

# Short-term outcome in patients treated with cytoreduction and HIPEC compared to conventional colon cancer surgery

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## Abstract

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an extensive procedure with considerable morbidity. Since only few hospitals perform CRS + HIPEC, this might lead to confounded outcomes between hospitals when audited. This study aims to compare outcomes between peritoneally metastasized (PM) colon cancer patients treated with CRS + HIPEC and patients undergoing conventional colon surgery. Furthermore, the impact of CRS + HIPEC on the risk of postoperative complications will be assessed, probably leading to better insight into how to report on postoperative outcomes in this distinct group of patients undergoing extensive colon surgery.

All patients with primary colon cancer who underwent segmental colon resection in a tertiary referral hospital between 2011 and 2014 were included in this prospective cohort study. Outcome after surgery was compared between patients who underwent additional CRS + HIPEC treatment or conventional surgery.

Consequently, 371 patients underwent surgery, of which 43 (12%) underwent CRS + HIPEC. These patients were younger and healthier than patients undergoing conventional surgery. Tumor characteristics were less favorable and surgery was more extensive in CRS + HIPEC patients. The morbidity rate was also higher in CRS + HIPEC patients (70% vs 41%;  $P < 0.001$ ). CRS + HIPEC was an independent predictor of postoperative complications (odds ratio 6.4), but was not associated with more severe postoperative complications or higher treatment-related mortality.

Although patients with colonic PM undergoing CRS + HIPEC treatment were younger and healthier, the postoperative outcome was worse. This is most probably due to less favorable tumor characteristics and more extensive surgery. Nevertheless, CRS + HIPEC treatment was not associated with severe complications or increased treatment-related mortality. These results stress the need for adequate case-mix correction in colorectal surgery audits.

**Abbreviations:** ASA = American Society of Anaesthesiologists, CCI = Charlson comorbidity index, CRS = cytoreductive surgery, CT = computed tomography, DSCA = Dutch Surgical Colorectal Audit, HIPEC = hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit, PM = peritoneal metastases.

**Keywords:** colonic neoplasms, cytoreduction surgical procedures, hyperthermic intraperitoneal chemotherapy, morbidity, outcome assessment, peritoneal neoplasms, postoperative complications

Editor: Xiao-Dong Chen.

Funding disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors declare that there is no conflict of interest.

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Medicine (2016) 95:41(e5111)

Received: 29 April 2016 / Received in final form: 30 August 2016 / Accepted: 20 September 2016

<http://dx.doi.org/10.1097/MD.0000000000000511>

## 1. Introduction

Treatment strategy of patients with colon cancer is subject to tumor characteristics such as location, TNM stage, and histological subtype, but also the physical condition of a patient. Consequently, the outcome of the desired treatment is the result of a complex interplay between patient, tumor, and treatment-related characteristics.<sup>[1,2]</sup>

Patients with unfavorable tumor characteristics are those diagnosed with colonic peritoneal metastases (PM), a condition with a median survival up to 17 months if treated with palliative systemic chemotherapy.<sup>[3,4]</sup> A selected group of colorectal PM patients is able to undergo cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC), resulting in median survival rates up to 40 months.<sup>[5]</sup> However, the promising survival benefit of this extensive treatment comes with the costs of considerable treatment-related morbidity and mortality.<sup>[6]</sup>

Currently, several countries around the world, including the Netherlands, have national colorectal surgery audits to monitor the quality of surgical care.<sup>[7–10]</sup> In these systems, patients treated with CRS + HIPEC are registered similarly as patients undergoing

less complex colorectal surgery. Therefore, the increasing use of CRS+HIPEC possibly leads to confounded outcomes between hospitals.<sup>[1]</sup> Additionally, CRS+HIPEC treatment is often not included as case-mix factor in the current audit systems. This may pose problems in assessing quality of care in specific hospitals and lead to bias in scientific research.

Therefore, the aim of this study is to assess patient and tumor characteristics, operative details, and postoperative outcomes of patients treated with CRS+HIPEC compared with those undergoing conventional colon surgery in a tertiary referral hospital in the Netherlands. The secondary aim is to determine the impact of CRS+HIPEC on postoperative complications. These results may lead to better insight into how to report on postoperative outcomes in this distinct group of patients undergoing extensive colon surgery.

## 2. Methods

### 2.1. Patients

All patients with primary colon cancer undergoing an elective (segmental) colon resection between January 2011 and December 2014 in a large tertiary referral hospital in the Netherlands were included in this prospective cohort study. Patients who underwent a colon resection for recurrent colon cancer, a malignant disease of other than colon origin, or pseudomyxoma peritonei, were excluded. Patients undergoing emergency surgery or with nonmalignant indications for surgery were excluded as well. Colon cancer was defined as microscopic malignant cells in the colon resection specimen or based on the histological examination before surgery if no residual tumor was present after surgery.

Relevant patient, tumor, and treatment-related characteristics were prospectively collected in a database. Patients were divided into 2 groups based on whether they underwent primary colon tumor resection followed by CRS+HIPEC or underwent conventional colon surgery without the combination treatment of CRS+HIPEC. Follow-up for postoperative complications was complete until 3 months after surgery by reviewing relevant patients' charts. The local medical ethical committee (Medical review Ethics Committees United, ref nr. 2015-11) approved this study protocol.

### 2.2. Selection criteria for CRS+HIPEC

All patients in this study underwent (segmental) colon resection. According to international consensus guidelines, patients with synchronous PM of colon origin without other systemic metastases were additionally treated with CRS+HIPEC. Selected patients with limited resectable liver or lung metastases on abdominal computed tomography (CT) scan or thoracic x-ray/CT scan were considered for CRS+HIPEC as well. Only patients considered eligible for complete macroscopic (R1) cytoreduction underwent this extensive treatment.

### 2.3. CRS+HIPEC technique

The CRS+HIPEC treatment was performed by a specialized surgical team as described previously.<sup>[11]</sup> During all procedures, general anesthesia was performed. Generally, additional spinal anesthesia for enhanced postoperative recovery was performed as well. Central venous access and an arterial line to monitor vital parameters were placed in all patients.

The first component of the treatment consisted of the cytoreduction phase, with the objective to achieve macroscopic removal of all tumor spots. Therefore, both visceral and

peritoneal resections were performed, according to the extent of peritoneal disease. Secondly, the remaining microscopic tumor cells were eliminated by perfusing the abdominal cavity with heated chemotherapy at approximately 41°C (mitomycin C 35 mg/m<sup>2</sup> for 90 minutes until June 2014 and oxaliplatin 460 mg/m<sup>2</sup> for 30 minutes after June 2014). Oxaliplatin was administered immediately after intravenous administration of leucovorin/5-fluorouracil 20/400 mg/m<sup>2</sup>.

### 2.4. Scoring systems

Comorbidities were scored according to the International Classification of Diseases and Related Health Problems version of the Charlson comorbidity index (CCI) score.<sup>[12,13]</sup> Postoperative complications were staged according to the Clavien–Dindo classification of surgical complications.<sup>[14]</sup> Severe complications were defined as complications with Clavien–Dindo  $\geq 3$ , indicating a complication requiring a surgical, radiological or endoscopic intervention or admission to the intensive care unit (ICU).

### 2.5. Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Sciences, Version 21.0 (IBM Corporation, Armonk, NY). Binary and categorical variables were expressed as n (%) and were analyzed using chi-square or Fisher exact test if  $>20\%$  of the cells had an expected count of  $<5$ . Continuous variables were expressed as median (range) and were analyzed with the Mann–Whitney *U* test. All tests were performed 2-sidedly and  $P < 0.05$  was considered statistically significant. In case of patients with missing values, those patients were excluded from the specific analysis. The impact of CRS+HIPEC on postoperative complications, corrected for relevant confounding variables, was assessed with multivariate binary regression analysis. The Dutch Surgical Colorectal Audit (DSCA) previously identified age, sex, American Society of Anaesthesiologists (ASA) classification, CCI, and urgency of resection as independent predictors for mortality after colon cancer surgery.<sup>[1]</sup> Except for urgency of resection, these factors were manually forced into the regression model together with the variable “CRS+HIPEC.”

## 3. Results

A total of 371 patients with colon cancer underwent a primary tumor resection, of whom 43 (11.6%) underwent additional CRS+HIPEC. The median age of the entire group was 71.1 (24.3–95.2) years and 46.9% of the patients were female. During the first 3 months after surgery, no loss to follow-up occurred.

### 3.1. Baseline characteristics

Patients who underwent CRS+HIPEC were significantly younger compared with those who did not receive CRS+HIPEC (66.2 [24.3–78.6] vs 71.9 [24.4–95.2] years;  $P < 0.001$ ; Table 1). Comorbidities were present less frequently in CRS+HIPEC patients (60.5% vs 84.1%;  $P < 0.001$ ). This was also reflected in the lower number of CRS+HIPEC patients with an ASA score of 3 or higher (9.3% vs 32.3%;  $P = 0.002$ ). Thirty-three patients treated with CRS+HIPEC (76.7%) underwent previous abdominal surgery compared with 144 patients (43.9%) who only underwent conventional colon surgery ( $P < 0.001$ ). The percentage of patients with prior abdominal surgery related to colon cancer was also higher in the CRS+HIPEC group and is specified in Table 1 (60.5% vs 3.0%;  $P < 0.001$ ).

**Table 1**  
**Patient and tumor characteristics of patients with peritoneal metastases of the colon treated with cytoreduction and HIPEC compared with patients with colon cancer treated with conventional surgery.**

Variable	CRS + HIPEC (n=43)		Conventional procedures (n=328)		P
	n	(%)	n	(%)	
Sex	Male	21 (48.8)	176	(53.7)	0.55
	Female	22 (51.2)	152	(46.3)	
Age (median [range])	66.2 [24.3–78.6]		71.9 [24.4–95.2]		<0.001
Body mass index (median [range])	25.8 [20.3–36.5]		25.7 [16.0–51.1]		0.72
ASA score	1 or 2	39 (90.7)	222	(67.7)	0.002
	3 or higher	4 (9.3)	106	(32.3)	
Charlson comorbidities	≥2	4 (9.3)	62	(18.9)	.12
Overall comorbidity		26 (60.5)	276	(84.1)	<0.001
	Cardiovascular comorbidity	20 (46.5)	208	(63.4)	0.032
	Diabetes mellitus	7 (16.3)	62	(18.9)	0.68
	Pulmonary comorbidity	4 (9.3)	49	(14.9)	0.32
	Neurological comorbidity	0	46	(14.0)	0.009
Prior abdominal surgery		33 (76.7)	144	(43.9)	<0.001
Prior surgery related to colon cancer		26 (60.5)	10	(3.0)	<0.001
	Stoma formation	12 (27.9)	10	(3.0)	<0.001
	Local metastasis resection	2 (4.7)	0		
	Colon enterostomy	1 (2.3)	0		
	Diagnostic laparotomy	2 (4.7)	0		
	Diagnostic laparoscopy	9 (20.9)	0		
	Right colon	21 (48.8)	169	(51.5)	0.18
	Transverse colon	5 (11.6)	30	(9.1)	
Left colon	5 (11.6)	14	(4.3)		
Sigmoid colon	12 (27.9)	115	(35.1)		
Histological subtype and differentiation grade	Adenocarcinoma	28 (65.1)	282	(86.0)	0.001
	Well-differentiated	0	40	(14.2)	0.003
	Moderately differentiated	17 (60.7)	199	(70.6)	
	Poorly differentiated	9 (32.1)	33	(11.7)	
	Unknown	2 (7.1)	10	(3.5)	
	Mucinous adenocarcinoma	12 (27.9)	33	(10.1)	
	Signet ring cell carcinoma	3 (7.0)	5	(1.5)	
	Other	0	8	(2.4)	
Venous invasion		9 (20.9)	30	(9.1)	0.028
Pathological T4 primary tumor		29 (67.4)	60	(18.3)	<0.001
Pathological lymph node status	N0	7 (16.3)	201	(61.3)	<0.001
	N1	12 (27.9)	74	(22.6)	
	N2	24 (55.8)	53	(16.2)	
Synchronous peritoneal metastases		43 (100)	11	(3.4)	<0.001
Synchronous liver metastases		4 (9.3)	22	(6.7)	0.52
Synchronous lung metastases		1 (2.3)	4	(1.2)	0.46
Neoadjuvant chemoradiation		0	7	(2.1)	>0.99
Neoadjuvant chemotherapy		8 (18.6)	14	(4.3)	0.002

Data are expressed as n (%) unless otherwise specified.

Bold values indicate the difference between groups being statistically significant.

ASA=American Society of Anaesthesiologists, CRS=cytoreductive surgery, HIPEC=hyperthermic intraperitoneal chemotherapy, SD=standard deviation.

### 3.2. Tumor characteristics

Patients treated with CRS+HIPEC had less favorable tumor characteristics compared with those who underwent conventional colon surgery. This was reflected in less favorable histological subtype, differentiation grade, and venous invasion percentage (Table 1). Furthermore, CRS+HIPEC patients more often had a pathologically proven T4 tumor (67.4% vs 18.3%;  $P < 0.001$ ) and lymph node metastases (83.7% vs 38.7%;  $P < 0.001$ ). All CRS+HIPEC patients had peritoneal metastases, compared with 3.4% of patients in the conventional group ( $P < 0.001$ ). The number of patients with synchronous liver or lung metastases did not differ between both groups ( $P = 0.52$  and  $0.46$ , respectively).

### 3.3. Procedure characteristics

The primary procedure type did not differ significantly between both groups ( $P = 0.30$ ; Table 2). One patient in the conventional surgery group underwent abdominoperineal resection due to a locally advanced sigmoid tumor. All CRS+HIPEC procedures were performed by an open procedure compared with 53.4% of the procedures in the conventional group ( $P < 0.001$ ). Additional resection of tumor tissue because of metastases or local involvement of surrounding tissue was required in all CRS+HIPEC patients and in 9.5% of the conventional surgery patients ( $P < 0.001$ ). Except for 2 CRS+HIPEC patients with synchronous resection of liver metastases, systemic metastases were either not operated on, or resected during a second procedure. The need

**Table 2****Procedural characteristics of patients with peritoneal metastases of the colon treated with cytoreduction and HIPEC compared with patients with colon cancer treated with conventional surgery.**

Variable	CRS+HIPEC (n=43)		Conventional procedures (n=328)		P
	n	(%)	n	(%)	
Procedure type	Right hemicolectomy	23	181	55.2	0.30
	Transverse resection	0	7	2.1	
	Left hemicolectomy	8	25	7.6	
	(low) anterior resection	11	102	31.1	
	APR	0	1	0.3	
Type of surgery	(sub)total colectomy	1	12	3.7	<0.001
	Laparotomy	42	158	48.2	
	Laparoscopy	0	153	46.6	
Additional resection locally advanced primary tumor/peritoneal metastases	Converted laparoscopy	1	17	5.2	<0.001
		43	31	9.5	
Synchronous liver resection		2	0		0.01
Bowel anastomosis		40	316	96.3	0.40
Postoperative enterostomy		21	29	8.8	<0.001
	Temporary ileostomy	14	7	24.1	
	Definitive ileostomy	0	4	13.8	
	Temporary colostomy	4	10	34.5	
	Definitive colostomy	3	8	27.6	
Intraoperative radiotherapy		1	2	0.6	0.31
Operative time, * min (median [range])		258 [167–410]	112 [28–498]		<0.001
Perioperative complication		4	8	2.4	0.04

Data are expressed as n (%) unless otherwise specified.

Bold values indicate the difference between groups being statistically significant.

APR=abdominoperineal resection, CRS=cytoreductive surgery, HIPEC=hyperthermic intraperitoneal chemotherapy.

\* Operative time was corrected for HIPEC circulation time.

for a postoperative colostomy was higher in CRS+HIPEC patients (48.8% vs 8.8%;  $P < 0.001$ ). Operative time corrected for HIPEC circulation time was significantly longer in the CRS+HIPEC group (258 [167–410] vs 112 [28–498] minutes;  $P < 0.001$ ). The HIPEC procedure was performed with mitomycin C in 35 patients and with oxaliplatin in the 7 remaining patients.

### 3.4. Postoperative outcomes

Postoperative complications were present in 69.8% of the CRS+HIPEC patients compared with 40.5% of the conventional patients ( $P < 0.001$ ; Table 3). Severe complications were present in 23.3% of the CRS+HIPEC patients and in 14.9% of the conventional patients ( $P = 0.16$ ; Fig. 1). None of the CRS+HIPEC patients died within 30 days after surgery or during the initial hospital admission, compared with 11 patients undergoing conventional colon surgery ( $P = 0.62$ ). Prolonged postoperative ileus occurred in 34.9% of the CRS+HIPEC patients and in 12.5% of the conventional patients ( $P < 0.001$ ). The percentage of patients with an ICU stay of more than 1 day was higher in the CRS+HIPEC group (37.2% vs 13.4%;  $P < 0.001$ ). Median hospital stay was with 11 (6–42) versus 7 days (2–70) longer in the CRS+HIPEC group ( $P < 0.001$ ). Furthermore, the readmission rate in CRS+HIPEC patients was higher (20.9% vs 6.4%;  $P = 0.004$ ).

### 3.5. Predictors of morbidity

To assess the impact of CRS+HIPEC on (severe) postoperative complications, a multivariate regression model with previously identified predictors except for emergency surgery was

constructed (see “Methods” section). CRS+HIPEC was the strongest predictor of postoperative complications after colon surgery (odds ratio [OR] 6.43, 95% confidence interval [CI] 3.03–13.06; Table 4). However, CRS+HIPEC was no independent predictor for severe postoperative complications (OR 2.22, 95% CI 0.96–5.10).

## 4. Discussion

In this study, cytoreductive surgery followed by HIPEC was a major independent predictor for postoperative morbidity after correction for previously identified predictors of mortality after elective colon surgery.<sup>[1]</sup> Patients treated with CRS+HIPEC developed significantly more postoperative complications compared with those undergoing conventional types of elective colon surgery. Additionally, ICU stay was longer and the readmission rate was significantly higher in the CRS+HIPEC group. For the greater part, this difference can be explained by the high percentage of relatively mild complications among CRS+HIPEC patients. Indeed, the number of severe complications and reinterventions did not significantly differ between patients undergoing CRS+HIPEC or conventional surgery. Furthermore, treatment-related mortality after CRS+HIPEC was absent, suggesting complications after CRS+HIPEC can be treated adequately in a specialized HIPEC center with extensive experience in this treatment.<sup>[15]</sup> The observed differences in outcome between CRS+HIPEC and conventional surgery can be explained by major variation in tumor, patient, and treatment-related characteristics. Although the current results could be expected, they illustrate an important difference in outcome in patients treated with CRS+HIPEC that is addressed insufficiently in current clinical audit systems.

**Table 3**  
**Postoperative outcome of patients with peritoneal metastases of the colon treated with cytoreduction and HIPEC compared with patients with colon cancer treated with conventional surgery.**

Variable	CRS + HIPEC (n = 43)		Conventional procedures (n = 328)		P
	n	(%)	n	(%)	
Patients with complications	30	(69.8)	133	(40.5)	<0.001
Patients with severe complications (Clavien–Dindo ≥3)	10	(23.3)	49	(14.9)	0.16
Patients with ICU stay >1 d	16	(37.2)	44	(13.4)	<0.001
Patients receiving blood transfusion	16	(37.2)	73	(22.3)	0.03
Patients requiring reintervention	8	(18.6)	34	(10.4)	0.12
Laparotomy	5	(62.5)	24	(70.6)	0.27
Laparoscopy	0		3	(8.8)	
Surgical drainage	2	(25.0)	1	(2.9)	
Radiological drainage	1	(12.5)	4	(11.8)	
Other	0		2	(5.9)	
Hospital stay, d (median [range])	11 [6–42]		7 [2–70]		<0.001
30-d/inhospital mortality	0		11	(3.4)	0.62
Patients with readmission	9	(20.9)	21	(6.4)	0.004
Occurrence of specific complications					
Anastomotic leakage	2	(4.7)	13	(4.0)	0.69
Other gastrointestinal perforation	1	(2.3)	1	(0.3)	0.22
Intra-abdominal abscess	3	(7.0)	11	(3.4)	0.21
Postoperative ileus	15	(34.9)	41	(12.5)	<0.001
Pneumonia	5	(11.6)	32	(9.8)	0.79
Urinary tract infection	5	(11.6)	13	(4.0)	0.05
Paroxysmal atrial fibrillation	6	(14.0)	10	(3.0)	0.006
Postoperative bleeding	1	(2.3)	6	(1.8)	0.58
Surgical wound infection	7	(16.3)	27	(8.2)	0.09
Wound dehiscence	0		3	(0.9)	>0.99
Fascia dehiscence	3	(7.0)	6	(1.8)	0.07
Pulmonary embolism	0		5	(1.5)	>0.99
Cardiac event	0		2	(0.6)	>0.99
Delirium	4	(9.3)	11	(3.4)	0.08
Systemic inflammatory response syndrome	0		2	(0.6)	>0.99
Heart failure	0		8	(2.4)	0.60

Data are expressed as n (%) unless otherwise specified.

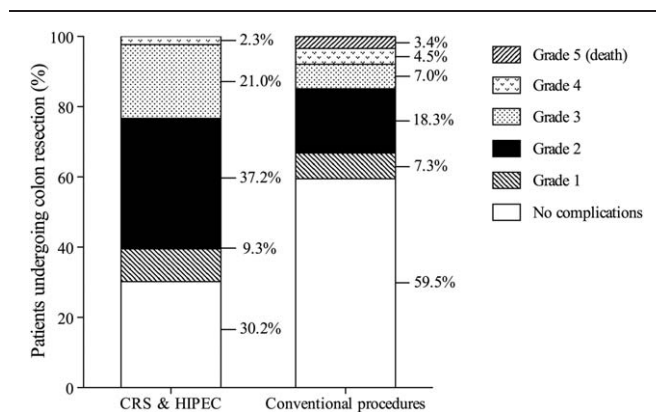
Bold values indicate the difference between groups being statistically significant.

CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit.

An important part of the difference in postoperative complications can be explained by the high incidence of prolonged postoperative ileus in CRS+HIPEC patients. The cause of postoperative ileus is multifactorial and the high ileus

percentage after CRS+HIPEC is probably explained by the extensive bowel manipulation in combination with the toxic and hyperthermic intraperitoneal chemotherapy.<sup>[16]</sup> The reported incidence of postoperative ileus after colorectal surgery varies widely due to a lack of an internationally accepted standardized clinical definition for postoperative ileus.<sup>[17]</sup> In the current study, prolonged postoperative ileus was defined as a paralytic bowel with the inability to tolerate oral feeding requiring total parenteral feeding. Therefore, the differences between both groups within the current study are consistent, although comparing with other studies is less reliable.

The majority of patients with colorectal PM are over 70 years of age. Nevertheless, CRS+HIPEC patients were younger compared with patients undergoing conventional types of colon surgery, underlining the strict patient selection for this extensive procedure.<sup>[18]</sup> However, more than age, the outcome after colorectal surgery is determined by a patients' comorbidity status.<sup>[19,20]</sup> Therefore, because of major improvements in surgical techniques and perioperative care, an increasing number of relatively healthy older patients become suitable for curative colorectal cancer surgery.<sup>[21–23]</sup> As a consequence, it may be expected that in the near future, more and more older patients become candidates for CRS+HIPEC treatment, as long as comorbidity and performance status are taken into consideration.



**Figure 1.** Incidence of postoperative complications according to the Clavien–Dindo classification in patients with peritoneal metastases of the colon treated with CRS+HIPEC compared with patients with colon cancer treated with conventional surgery. CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy.



**Table 4****Multivariate analysis of predictors of morbidity and severe morbidity in patients with colon cancer who underwent elective surgery.**

Variable	Patients with complications				P	Odds ratio	95% CI
	Yes (n = 163)		No (n = 208)				
	n	(%)*	n	(%)*			
CRS + HIPEC	30	(69.8)	13	(30.2)	<0.001	6.43	3.03–13.6
ASA score 3 or higher	71	(64.5)	39	(35.5)	<0.001	3.03	1.77–5.18
Male sex	99	(50.3)	98	(49.7)	<b>0.008</b>	1.86	1.18–2.94
Age (median [range])	72.2 [24.3–92.4]		70.1 [24.4–95.2]		<b>0.02</b>	1.03	1.01–1.05
CCI score 2 or higher	42	(63.6)	24	(36.4)	0.19	1.52	0.81–2.86

Variable	Patients with complications Clavien–Dindo ≥3				P	Odds ratio	95% CI
	Yes (n = 59)		No (n = 312)				
	n	(%)*	n	(%)*			
ASA score 3 or higher	28	(25.5)	82	(74.5)	<b>0.001</b>	3.13	1.56–6.25
Male sex	40	(20.3)	157	(79.7)	<b>0.03</b>	1.95	1.07–3.59
CRS + HIPEC	10	(23.3)	33	(76.7)	0.06	2.22	0.96–5.10
Age (median [range])	70.1 [24.3–90.8]		71.3 [24.4–95.2]		0.16	0.98	0.96–1.01
CCI score 2 or higher	15	(22.7)	51	(77.3)	0.83	1.09	0.51–2.35

Data are expressed as n (%) unless otherwise specified.

Bold values indicate the difference between groups being statistically significant.

ASA = American Society of Anaesthesiology, CCI = Charlson comorbidity index, CI = confidence interval, CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy.

\* Percentages are calculated horizontally.

In the current study, tumor characteristics of patients treated with CRS + HIPEC were less favorable compared with patients undergoing conventional surgery. Obviously, the most striking difference is that all CRS + HIPEC patients had peritoneal metastases, which explains most of the other differences in tumor characteristics in the current study as well. Risk factors for synchronous PM are tumors penetrating through the surface of the visceral peritoneum (pT4), and also tumors with an advanced N-stage or poor differentiation grade.<sup>[18,24]</sup> All of these conditions were frequently present in the CRS + HIPEC group. The percentage of patients with liver or lung metastases was low in both groups, which illustrates only highly selected PM patients with other systemic metastases are candidate for CRS + HIPEC.

Due to peritoneal metastases, and also more locally advanced tumors, the cytoreductive surgery required to achieve macroscopic complete resection in CRS + HIPEC patients is much more extensive compared with standard colon resections. In the current study, this was reflected in the 100% additional resection percentage and the much longer procedure time in the CRS + HIPEC group, even if corrected for the HIPEC circulation time. In HIPEC literature, extensive surgery has repeatedly been associated with higher morbidity.<sup>[25,26]</sup> Additionally, according to data from the DSCA, extensive surgery leads to impaired postoperative outcomes.<sup>[1,27]</sup> Therefore, an important part of the difference in morbidity in the current study may be explained by the difference in the extent of surgery.

Another factor possibly influencing the risk of postoperative complications is the intraperitoneal treatment with heated chemotherapy (HIPEC). A small case-control study reported a higher percentage of severe postoperative complications in patients receiving CRS + HIPEC compared with cytoreductive surgery alone, although this difference was not statistically significant.<sup>[28]</sup> Until the results of the randomized multicenter trial investigating the difference between CRS + HIPEC versus cytoreduction alone (Prodige 7) become available, the effect of the HIPEC component on morbidity remains unclear.

Furthermore, the risk of receiving a stoma after CRS + HIPEC was higher than after conventional colon surgery. This is in line with other studies, in which stoma formation after CRS + HIPEC

is common.<sup>[29,30]</sup> The pelvic space is a preferred location for peritoneal metastases, which often leads to rectosigmoid resections with low colorectal anastomoses. These low anastomoses are known for the high risk of anastomotic leakage, especially if multiple other bowel resections are required to achieve complete macroscopic cytoreduction. Additionally, during every CRS + HIPEC procedure, an omentectomy is performed, resulting in the loss of the ability to cover small perforations by the omentum. To protect anastomoses and prevent other perforations, diverting stoma formation after CRS + HIPEC is no exception. Only a small portion of these patients undergoes successful restoration of bowel continuity, with a substantial risk of infectious complications after colostomy reversal.<sup>[29]</sup>

Taken together, CRS + HIPEC patients are healthier and younger, but have less favorable tumor characteristics and undergo more extensive surgery. Since the postoperative course was more complicated in patients undergoing CRS + HIPEC, the increased extent of surgery seems to weigh heavier than the better physical condition of these patients. The DSCA identified age, ASA classification, CCI, and emergency surgery as important factors in determining high-risk patients in colon surgery.<sup>[1]</sup> When solely looking at these factors, CRS + HIPEC patients seem to be at low risk of postoperative problems. However, based on the current results, an important factor in determining postoperative outcome is the extent of surgery. In the current study, this is illustrated by the CRS + HIPEC treatment being a major risk factor for postoperative morbidity.

For several years now, quality measurements of surgical care are subject of political debate in numerous countries. Clinical auditing initiatives for colorectal cancer surgery have been implemented successfully with high participation grades.<sup>[7–10,31]</sup> Since large variations between hospitals exist, case-mix adjustments are performed to compare outcomes between different hospitals.<sup>[32]</sup> The current study shows that colon PM patients treated with CRS + HIPEC are a different entity and therefore this treatment modality might be difficult to compare with conventional types of colon surgery. In the current situation, this may lead to an underestimation of the performance of tertiary referral

centers for CRS+HIPEC due to insufficient case-mix correction. Therefore, further improvements in the correction of factors influencing the postoperative outcome are needed to make reliable comparisons between different types of hospitals with different types of surgery.

The current study retrospectively analyzed data that were prospectively collected for quality control purpose. Therefore, some degree of selection and registration bias cannot be ruled out. However, because of consistent patient selection criteria for colon surgery and in particular CRS+HIPEC over the past few years, the current cohort is representative for other centers, and also future research. Furthermore, the number of patients treated with CRS+HIPEC is relatively small, but large enough to show the differences in characteristics between both groups.

## 5. Conclusions

Although patients with PM of colon origin treated with CRS+HIPEC were younger and healthier compared with patients treated with conventional colon surgery, the postoperative outcomes were worse. This is most probably due to more extensive surgery and less favorable tumor characteristics. Furthermore, CRS+HIPEC treatment was a strong and independent predictive factor for postoperative complications. These results stress the need for adequate case-mix correction for patients undergoing extensive surgery in colorectal surgery audits.

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