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Long-term survival after hyperthermic intraperitoneal chemotherapy using mitomycin C or oxaliplatin in colorectal cancer patients with synchronous peritoneal metastases: A nationwide comparative study

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ABSTRACT

Objectives: In the Netherlands, limited variability exists in performance of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) among centers treating colorectal peritoneal metastases (PM), except for the intraperitoneal drug administration. This offers a unique opportunity to investigate any disparities in survival between the two most frequently used HIPEC regimens worldwide: mitomycin C (MMC) and oxaliplatin.

Methods: This was a comparative, population-based cohort study of all Dutch patients diagnosed with synchronous colorectal PM who underwent CRS-HIPEC between 2014 and 2017. They were retrieved from the Netherlands Cancer Registry. Main outcome was overall survival (OS). The effect of the intraperitoneal drug on OS was investigated using multivariable Cox regression analysis.

Results: In total, 297 patients treated between 2014 and 2017 were included. Among them, 177 (59.6%) received MMC and 120 (40.4%) received oxaliplatin. Only primary tumor location was different between the two groups: more left-sided colon in the Oxaliplatin group (47.5% vs. 33.3%, respectively, *p=0.048*). The 1-, 2- and 3-year OS were 84.6% vs. 85.8%, 61.6% vs. 63.9% and 44.7% vs. 53.5% in patients treated with MMC and oxaliplatin, respectively. Median OS was 30.7 months in the MMC group vs. 46.6 months in the oxaliplatin group *(p=0.181)*. In multivariable analysis, no influence of intraperitoneal drug on survival was observed (adjusted HR 0.77 [0.53–1.13]).

Conclusions: Long-term survival between patients treated with either MMC or oxaliplatin during CRS-HIPEC was not significantly different.

Introduction

Synchronous peritoneal metastases (PM) are present in approximately 5% of all patients with colorectal cancer (CRC) [1–4]. Nowadays, a selection of these patients may undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) [5–7].

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In the past, treatment of colorectal peritoneal metastases comprised palliative systemic therapy and surgery only for symptomatic metastases. As a result, survival rates were poor with a reported median survival of 7–8 months [8]. This changed after a Dutch randomized trial, published in 2003, which demonstrated improved survival in patients treated with CRS-HIPEC plus systemic chemotherapy over patients treated with systemic therapy alone (22.3 vs. 12.6 months) [9]. Ever since, CRS-HIPEC for PM of colorectal origin is implemented as standard of care for selected patients in the Netherlands.

In 2004, about 10% of the patients with PM of colorectal origin were treated with CRS-HIPEC in the Netherlands. This proportion increased to 23% of patients presenting with colorectal PM without distant metastases in 2014 treated in nine specialized HIPEC-centers [8]. All these centers adhere to the same nationwide protocol with regard to the selection and treatment of patients and therefore, variability between centers is limited [10].

The only parameter that differs among Dutch HIPEC centers is the choice of intraperitoneal drug. Following the aforementioned trial, all CRS-HIPEC procedures were initially performed using the 90 min triple-dose MMC protocol [9]. Over time, some HIPEC centers switched to the 30 min bidirectional oxaliplatin protocol as introduced in France, as this appeared feasible and was associated with a shorter HIPEC phase [11]. As a result, both oxaliplatin and Mitomycin C (MMC) are currently used during CRS-HIPEC for colorectal PM in the Netherlands according to surgeon's or hospital's preference. [12].

No guidelines or consensus on the intraperitoneal drug during HIPEC yet exist, as no survival benefit of either drug can be discerned from available literature [13]. The situation in the Netherlands offers a unique opportunity to compare the oncologic outcome of MMC and oxaliplatin based CRS-HIPEC in colorectal PM. The aim of this comparative population-based cohort study was to determine the effect of each of the two intraperitoneal drugs on survival.

Methods

Patients and setting

This was a population-based comparative cohort study of all patients that underwent CRS-HIPEC as treatment for synchronous colorectal PM. Data were retrieved from the Netherlands Cancer Registry (NCR), which is a nation-wide registry comprising all newly diagnosed malignancies in the Netherlands.

From the start of the registration of patients undergoing CRS-HIPEC by the NCR in 2005 until 2013, only MMC was used during CRS-HIPEC for colorectal PM, except for 2 patients being treated with oxaliplatin. From 2014 onwards, the oxaliplatin based HIPEC was also implemented as a routine in several Dutch HIPEC centers. In order to accurately compare both regimens, only patients treated for synchronous PM with CRS-HIPEC between 2014 and 2017 were analyzed in the present study. Detailed information about the application of MMC and oxaliplatin during CRS-HIPEC for colorectal PM over time is attached as Appendix A.

Data on patient, tumor, and treatment characteristics are routinely collected by trained data managers of the NCR. The tumor-node-metastasis (TNM) classification was used for stage notification of the primary tumor, according to the edition valid at time of cancer diagnosis. Information on vital status was obtained by annual linkage to the municipal administration database, in which all deceased and emigrated inhabitants are registered.

Follow-up was complete until January 31, 2019. At time of analysis, not all patients diagnosed in 2017 were imported by the NCR yet. Therefore, the incidence rate of patients treated in 2017 is dissimilar compared to the other years included in this study. Since all data was anonymized, no ethics approval was required for this study.

Only patients undergoing CRS-HIPEC for synchronous colorectal PM (i.e. no patients with recurrent or metachronous PM) were included in this study. PM were defined as synchronous PM if diagnosed simultaneous with the primary tumor or before initiation of the primary tumor treatment. Patients with appendiceal carcinoma, unspecified primary tumor location or histology other than adenocarcinoma (signet cell ring carcinoma, neuro-endocrine tumors) were excluded. Patients treated abroad and patients with an unknown date of HIPEC were excluded. For patients with multiple primary colorectal tumors, the tumor with the highest stage was included. Tumor location was subdivided into 3 anatomical subsites defined by the International Classification of Disease – Oncology (ICD-O) codes: 1) *right-sided colon* (C18.0, C18.2-C18.4: caecum, ascending colon, hepatic flexure and transverse colon), 2) *left-sided colon* (C18.5-C18.7: splenic flexure, descending colon and sigmoid) and 3) *rectum* (C19.9-C20.9: rectosigmoid and rectum). Histology was subdivided into *adenocarcinoma* (8140, 8144, 8510) and *mucinous adenocarcinoma* (8480, 8481). Data on the presence of any extraperitoneal metastases (e.g. lung, liver), the administration of any neoadjuvant and/or adjuvant chemotherapy and period of diagnosis were included. Information about the HIPEC regimen in the different hospitals was not recorded in the NCR but was based on the hospital's HIPEC-protocol at the time of treatment, considering that all primary CRS-HIPEC's for colorectal PM were performed using the hospital's first choice regimen, according to their protocol. As toxicity during previous systemic treatment with oxaliplatin may be a contraindication for oxaliplatin-based HIPEC, the actual regimens were verified in these hospitals. This confirmed that all patients indeed received oxaliplatin-based HIPEC according to the hospital's preference.

Statistical analyses

Baseline characteristics of the two groups based on HIPEC regimen were compared using the Chi Square test or Fisher's exact test as appropriate for categorical variables, and the Wilcoxon rank sum test for not-normally distributed continuous variables. Kaplan-Meier curves with the Log rank test were used to analyze overall survival (OS) for patients treated with MMC and oxaliplatin in 2014–2017. OS was defined as the time from CRS-HIPEC to death of any cause. Patients still alive on January 31st, 2019 were censored. Multivariable Cox regression analysis with correction for sex, age, comorbidity, tumor location, T stage, N stage, histology, differentiation, presence of extraperitoneal metastases, neoadjuvant treatment and adjuvant systemic therapy was performed to investigate the direct influence of the used HIPEC regimen on overall survival. All tests were two-sided and conducted at the 5% level of significance. All analyses were performed using SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC, US).

Results

Study population

Between January 2014 and December 2017, 297 patients who underwent CRS-HIPEC for synchronous PM were registered in the NCR. Among them, 177 patients (59.6%) received MMC and 120 patients (40.4%) received oxaliplatin during CRS-HIPEC (Fig. 1).

Patient characteristics

Patient and tumor characteristics were similar between the two

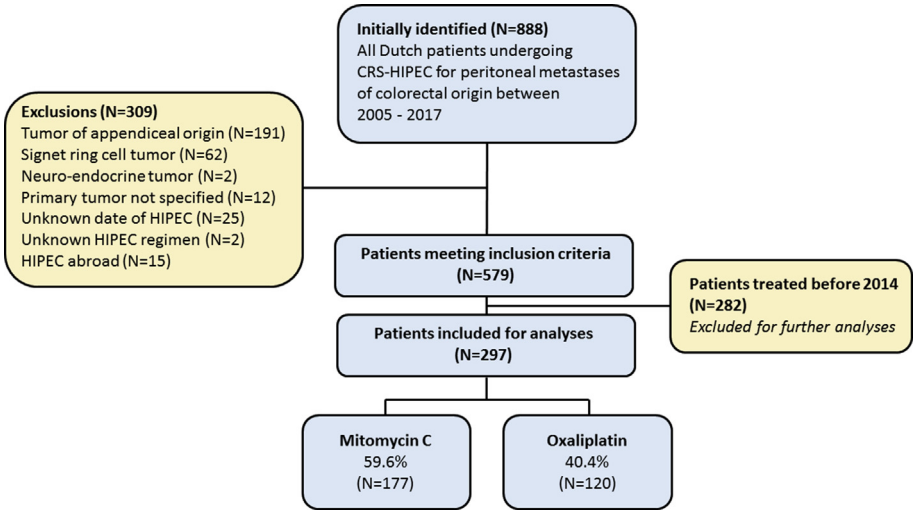


Fig. 1. Number of patients with peritoneal metastases of colorectal origin, treated with CRS-HIPEC, using either mitomycin C or oxaliplatin. CRS-HIPEC; Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy.

groups, except for tumor location (Table 1). The primary tumor of patients treated with oxaliplatin was mostly located in the left-sided colon (47.5%) while in patients treated with MMC, primary tumors were mostly located at the right-sided colon (52.0%, *p=0.048)*. The presence of synchronous extraperitoneal metastases was not different between both groups (16.9% vs. 20.3% in the MMC

Table 1
Baseline characteristics of the study population.

	Mitomycin C (N = 177)	**Oxaliplatin** (N = 120)	**Significance (p)**
Gender			
Male	76 (42.9%)	45 (37.5%)	0.349
Female	101 (57.1%)	75 (62.5%)	
Age			
years, median (IQR)	64.0 (14)	62.5 (11.5)	0.509
N of comorbidities[a]			
0	49 (41.5%)	11 (28.2%)	0.314
1	37 (31.4%)	14 (35.9%)	
≥2	32 (27.1%)	14 (35.9%)	
Tumor location			
Right-sided colon	92 (52.0%)	50 (41.7%)	0.048
Left-sided colon	59 (33.3%)	57 (47.5%)	
Rectum	26 (14.7%)	13 (10.8%)	
T stage			
0-3	51 (28.8%)	39 (32.5%)	0.756
4	125 (70.6%)	80 (66.7%)	
Unknown	1 (0.6%)	1 (0.8%)	
N stage			
0	37 (20.9%)	22 (18.3%)	0.419
1-2	140 (79.1%)	97 (80.8%)	
Unknown	0 (0.0%)	1 (0.8%)	
Histology			
Adenocarcinoma	117 (66.1%)	91 (75.8%)	0.072
Mucinous	60 (33.9%)	29 (24.2%)	
Differentiation			
Well/moderate	106 (59.9%)	78 (63.3%)	0.222
Poor	23 (13.0%)	21 (17.5%)	
Unknown	48 (27.1%)	23 (19.2%)	
Extraperitoneal metastases			
Yes	30 (16.9%)	25 (20.3%)	0.398
No	147 (83.1%)	95 (79.2%)	
Neoadjuvant treatment			
Yes	45 (25.4%)	33 (27.5%)	0.700
No	132 (74.6%)	87 (72.5%)	
Adjuvant treatment			
Yes	42 (23.7%)	33 (27.5%)	0.463
No	135 (76.3%)	87 (72.5%)	

[a] Data on comorbidities was only available on a subset of patients. Numbers may not add up to 100% due to rounding.

group and the oxaliplatin group, respectively, *p=0.398*), and the administration of both neoadjuvant and adjuvant systemic therapy also was comparable between the two groups: 25.4% vs. 27.5%, *p=0.700* and 23.7% vs. 27.5%, *p=0.463,* respectively.

Survival

In the total study population, median OS was 33.2 months. For patients treated with MMC, median OS was 30.7 months and for patients treated with oxaliplatin, median OS was 46.6 (*p=0.181,* unadjusted HR 0.79 (0.56–1.12), *Fig. 2).* The 1-, 2- and 3-year OS were 84.6% vs. 85.8%, 61.6% vs. 63.9% and 44.7% vs. 53.5% in patients treated with MMC and oxaliplatin, respectively (Table 2). In multivariable analysis, no significant difference in OS was observed between the two groups after correction for confounding factors (adjusted HR 0.77 [0.53–1.13], Table 3).

Discussion

This population-based cohort study assessed OS in patients treated with either MMC or oxaliplatin during CRS-HIPEC for synchronous PM of colorectal origin. Although median overall survival appears to be markedly higher in the group treated with Oxaliplatin, this difference disappears after correction for confounding factors. Besides, no significant differences were observed in median and 1-, 2- and 3-year OS.

Treatment of colorectal PM by CRS-HIPEC is not standardized throughout the world. A recent review of variations in HIPEC regimens demonstrated a broad heterogeneity in over 60 HIPEC-protocols regarding the usage of different drugs and concentrations [14]. MMC is the most commonly used drug during HIPEC for colorectal PM worldwide, closely followed by oxaliplatin [14–16]. This is in line with practice in the Netherlands. Given the lack of evidence supporting one drug over the other, the choice of the drug is now mainly based on the surgeon's or hospital's preference. The shorter perfusion time of oxaliplatin-based HIPEC as compared to MMC-based HIPEC (30 versus 90 min) is an important argument to prefer oxaliplatin over MMC.

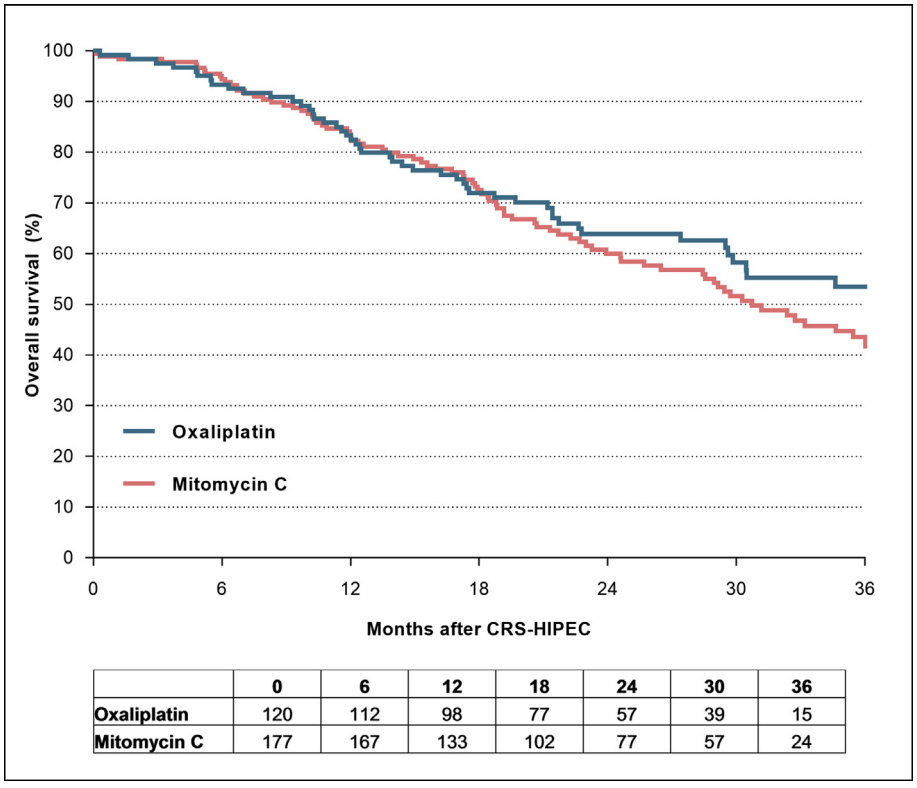
Table 2
Overall survival of patients treated with either Mitomycin C or Oxaliplatin during CRS-HIPEC between 2014 and 2017.

	N	Overall survival			
		1-year	2-year	3-year	Median
Mitomycin C	177	84.6%	61.6%	44.7%	30.7
Oxaliplatin	120	85.8%	63.9%	53.5%	46.6

Administration of neoadjuvant and/or adjuvant systemic therapy in addition to CRS-HIPEC also varies throughout the world. Some advocate the administration of in particular neoadjuvant systemic therapy to prolong long-term survival. This is standard of care in most countries. In the Netherlands, however, perioperative systemic therapy is not standard of care in patients undergoing CRS-HIPEC, as there is no strong evidence for a survival benefit [17]. This is reflected by the high percentage (approximately 75%) of patients not treated with systemic therapy in the current cohort. The value of systemic therapy is currently investigated in a randomized controlled trial [18].

In the current study, the location of the primary tumor differed significantly between both groups with more right-sided tumors in the MMC group. As right-sided tumors are thought to have worse prognosis, this may contribute to the shorter uncorrected survival in the MMC-group [19]. Therefore, tumor sidedness was included in the multivariable analysis which showed no significant differences between both groups.

Recently presented results of the PRODIGE-7 randomized



	0	6	12	18	24	30	36
Oxaliplatin	120	112	98	77	57	39	15
Mitomycin C	177	167	133	102	77	57	24

Fig. 2. Overall survival after CRS-HIPEC for synchronous peritoneal metastases of colorectal origin, in patients treated with mitomycin C or oxaliplatin between 2014 and 2017.

Table 3
Multivariable cox regression analyses to assess the influence of different patient- and tumor characteristics on overall survival.

	HR	CI
Sex		
Male	Ref.	
Female	1.09	0.76–1.58
Age	1.03	1.01–1.05
N of comorbidities		
0	Ref.	
1	1.47	0.84–2.57
≥2	1.00	0.56–1.81
Unknown	1.08	0.65–1.78
Primary tumor location		
Left colon	Ref.	
Right colon	0.69	0.47–1.00
Rectum	1.03	0.57–1.87
T stage		
0-3	Ref.	
4	1.60	1.04–2.45
Unknown	4.70	1.06–20.89
N stage		
0	Ref.	
1-2	1.30	0.78–2.17
Unknown	6.35	1.67–24.13
Histology		
Adenocarcinoma	Ref.	
Mucinous adenocarcinoma	0.67	0.43–1.05
Differentiation		
Good/moderate	Ref.	
Poor/undifferentiated	1.38	0.85–2.24
Unknown	0.98	0.61–1.58
Systemic metastases		
No	Ref.	
Yes	1.28	0.82–2.00
Neoadjuvant systemic treatment		
No	Ref.	
Yes	0.81	0.51–1.27
Adjuvant systemic treatment		
No	Ref.	
Yes	0.87	0.57–1.31
HIPEC regimen		
Mitomycin C	Ref.	
Oxaliplatin	0.79	0.54–1.15

controlled trial demonstrated no survival benefit of HIPEC in addition to CRS compared to CRS alone [20]. Further, a recent matched-control study by Baratti et al. demonstrated no survival benefit in patients treated with CRS and MMC-based HIPEC over patients treated with neoadjuvant systemic therapy and CRS only [21]. These studies question the additional value of HIPEC after CRS for colorectal PM. However, it is important to realize that in both studies, patients were extensively treated with neoadjuvant systemic chemotherapy and consequently, this may have influenced the responsiveness of peritoneal tumor cells to intraperitoneal chemotherapy. In the Netherlands, systemic therapy is only given to a minority of the patients and as such, HIPEC -either oxaliplatin or MMC based-may still be beneficial in this setting. However, this clearly needs further evaluation in future trials, as well as a search for more effective intra-peritoneal chemotherapeutic agents to overcome drug resistance in neoadjuvant treated patients. The same accounts for the added value of systemic therapy as is currently investigated in the CAIRO6-trial [18].

Previously published studies show an inconsistency in terms of either MMC or oxaliplatin favoring OS and/or disease-free survival (DFS). Two retrospective studies on the comparison of MMC and oxaliplatin showed no differences in both disease-free survival (DFS) and OS between MMC and oxaliplatin. The study by van Eden et al. reported DFS of 12.5 months in MMC vs. 13.1 months in oxaliplatin, and OS of 37.2 in MMC vs. 29.4 months in oxaliplatin [22]. Hompes et al. reported DFS of 13.8 vs. 12.2 months and OS of 26.5 vs 37.1 months in the MMC group and the oxaliplatin group, respectively [23]. Another study reported OS of 32.7 months in MMC treated patients vs. 31.4 months in oxaliplatin-treated patients [24]. An Australian study showed discordant results. A survival benefit was observed in patients treated with oxaliplatin as compared to MMC (median OS of 56 vs. 29 months respectively, $p=0.017$), most pronounced in patients with a PCI of 10–15 [25]. A recent systematic review including all these studies concluded that neither MMC or oxaliplatin can be considered the preferred HIPEC regimen in terms of DFS and OS, mainly based on the fact that published literature on each of the two HIPEC regimens is incomparable due to variability in patient cohorts with for example different proportions of patients who received perioperative systemic chemotherapy [13]. The present study adds to the available literature, because of optimal comparability regarding use of perioperative systemic therapy between the two regimens, thereby providing a fair comparison.

A strength of this study is the homogeneity in the selection and treatment of this population-based cohort, as all HIPEC-centers in the Netherlands followed the same protocol [10]. However, minor variation between the different centers is inevitable.

Although this study describes the first nationwide cohort to investigate differences in survival between MMC and oxaliplatin used during CRS-HIPEC for patients with synchronous colorectal PM, it has some drawbacks. Due to the unavailability of data on the occurrence and timing of recurrent disease, the influence of HIPEC regimen on disease free survival (DFS) could not be investigated in this study. Also, the NCR does not contain information on the extent of peritoneal disease (peritoneal cancer index; PCI). Theoretically, the effect of oxaliplatin or MMC might be depending on the PCI [25]. Therefore, future studies should ideally include this information. However, as all centers in the Netherlands adhere to the same protocol for the selection of patients for CRS-HIPEC, a significant imbalance between both groups with respect to extend of peritoneal disease is unlikely. Furthermore, this study did not include patients presenting with metachronous PM. Particularly patients who received adjuvant systemic therapy following primary colon resection in the past could hypothetically respond different to MMC and oxaliplatin. Adjuvant systemic therapy after primary colon resection usually consists of a combination of Capecitabine or 5-Fluorouracil with oxaliplatin (CAPOX or FOLFOX). In patients presenting with PM after systemic treatment with oxaliplatin, CRS-HIPEC using oxaliplatin might be less effective. Moreover, this study does not contain information about postoperative complications. If either HIPEC regimen might be equally effective, possible differences in complication rates may be an argument for the choice of one regimen over another. The available literature on the effect of the intraperitoneal drug on postoperative complications is inconclusive. Some have reported increased complication rates with oxaliplatin as intraperitoneal drug in particular intra-abdominal bleeding [26]. Others did not observe a different complication rate [22]. Future studies should focus on patients with metachronous PM and ideally include data on DFS, quality of life and costs.

Conclusions

Both MMC and oxaliplatin are used in the Netherlands during HIPEC for patients presenting with synchronous peritoneal metastases. The present study demonstrated no significant statistical difference in overall survival between both HIPEC regimens and therefore no preferred drug can be advised for these patients.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

De Hingh: An unrestricted research grand from RanD/QPS and Roche, paid to the institute.

CRediT authorship contribution statement

C. Bakkers: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **F.N. van Erning:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **K.P. Rovers:** Writing - original draft, Writing - review & editing, Formal analysis. **S.W. Nienhuijs:** Writing - review & editing. **J.W. Burger:** Writing - review & editing. **V.E. Lemmens:** Writing - review & editing, Methodology. **A.G. Aalbers:** Writing - review & editing. **N.F. Kok:** Conceptualization, Methodology, Writing - review & editing. **D. Boerma:** Writing - review & editing. **A.R. Brandt:** Writing - review & editing. **P.H. Hemmer:** Writing - review & editing. **W.M. van Grevenstein:** Writing - review & editing. **P.R. de Reuver:** Writing - review & editing. **P.J. Tanis:** Conceptualization, Methodology, Writing - review & editing. **J.B. Tuynman:** Writing - review & editing. **I.H. de Hingh:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision.

Appendix A. . Use of mitomycin C (MMC) and oxaliplatin and the total number of patients treated by CRS-HIPEC for synchronous colorectal peritoneal metastases undergoing CRS-HIPEC over time.

* Not all patients treated in 2017 were registered in the NCR yet at time of analyses.

Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2020.04.018.

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