer index (PCI)-score and the completeness of cytoreduction regarding peritoneal carcinomatosis. Multivariate analysis of survival confirmed primary distant metastasis and primary tumour resection status to have a significant impact on survival and likewise peritoneal cancer index-scoring regarding peritoneal carcinomatosis.

CONCLUSION

In this single-institution retrospective review of patients undergoing CRS with either oxaliplatin or MMC HIPEC, overall survival was not different, though oxaliplatin was associated with a higher postoperative complication rate, indicating treatment favourably with MMC. Further studies comparing HIPEC regimens would improve evidence-based decision-making.

Key words: Colorectal cancer; Peritoneal carcinomatosis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Chemotherapy; Mitomycin

Core tip: We evaluated the therapeutic efficiency of cytoreductive surgery in combination with two different hyperthermic intraperitoneal chemotherapy (HIPEC) regimens, comparing mitomycin C HIPEC *vs* oxaliplatin HIPEC. We therefore retrospectively evaluated 102 patients undergoing cytoreductive surgery and HIPEC and statistically analysed demographics, perioperative complication and survival outcome. We found no difference in median overall survival between mitomycin C and oxaliplatin HIPEC. Regarding postoperative complications, patients treated with oxaliplatin HIPEC suffered an increased complication rate. Regarding multivariate analysis of survival, primary distant metastasis and primary tumour resection seem to have a significant impact on survival and likewise peritoneal cancer index-scoring regarding peritoneal carcinomatosis. Further prospective studies comparing HIPEC regimens would improve therapeutic decision-making.

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INTRODUCTION

Among patients with resected colorectal cancer (CRC), approximately 50% develop distant metastases either synchronously or metachronously. Most common locations are liver (35%-55%), lungs (10%-20%) and peritoneal carcinomatosis (PC) (10%-25%)[1]. In the past, the median overall survival (OS) of patients diagnosed with PC of CRC origin was 4-7 mo, for patients undergoing palliative surgery or 5-fluorouracil (5-FU)-based systemic chemotherapy[2-4]. Improvement in systemic chemotherapy, using chemotherapeutic agents such as oxaliplatin and irinotecan, along with anti-angiogenesis molecular targeting agents cetuximab and bevacizumab, led to an increased OS of about 12 mo[5].

The introduction of multimodal treatment strategies including systemic chemotherapy and cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) showed promising progress in long-term survival. The HIPEC procedure is intended to destroy any remaining tumour cells after surgical tumour debulking by local administration of chemotherapy to the peritoneal cavity for homogeneous drug distribution and enhanced cytotoxicity induced by heat[6]. Depending on the extent of intraabdominal tumour load, remarkable survival benefits

have been reported compared to systemic chemotherapy with 5-FU/leucovorin alone in a randomized controlled trial[7]. Median OS of selected patients with CRC PC improved to 21-63 mo with a 5-year survival rate up to approximately 58%[8]. The most frequently used cytotoxic drugs for HIPEC in CRC are mitomycin C (MMC) and oxaliplatin combined with systemic 5-FU and leucovorin[9].

Initially, HIPEC regimen was most commonly conducted with MMC but subsequently the addition of oxaliplatin became the standard systemic treatment in CRC[10-12]. This brought about a change of regimen for HIPEC with MMC being only used as salvage treatment[13]. The combination of cisplatin and MMC is also frequently used and seems to be a valid HIPEC protocol in peritoneal metastases of CR origin. Recent studies evaluating this protocol demonstrated prolonged survival with limited toxicity[14,15].

Upfront CRS with HIPEC (CRS-HIPEC) is currently the standard treatment for colorectal peritoneal metastases in eligible patients due to the proven superiority to palliative chemotherapy alone[16,17]. Nevertheless, therapeutic efficacy of this treatment strategy for CRC PC patients remains controversial due to contradicting evidence, especially regarding the value of HIPEC.

The first formal randomized controlled trial for CRC assessing the benefit of a 30 min oxaliplatin-based HIPEC added to surgery failed to show survival improvement[18]. Leung *et al*[19] demonstrated that patients with CRC treated with oxaliplatin HIPEC had better OS than those receiving MMC-based HIPEC (median survival: 56 mo *vs* 26 mo, respectively). In contrast, Prada-Villaverde *et al*[20] reported that HIPEC with MMC may be superior to oxaliplatin-based HIPEC when patients have favourable histology or a low burden of PC (median survival: 54.3 mo *vs* 30.4 mo, respectively). At present there is no prospective study that compares these two HIPEC regimens for treatment of peritoneal metastasized CRC. Thus, a reassessment of HIPEC and the need for structured treatment protocols should be addressed. In this retrospective clinical analysis, we evaluated the outcome of patients undergoing CRS HIPEC at the university medical centre of Freiburg.

MATERIALS AND METHODS

This study evaluated the outcome of 102 consecutive patients with PC of colorectal origin, who underwent CRS and HIPEC between January 2007 and March 2019 at the Medical Center of the University Freiburg (MCUF). Patients receiving HIPEC with either palliative or CRS were included.

Patients with appendiceal tumours/pseudomyxoma peritonei and PC of other origin (non-colorectal) were excluded as well as patients who were planned for HIPEC but had not received HIPEC treatment due to surgeon's intraoperative decision. HIPEC regimens were chosen regarding current available data with MMC or oxaliplatin.

From 2007 until 2014, MMC was used, and from 2014 to 2018 it changed to oxaliplatin. Analogous to PRODIGE7 trial, HIPECs since 2018 were conducted with MMC.

Informed consent was obtained from all patients before their inclusion in the cancer registry. The study was approved by the Medical Ethics Committee of the University of Freiburg (EK-FR 4/20). The analysed data was extracted from the anaesthetic protocols and the electronic health records.

Pretherapeutic work-up

Preoperative work-up started in the outpatient setting of MCUF. Previous oncological therapies and comorbidities were recorded, and pulmonary and cardiac check-ups were routinely performed in high-risk patients. Pretherapeutic diagnostics included thoraco-abdominal computerized tomography in all patients and endoscopy or diagnostic laparoscopy with biopsies when appropriate. All patients were discussed in our interdisciplinary cancer conference, and decision for CRS with HIPEC was made if a complete resection seemed achievable. Extensive liver metastases as well as extra abdominal or retroperitoneal metastases were seen as contraindication for surgical intervention.

Depending on the treating physician's protocol and interdisciplinary consensus as well as timing of diagnosis and previous chemotherapy courses, perioperative systemic therapy consisted of either neoadjuvant and adjuvant cycles of capecitabine with oxaliplatin, neoadjuvant and adjuvant cycles of 5-FU/leucovorin with oxaliplatin, or neoadjuvant cycles of 5-FU/leucovorin with irinotecan followed by capecitabine or

adjuvant cycles of fluoropyrimidine monotherapy.

For patients with intestinal obstruction, palliative resections and palliative HIPEC were considered according to interdisciplinary cancer conference decision.

Surgical therapy

The operative procedure was chosen according to the extent and location of the primary tumour and the peritoneal metastases. After explorative midline laparotomy, the complete abdominal cavity was inspected to assess the extent of peritoneal carcinomatosis, defined by the peritoneal cancer index (PCI). According to Sugarbaker's original work, the PCI system divides the abdomen and the pelvis into 13 regions. The lesions are graded according to size (0 through 3) in each abdominopelvic region and are added as a numerical score[21].

Afterwards, the Sugarbaker protocol (Sugarbaker *et al*[6], 1995) was adhered, which assessed tumour resection and resection of visceral organs and peritoneum. Here, resections were classified and subdivided into large intestine, small intestine, liver, diaphragm, omentum and peritoneum.

The Completeness of Cytoreduction (CC) Score, which quantifies the completion of CRS, was assessed after resection. Before closure of the abdominal cavity at least four 24CH silicon-drainages and a temperature probe for the HIPEC were placed.

HIPEC

Simultaneous application of cytotoxic drugs both intraperitoneal and intravenously (i.v.) was used when performing an oxaliplatin based HIPEC with 5-FU + leukovorin i.v. (bidirectional HIPEC). Cytotoxic drugs were prepared by our clinic pharmacy using saline solution as carrier solution in a 50 mL syringe. Dosage level was 30 mg/m² body surface for MMC, 300 mg/m² for oxaliplatin, 400 mg/m² for 5-FU and 20 mg/m² for leukovorin.

The chemo infusion was performed in a closed abdominal system using an extra corporal roller pump system with heat exchanger. Three silicon-drainages were used as fluid inlets and one as outlet. After establishing a stable circulation of saline solution, the cytotoxic drug was added. The degree of hyperthermia ranged between 39 °C to 43 °C using 42 °C as target level. The intraperitoneal circulating time of oxaliplatin was 30 min, respectively 90 min for MMC. After completing the circulation time, the roller pump was used to aspirate the intraabdominal fluids. Silicon drainages were left in the early postoperative setting to allow drainage of remaining accumulated fluids. All patients were transferred postoperatively to the intensive care unit (ICU) for further monitoring.

Follow-up

Perioperative complications were recorded up to 90 d after surgery and were graded according to Clavien/Dindo-Classification[22]. Grade 1 complications (minor deviation) were not recorded. Discharged patients were followed up at least once in the surgical outpatient department and referred back either to the oncology department or to a resident oncologist for further follow-up. The survival data were systematically obtained from the cancer registry of the MCUF Cancer Center. Data regarding postoperative chemotherapy were directly obtained from the resident oncologist or general physician.

Statistical analysis

The results of our study were gained by retrospective analysis of our prospective CRC databases. SPSS 22 for Windows™ was used for statistical analysis (SPSS, Armonk, NY, United States). Categorical variables were given in absolute and relative frequencies; differences were evaluated by Fisher's exact test. Quantitative values were expressed as mean ± standard deviation and medians with range, as appropriate, and differences were measured using the Kruskal-Wallis test. A Mann-Whitney-U-test was added to compare groups. Survival was univariately analysed by the Kaplan-Meier method with a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed by the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic) including the report of relative risks and their 95%-confidential intervals. A P value < 0.05 was considered statistically significant.

RESULTS

Demographics

From January 2007 to March 2019, 102 patients underwent CRS-HIPEC or palliative resections and HIPEC. The cohort contained 60 male patients and 42 female patients. Sixty-eight patients were treated with oxaliplatin/5-FU HIPEC and 34 patients with MMC HIPEC. Three patients in the MMC-group received early postoperative intraperitoneal chemotherapy during the first 48 hours after CRS.

The groups were balanced regarding baseline characteristics, besides a higher American Society of Anesthesiologists (ASA) (P = 0.002) score and a higher rate of T4b (P = 0.027) tumours in the Oxaliplatin group. Median PCI-score was not statistically different across groups but was lower by trend in the Oxaliplatin group [8 (range 0-30) *vs* 12 (range 0-39) in the MMC-group; P = 0.312].

Palliative resections without cytoreduction were performed in one patient receiving oxaliplatin/5-FU HIPEC and in two patients treated with MMC-HIPEC (Table 1).

We had a loss to follow-up rate of 3.9 % (four patients). All of them were treated with MMC-HIPEC.

Perioperative results

There was no difference in the overall length of hospital stay [11.4 d (4-35)] for MMC *vs* 12.4 (2-46) for oxaliplatin; however, the oxaliplatin based HIPEC showed a significantly longer ICU stay [7.2 d (2-50) *vs* 4.4 d (2-9); P = 0.035].

Our data showed a total complication rate of 56%, with a statistically significant higher complication rate associated with oxaliplatin compared to MMC: 35% *vs* 66% (P = 0.003).

In further subgroup analysis we found an increased rate of intestinal atony (9% *vs* 29%; P = 0.015), abdominal infections (3% *vs* 21%; P = 0.013) and urinary tract infections (0% *vs* 9%; P = 0.034) for oxaliplatin HIPEC. The severity of complications, stratified according to the Clavien-Dindo classification, was also higher in the Oxaliplatin group (P = 0.029).

No patients died perioperatively, and 11 patients died during the first 90 d after surgery due to oncological or other medical reasons (Table 2).

Analysis of survival

Mean follow-up was 23.3 mo. There was no statistically significant difference recording median OS (P = 0.139). We performed a univariate survival analysis to compare potential prognostic factors. No differences in survival rates were found comparing sex, age, body mass index (BMI) and ASA-scoring (Table 3). Likewise, primary tumour location (colon *vs* rectum) did not affect survival rate in our cohort (P = 1.0). Our data showed no difference in median survival when comparing primary T-stage (49 mo for T1-3 *vs* 30 mo for T4a *vs* not reached for T4b) but a significant influence of primary nodal stage (88 mo for N0 *vs* 51 mo for N1 *vs* 30 mo for N2a and 18 mo for N2b; P = 0.013). Likewise, according to our data, synchronous diagnosis of the PC or other distant metastasis was associated with a worse median survival (57 mo for M0 *vs* 35 mo for M+; P = 0.046). Furthermore, tumour grading and primary resection level also affected median survival (Figure 1).

In addition, lower PCI-score and a CC0- resection were associated with higher median survival. Patients undergoing a simultaneous liver metastasis resection during CRS had a worse survival prognosis (51 mo *vs* 27 mo for liver metastasis resection; P = 0.024).

To analyse further survival outcome factors, we performed multivariate analysis (Cox regression) with forward selection strategy using a likelihood ratio statistic. Synchronous distant metastasis (P = 0.029) and primary tumour resection status (P = 0.016) were confirmed to have a significant impact on survival as well as PCI-scoring regarding PC (P = 0.001). After carrying out a separate multivariate analysis, adapting the cut-off P value for inclusion to include HIPEC regimen into the analysis, HIPEC regimen failed to prove significance regarding OS at a P value of 0.144 (Figure 2).

DISCUSSION

With varying evidence for the therapeutic value of CRS-HIPEC in metastatic colon cancer, attention has refocused upon standardization and optimization of this procedure. However, there is a severe lack of evidence regarding comparison of survival benefits for the most commonly utilized chemotherapeutic agents for HIPEC

Table 1 Patients, tumours and treatment, *n* (%)

	All, *n* = 102	MMC, *n* = 34	Oxaliplatin/5-FU, *n* = 68	*P* value[1]
Male sex	60 (59)	24 (40)	36 (60)	0.135
Age in yr, median (range)	57.2 (23-80)	56.3 (23-73)	57.7 (40-80)	0.884
BMI in kg/m²	25.3 (15.9-39.6)	25.5 (19.1-33.6)	25.2 (15.9-39.6)	0.266
ASA-score				0.002[b]
1-2	49 (48)	24 (71)	25 (37)	
3-4	53 (52)	10 (29)	43 (63)	
Tumour location				1.000
Colon	91 (89)	30 (88)	61 (90)	
Rectum	11 (11)	4 (12)	7 (10)	
Surgical approach				0.257
Complete cytoreduction	99 (97)	32 (94)	67 (99)	
Palliative resection	3 (3)	2 (6)	1 (2)	
Resection				
Peritoneum	81 (80)	29 (85)	52 (77)	0.437
Omentum	66 (65)	26 (77)	40 (59)	0.123
Colon/rectum	55 (54)	18 (53)	37 (54)	1.000
Small intestine	49 (48)	15 (44)	34 (50)	0.675
Liver	42 (41)	13 (38)	29 (43)	0.831
Diaphragm	16 (16)	9 (27)	7 (10)	0.045[a]
Other	63 (64)	21 (68)	42 (62)	0.655
Pretherapeutic T stage				0.027[a]
T1	2 (2)	0	2 (3)	
T2	2 (2)	0	2 (3)	
T3	34 (34)	13 (41)	21 (31)	
T4a	40 (40)	17 (53)	23 (34)	
T4b	22 (22)	2 (6)	20 (30)	
Pretherapeutic N stage				1.000
N0	26 (26)	8 (25)	18 (27)	
N+	73 (74)	24 (75)	49 (73)	
Pretherapeutic M stage				1.000
M0	36 (37)	12 (35)	24 (38)	
M+	62 (63)	22 (65)	40 (63)	
Tumour grading				1.000
G1	0	0	0	
G2	59 (63)	22 (65)	37 (63)	
G3	34 (37)	12 (35)	22 (37)	
PCI score (0-39)	9.4 (0-39)	12.0 (0-39)	8.1 (0-30)	0.312
Postop CC-level				0.350
CC0	89 (87)	28 (82)	61 (90)	
CC1	8 (8)	3 (9)	5 (7)	

CC2/3	5 (5)	3 (9)	2 (3)	
Mucinous cells	21 (21)	6 (18)	15 (22)	0.796

[1]Fisher's exact test.
[a]$P < 0.05$.
[b]$P < 0.01$. 5-FU: 5-Fluorouracil; ASA: American Society of Anesthesiologists; BMI: Body mass index; MMC: Mitomycin C; PCI: Peritoneal cancer index.

oxaliplatin and MMC. This study is one of a few to focus on prognostic factors and treatment strategies after the development of peritoneal metastasis. Furthermore, the two most commonly used cytotoxic agents were compared regarding survival benefits and outcome rates.

Oxaliplatin and MMC, both interfering with DNA and DNA-synthesis, can reach high intraperitoneal drug concentrations during HIPEC with simultaneous limited systemic absorption[23,24]. Furthermore, they have elevated cytotoxicity under hyperthermia with a concordant tissue penetration depth of 2 mm[9]. The most commonly used intraperitoneal dose for oxaliplatin is 460 mg/m² with a perfusion time limited to 30 min. In contrast, the recommended intraperitoneal dose for MMC is 35 mg/m² with a prolonged perfusion duration of 90 min[9,25,26]. With the objective of potentiating the oxaliplatin activity, patients in the Oxaliplatin group received intravenous 5-FU and folinic acid approximately 1 hour before starting intraperitoneal HIPEC circulation.

Our study shows a 3-year-survival rate of 43% after CRS/HIPEC for peritoneal metastasized CRC. We could not show any statistically significant survival benefit comparing HIPEC regimens with oxaliplatin/5-FU *vs* MMC. Nevertheless, a statistical trend towards the oxaliplatin/5-FU group was noticed (Figure 2; median survival 30 mo for MMC *vs* not reached for oxaliplatin/5-FU). In our cohort, MMC group had a trend towards a higher PCI-scoring and a smaller number of CC-0 resections, which could possibly be responsible for the observed trend towards a prolonged survival in the Oxaliplatin group as well as differences in systemic preoperative treatments regarding multi-agent and targeted systemic therapy and surgical approach.

Regarding PRODIGE 7 trial, subgroup analysis showed a significant survival benefit for CRS + oxaliplatin HIPEC *vs* CRS for a subgroup with PCI 10-15[15]. Thus, there is a need of further studies, stratifying patients by PCI and prospectively examining the relative therapeutic effectiveness of MMC and oxaliplatin.

On the other hand, our study demonstrates significant differences between the two regimes regarding postoperative morbidity and complication rates. In our collective, patients treated with oxaliplatin/5-FU suffered increased rates of postoperative complications, especially intraperitoneal infections, urinary tract infections and intestinal atony.

Postoperative morbidity has to be taken into account when selecting an appropriate cytotoxic agent. Oxaliplatin has been suggested to cause higher morbidity rates with Grade II and III complication compared to MMC[27], as confirmed in this study. Reported complications in oxaliplatin trials include fistula formation, pneumonia or intraabdominal abscess formation[28]. The PRODIGE 7 trial likewise reported enhanced complication rates for CRS + oxaliplatin HIPEC *vs* CRS. A similar study design focusing on hematologic changes after CRS and HIPEC with either MMC or oxaliplatin was not able to show an increased complication rate after oxaliplatin HIPEC but a different complication scheme[29]. Contrary to this study, our analysis focuses on surgical complications in the postoperative phase. Therefore, the difference in the results can be explained.

Increased postoperative complication rates, especially severe complications (grade IIIb and IV according to Clavien-Dindo analysis), were also associated with prolonged ICU stay for the Oxaliplatin group compared to MMC (7.2 d *vs* 4.4 d; $P = 0.035$), which adds to evidence supporting MC for CRS-HIPEC.

Furthermore, we were able to identify different primary tumour factors affecting OS in this collective of peritoneal metastasized CRC. Interestingly, clinical factors such as age, sex, BMI or even ASA-scoring at CRS-HIPEC operation time have no influence on OS. Literature describes poorly differentiated carcinoma, venous invasion, lymphatic invasion, T4 disease, lymph node metastasis, malignant bowel obstruction and adjuvant chemotherapy as having negative impact on OS[30].

Even though primary T-stage and tumour location (colon/rectum) had no influence on survival outcome, primary nodal positivity and poor differentiation grade seem to affect tumour recurrence and lower survival rates in our patients with peritoneal carcinomatosis. This agrees with numerous other studies[31-33].

Table 2 Impact of hyperthermic intraperitoneal chemotherapy regimen on perioperative outcome, *n* (%)

Parameter	Total, *n* = 102	Mitomycin, *n* = 34	Oxaliplatin/5-FU, *n* = 68	*P* value[1]
Median operative time in min	379 (95-774)	410 (95-774)	363 (96-722)	0.260
Median blood substitution in mL	105 (0-1800)	185 (0 -1800)	66 (0-1200)	0.068
Hospitalization in d	12 (2-46)	11,4 (4-35)	12,4 (2-46)	0.315
ICU stay in d	6.3 (2-50)	4.4 (2-9)	7.2 (2-50)	0.035[a]
In-hospital mortality				
Rate of complications	57 (56)	12 (35)	45 (66)	0.003[b]
Cardio-pulmonary morbidity				
Pneumonia	5 (5)	2 (6)	3 (4)	0.542
Re-intubation	2 (2)	0	2 (3)	0.442
Pulmonary embolism/thrombosis	2 (2)	0	2 (3)	0.442
Hematoma	2 (2)	1 (3)	1 (2)	0.558
Postoperative haemorrhage	4 (4)	1 (3)	3 (4)	0.593
Surgical morbidity				
Intestinal atony	23 (23)	3 (9)	20 (30)	0.015[a]
Wound infection	15 (15)	5 (15)	10 (15)	0.608
Abdominal abscess	13 (13)	5 (15)	8 (12)	0.448
Abdominal infection	15 (15)	1 (3)	14 (21)	0.013[a]
Burst abdomen	8 (8)	1 (3)	7 (10)	0.184
Peritonitis	6 (6)	0	6 (9)	0.081
Sepsis	6 (6)	0	6 (9)	0.081
Renal complications				
Urinary retention	4 (4)	0	4 (6)	0.192
Renal failure	7 (7)	2 (6)	5 (7)	0.344
Urinary tract infections	8 (8)	0	8 (12)	0.034[a]
Severity of complications[b]				0.029[a]
Grade 0/I	45 (44)	22 (65)	23 (34)	
Grade II	23 (23)	3 (9)	20 (30)	
Grade IIIa	16 (16)	5 (15)	11 (16)	
Grade IIIb	10 (10)	3 (9)	7 (10)	
Grade IV	8 (8)	1 (3)	7 (10)	
Grade V (in-hospital mortality)	0	0	0	
Mortality				0.139
30 d	5 (5)	4 (12)	1 (1)	
90 d	11 (10)	5 (15)	6 (9)	

[1]Mann-Whitney *U* test/Fishers exact test.
[a]$P < 0.05$.
[b]$P < 0.01$. 5-FU: 5-Fluorouracil; ICU: Intensive care unit.

In our cohorts, 21% of tumours (18% in the MMC group and 22% in the Oxaliplatin group) were mucinous carcinoma. Regarding univariate analysis, we found no survival benefits for mucinous carcinoma *vs* adenocarcinoma. Our cohort contains no patients with adenosquamous or squamous carcinoma. As both groups contain a similar percentage of mucinous carcinoma, we expect no selection bias due to this

Table 3 Impact of other prognostic factors on overall survival

Predictor	*n*	Median survival in mo	*P* value[1]
Sex			0.884
Male	60	49	
Female	42	57	
Age			0.147
< 50 yr	27	38	
≥ 50 yr	75	49	
Preoperative BMI			0.423
< 18.5	4	4	
18.5-25	49	53	
25-30	35	51	
> 30	14	49	
ASA score			0.457
1-2	49	49	
3-4	53	57	
Primary tumour location			0.620
Colon	91	49	
Rectum	11	23	
Primary T-stage			0.669
T1-3	38	49	
T4a	40	30	
T4b	22	Not reached	
Primary nodal stage			0.013[a]
N0	26	88	
N1	31	51	
N2a	19	30	
N2b	23	18	
Primary distant metastasis			0.046[a]
M0	36	57	
M+	62	35	
Primary tumour grading			0.010[a]
G2	59	51	
G3	34	29	
Primary tumour resection			0.035[a]
R0	76	51	
R1	20	30	
R2	4	16	
Cytoreduction level			< 0.001[b]
CC0	89	49	
CC1	10	12	
CC2-3 + palliative resections	3	3	

PCI-score			< 0.001[b]
< 10	56	51	
10-20	29	27	
20-30	11	10	
> 30	5	9	
Operation extent			
Partial colectomy	55	53	0.189
No colon resection	47	31	
Small bowel resection	49	30	0.355
No small bowel resection	53	51	
Liver metastasis resection	42	27	0.024[a]
No liver resection	60	51	
HIPEC regimen			0.139
MMC	34	30	
Oxaliplatin/5-FU	68	Not reached	

[1]Univariate analysis by Kaplan-Meier method with log-rank test for the comparison of subgroups.
[a]$P < 0.05$.
[b]$P < 0.01$. 5-FU: 5-Fluorouracil; ASA: American Society of Anesthesiologists; BMI: Body mass index; HIPEC: Hyperthermic intraperitoneal chemotherapy; MMC: Mitomycin C; PCI: Peritoneal cancer index.

histopathological criterion.

We also found R1-resections of primary tumours to be a prognostic factor after peritoneal metastasis, as well as synchronous metastatic spread. Two studies[34,35] analysed the prognostic influence of disease-free resection margins on survival and also found this to have independent prognostic value. These results are useful to identify optimal subgroups for high risk of recurrent PC.

An important prognostic factor of survival is the concept of tumour burden correlated with PCI-scoring. Oncologic results seem to be significantly better when PCI is < 10[36] or ≤ 13[37]. However, PCI ≥ 20 is associated with decreased survival according to many different studies[38-40]. This agrees with our results from univariate and multivariate analysis of survival. Patients with distant metastasis, especially liver metastasis, were included in this analysis. Current literature suggests that patients with distant metastasis amendable to resection should not be excluded from CRS and HIPEC[38,41]. Concordant to the literature, univariate analysis of survival of our data shows a significant reduced survival for patients undergoing liver resections during CRS and HIPEC (27 mo *vs* 51 mo without liver resection; $P = 0.024$).

There are several limitations in this study that should be considered. Mainly, the retrospective non-randomized study design lowers comparability between the groups. Furthermore, the retrospective database lacks complete information regarding Tumour Node Metastasis staging, preoperative treatments especially chemotherapy as well as varying follow-up duration. The patients were treated over a time period of 10 years with changes in perioperative management and systemic chemotherapy. Different surgeons performed HIPECs at the university hospital of Freiburg. Therefore, an individual learning curve cannot be assessed. Nevertheless, the learning curve of the complete surgical department could influence postoperative outcome depending on operation timing.

For this special collective of patients with PC based on a colorectal primary tumour, several outcome predictors were identified. We were also able to show comparable outcome results for CRS/HIPEC with oxaliplatin and MMC. Nevertheless, increased complication rates for oxaliplatin were demonstrated, which, according to the literature, significantly affects OS[42] indicating that patients should be treated favourably with MMC-HIPEC. As we could not show any survival benefit for patients treated with MMC or oxaliplatin HIPEC, it remains to be determined whether there is enough evidence for HIPEC. However, the importance of complete cytoreduction has been established, which has been broadly discussed in the literature and is consistent with our data.

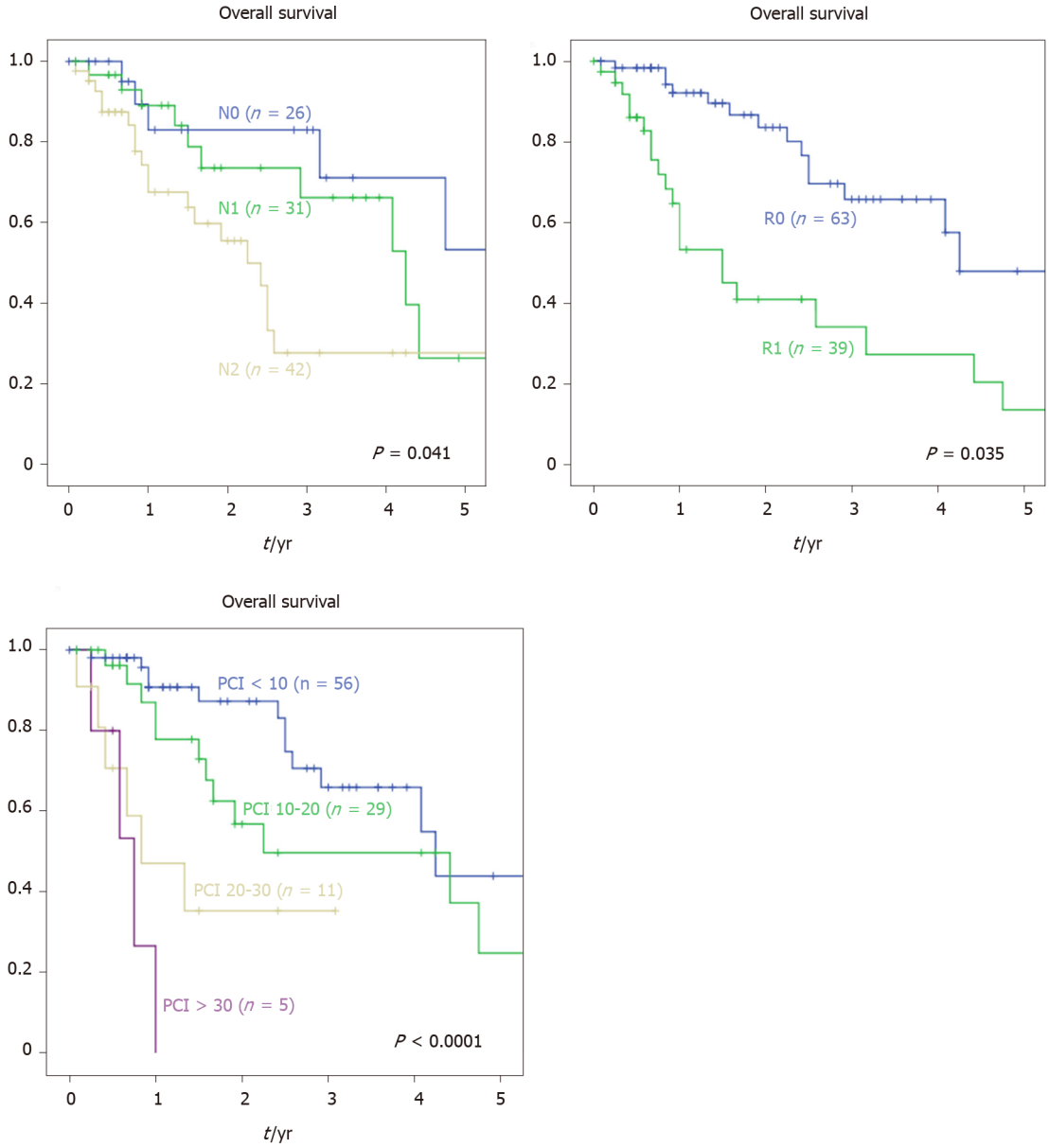

Figure 1 Kaplan-Maier: 5-year overall survival after cytoreductive surgery + hyperthermic intraperitoneal chemotherapy depending on different outcome factors. Univariate analysis of survival of patients with peritoneal metastasized colorectal cancer dependent on primary tumour nodal status, resection status and peritoneal cancer index scoring system.

Further studies, in particular a phase III clinical trial comparing both HIPEC regimens, would improve evidence-based decision-making.

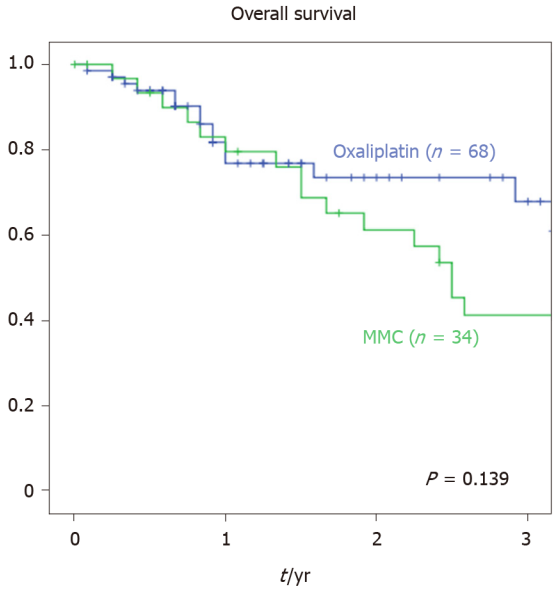

Figure 2 Kaplan-Maier: 3-year overall survival cytoreductive surgery + hyperthermic intraperitoneal chemotherapy. Kaplan-Maier analysis of 3-year overall survival of patients with peritoneal metastasized colorectal cancer being treated with cytoreductive surgery and oxaliplatin or mitomycin C-hyperthermic intraperitoneal chemotherapy.

ARTICLE HIGHLIGHTS

Research background

Cytoreductive Surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) improves patient survival in colorectal cancer (CRC) with peritoneal carcinomatosis (PC). Commonly used cytotoxic agents nowadays include mitomycin C (MMC) and oxaliplatin. Evidence for the choice of the HIPEC agent and uniform procedure protocols is scarce, with studies reporting varying results.

Research motivation

There's a severe lack of evidence regarding comparison of survival benefits for most commonly utilized chemotherapeutic agents for HIPEC oxaliplatin and MMC. At present there is no prospective study that compares these two HIPEC regimens for treatment of peritoneal metastasized CRC, thus leading to the reassessment of HIPEC and the need for structured treatment protocols. In this retrospective clinical analysis, we evaluated the outcome of patients undergoing CRS HIPEC at the university medical centre of Freiburg. Furthermore, this study is one of a few to focus on prognostic factors and treatment strategies after the development of peritoneal metastasis.

Research objectives

The aim of the study was to evaluate therapeutic benefits and operative and postoperative complications of CRS + MMC *vs* oxaliplatin HIPEC in patients with peritoneal metastasized CRC as well as prognostic factors for overall survival (OS).

Research methods

One hundred two patients who had undergone CRS and HIPEC for CRC PC between 2007 and 2019 at the Medical Center of the University Freiburg regarding interdisciplinary cancer conference decision were retrospectively analysed. Oxaliplatin and MMC were used in 68 and 34 patients, respectively. Each patient's demographics and tumour characteristics, operative details, postoperative complications and survival were noted and compared. Complications were stratified and graded using Clavien/Dindo analysis. Prognostic outcome factors were identified using univariate and multivariate analysis of survival.

Research results

The two groups did not differ significantly regarding baseline characteristics. We found no difference in median OS. Patients treated with oxaliplatin HIPEC suffered

increased postoperative complications (66.2% *vs* 35.3%; P = 0.003), particularly intestinal atony, intraabdominal infections and urinary tract infections, and had a prolonged intensive care unit (ICU) stay compared to the MMC group (7.2 d *vs* 4.4 d; P = 0.035). Regarding univariate analysis of survival, we found primary tumour factors, nodal positivity and resection margins to be of prognostic value as well as PC index (PCI)-score and the completeness of cytoreduction regarding peritoneal carcinomatosis. Multivariate analysis of survival confirmed primary distant metastasis and primary tumour resection status to have a significant impact on survival and likewise PCI-scoring regarding peritoneal carcinomatosis.

Research conclusions

We could not show any survival advantage for neither HIPEC regimens. Oxaliplatin showed an increased complication rate. Increased postoperative complication rates, especially severe complications (grade IIIb and IV according to Clavien-Dindo analysis), were also associated with prolonged ICU stay for the Oxaliplatin group compared to MMC (7.2 d *vs* 4.4 d; P = 0.035), which improves evidence to choose MMC for CRS-HIPEC.

Primary distant metastasis and primary tumour resection seem to have a significant impact on survival and likewise PCI-scoring regarding peritoneal carcinomatosis.

Research perspectives

For this special collective of patients with PC based on a colorectal primary tumour, several outcome predictors could be identified. We were also able to show comparable outcome results for CRS/HIPEC with oxaliplatin and MMC. Nevertheless, increased complication rates for oxaliplatin were demonstrated, which, according to literature, significantly affects OS, indicating that patients should be treated favourably with MMC-HIPEC. Further studies, in particular a phase III clinical trial comparing both HIPEC regimens would improve evidence-based decision-making.

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