


Impact of cumulative complications on 1-year treatment-related healthcare costs in patients with colorectal peritoneal metastases undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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Abstract

Background: The aim of this study was to evaluate the impact of all minor and major complications on treatment-related healthcare costs in patients who undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of colorectal peritoneal metastases (PMs).

Method: Patients with histologically proven colorectal PMs who underwent CRS + HIPEC from March 2006 to October 2019 in a tertiary referral centre were retrospectively identified from a prospectively maintained database. Patients were divided into six subgroups according to the severity of the complications, which were scored using the comprehensive complication index (CCI) (CCI 0–9.9, CCI 10–19.9, CCI 20–29.9, CCI 30–39.9, CCI 40–49.9, and CCI 50 or higher). Treatment-related healthcare costs up to 1 year after CRS + HIPEC were obtained from the financial department. Differences in costs and survival outcomes were compared using the chi-squared test and Kruskal–Wallis *H* test.

Results: A total of 142 patients were included (CCI 0–9.9, 53 patients; CCI 10–19.9, 0 patients; CCI 20–29.9, 45 patients; CCI 30–39.9, 14 patients; CCI 40–49.9, 9 patients; and CCI 50 or higher, 21 patients). Median (interquartile range) treatment-related healthcare costs increased significantly and exponentially for the CCI 30–39.9, CCI 40–49.9, and CCI 50 or higher groups (€48 993 (€44 262–€84 805); €57 167 (€43 047–€67 591); and €82 219 (€55 487–€145 314) respectively) compared with those for the CCI 0–9.9 and CCI 20–29.9 groups (€33 856 (€24 433–€40 779) and €40 621 (€31 501–€58 761) respectively, *P* < 0.010).

Conclusion: Treatment-related healthcare costs increase exponentially as more complications develop among patients who undergo CRS + HIPEC for the treatment of colorectal PMs. Anastomotic leakages after CRS + HIPEC lead to an increase of 295 per cent of treatment-related healthcare costs.

Introduction

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment option in selected patients with limited and resectable colorectal peritoneal metastases (PMs). The median overall survival (OS) of patients with colorectal PMs undergoing CRS + HIPEC is reported to be up to 63 months with 5-year survival rates of up to 54 per cent^{1–5}. The surgical procedure consists of removing all macroscopically visible tumour deposits from the abdominal cavity (cytoreduction) and subsequently flushing the abdominal cavity with a heated chemotherapeutic agent (HIPEC) to treat remaining tumour cells.

CRS + HIPEC is a complex oncological procedure prone to serious postoperative complications, with reported major

postoperative morbidity rates of 12–52 per cent and mortality rates of 0.9–5.8 per cent⁶. Major postoperative complications are also reported as a significant risk factor for early recurrence of disease after CRS + HIPEC and may lead to a reduction in OS⁷.

The Clavien–Dindo classification is often used to classify the severity of postoperative complications^{8–12}. This classification reports the most severe postoperative complications for each patient and is limited because the full cumulative burden of all minor and major complications per CRS + HIPEC patient are not assessed.

The comprehensive complication index (CCI) was introduced taking all cumulative complications per patient into consideration which results in a continuous score from 0 (no

Received: May 31, 2022. Revised: July 27, 2022. Accepted: August 01, 2022

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complications) to 100 (death)^{13,14}. The CCI score has demonstrated to have a higher sensitivity for assessing various surgical-related and cancer-related outcomes, including CRS+HIPEC when compared with the Clavien–Dindo classification^{15–18}. The CCI score being cumulative and covering the range of complications is a better tool for calculating complication-related healthcare costs¹⁹.

The burden of increasing healthcare costs is a major global issue requiring challenging considerations to balance treatment-related healthcare costs with potential survival gain of extensive procedures such as CRS+HIPEC with respect to quality-adjusted life-years. Several studies have reported estimated healthcare costs in the field of CRS+HIPEC, including some cost-effectiveness analyses reporting the correlation of various factors of CRS+HIPEC with healthcare costs^{20–31}; however, studies reporting the hospital-based cumulative financial consequences of multiple complications after CRS+HIPEC, assessed with the CCI score, have never been published. Simkens *et al.* did report a major impact of complications after CRS+HIPEC using the Clavien–Dindo classification leading to a 320 per cent increase in hospital costs⁷. These data suggest that a more tailored classification such as the CCI score, would result in an even stronger correlation of cumulative complications with treatment-related healthcare costs.

The present study aims to identify the true cumulative impact of all minor and major postoperative complications, using the CCI score, on treatment-related healthcare costs up to 1 year after CRS+HIPEC for the treatment of colorectal PMs, highlighting the importance of prevention of any postoperative complication after CRS+HIPEC.

Methods

Design, setting, and patients

Data from all consecutive patients with histologically proven colorectal PMs who were treated with CRS+HIPEC at a single Dutch tertiary referral centre between March 2006 and October 2019 were retrospectively extracted from a merged prospectively maintained institutional database. Patients with mucinous appendiceal neoplasms were excluded. This study was approved by the Institutional Ethics Committee of the University Medical Center Groningen (UMCG) (protocol number 201800395). The STROBE checklist of this cohort study can be found in the supplementary material.

Patients were divided in subgroups according to their CCI score after CRS+HIPEC (CCI 0–9.9, CCI 10–19.9, CCI 20–29.9, CCI 30–39.9, CCI 40–49.9, or CCI 50 or higher). These groups were selected based on the statement from Staiger *et al.* that every 10-point increase in CCI score causes a 14 per cent increase in healthcare costs¹⁹.

Preoperative evaluation and management

For all patients with colorectal PMs, a standardized preoperative assessment was used to evaluate suitability for CRS+HIPEC. All patients were staged with a CT of thorax, abdomen, and pelvis to investigate the extent and resectability of disease and to rule out distant metastases. Since 2012, diagnostic laparoscopy (DLS) has been included in the standardized preoperative assessment to assess the extent of colorectal PMs and the possibility of performing a complete cytoreduction. A multidisciplinary team meeting consisting of radiologists, medical oncologists, gastroenterologists, and surgical oncologists, determined the patient's eligibility for CRS+HIPEC. In general, those patients

with complete resectable colorectal PMs, a peritoneal cancer index (PCI) score below 20, no extra-abdominal metastases, and a performance status that permitted major surgery were considered eligible candidates for CRS+HIPEC. Up to three resectable liver metastases were not considered to be an absolute contraindication.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

All CRS+HIPEC procedures were performed according to our national standardized Dutch HIPEC protocol, as previously described⁵. An explorative laparoscopy was performed to assess the extent and distribution of the peritoneal deposits using the PCI score and to determine resectability of the colorectal PMs. In patients not suitable for CRS+HIPEC, palliative surgery was performed at the discretion of the surgical team (non-therapeutic laparotomy). These patients were not included in our present study. When the colorectal PMs were deemed to be resectable, CRS was performed to remove all macroscopic visible tumour tissue and hereafter the completeness of cytoreduction (CC score) was determined (CC 0, no residual tumour visible or palpable in the peritoneal cavity; CC 1, presence of a residual tumour smaller than 2.5 mm; CC 2, presence of a residual tumour between 2.5 mm and 2.5 cm; and CC 3, presence of a residual tumour larger than 2.5 cm or presence of a confluence of nodules)³².

In patients with a (nearly) complete cytoreduction (CC 0 or CC 1), HIPEC was subsequently performed and only these patients were included in this study. Mitomycin C (35 mg/m²) was circulated with a temperature between 41–42°C for 90 min in the abdominal cavity. The surgical procedure was concluded with reconstruction surgery as required, possibly including anastomoses and/or a colostomy.

Neoadjuvant or adjuvant chemotherapy was only administered to patients when indicated according to our current national Dutch HIPEC protocol. Contrary to other countries, both therapy options are not considered standard treatment in The Netherlands⁵. After surgery, all patients were admitted to the intensive care unit (ICU) for a minimum of 1 day until cardiac and pulmonary functions were deemed to be stable.

Follow-up

Clinical follow-up was arranged 1 month after hospital discharge and was continued on a 6–12-monthly basis for a minimum of 5 years. In case of suspected disease, indicated by clinical symptoms or an increase in carcinoembryonic antigen level, a CT of the thorax and abdomen/pelvis was performed.

Treatment costs

All treatment-related healthcare costs from one day before CRS+HIPEC up to 1 year afterwards were obtained from our financial department. These costs included all components of the surgical procedure, the postoperative in-hospital care, postoperative hospital visits (to the outpatient clinic and the emergency department), and the in-hospital rehabilitation programme. These data concentrated on the actual individual patient-related costs incurred to treat the specific patient for CRS+HIPEC. Thus, a prolonged surgical procedure or an extended hospital stay resulted in higher costs. Any costs for the preoperative workup and costs from the general practitioner or other medical centres were not included.

For further analyses, all components of costs were classified into eight domains (ward admission costs, ICU admission costs,

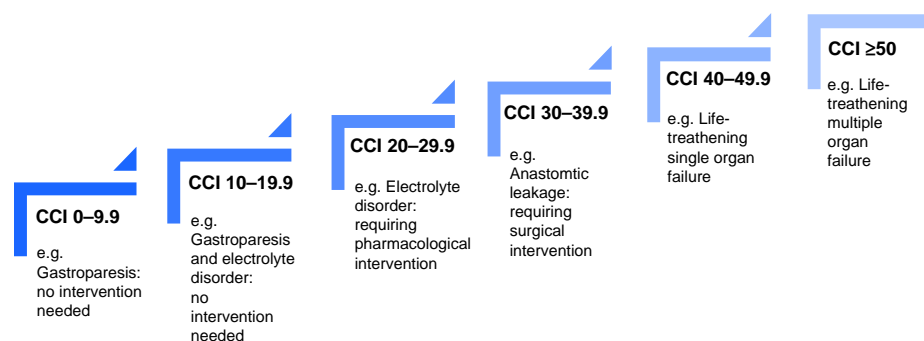


Fig. 1 Subgroups of patients with colorectal peritoneal metastases who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, according to the comprehensive complication index

surgical costs, diagnostic costs, therapeutic costs, consulting department costs, outpatient visit costs, and in-hospital rehabilitation programme costs). Ward admission costs were defined as total ward costs and consisted of primary admission costs and re-admissions within 1 year after CRS+HIPEC. Surgical costs included all costs of the operating room, use of consumables during surgery, surgical debulking, hyperthermia treatment, perfusionist costs, chemotherapeutic drugs, anaesthetics, and all re-interventions (for example, surgical or radiological interventional drains). Consulting department costs incorporated all costs of consulting by other medical disciplines, physiotherapy, and dieticians. Outpatient visit costs included all costs for treatment-related visits at the outpatient clinic or emergency department. Cost for neoadjuvant chemotherapy or adjuvant chemotherapy were not included in this study. Both are not considered standard treatments in The Netherlands and, in general, when indicated were carried out in other local hospitals.

No discounting was applied because all costs incurred within 1 year after treatment. Analysis was performed using the 2019 cost level in Euros (€) for all patients.

Data collection

Relevant data on patient characteristics, tumour characteristics, operating characteristics, postoperative outcome, OS, and disease-free survival (DFS) were obtained prospectively. All postoperative complications were collected up to 60 days after CRS+HIPEC and registered according to the Clavien–Dindo classification system¹⁰. The CCI score was calculated by using the online calculator provided by www.assessurgery.com.³³ All relevant financial data were collected with assistance from our financial department.

Primary and secondary outcomes

Primary outcome for this study was overall treatment-related healthcare costs up to 1 year after CRS+HIPEC, considering the severity of postoperative complications (CCI 0–9.9, CCI 10–19.9, CCI 20–29.9, CCI 30–39.9, CCI 40–49.9, or CCI 50 or higher). Secondary outcomes included overall costs per month of OS and overall costs per month of DFS. For this study, DFS was defined as the time in months between CRS+HIPEC and the date of the first recurrence of disease or the last follow-up visit in censored cases. OS was defined as the time in months between CRS+HIPEC and the date of death or the last follow-up visit in censored cases.

Statistical analyses

All statistical analyses were performed using SPSS® Statistics version 24.0 (IBM, Armonk, NY, USA). Financial data were analysed using RStudio (RStudio, PBC, Boston, MA, USA) with R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and $P < 0.05$ was considered statistically significant. Continuous values with a normal distribution are reported as mean(s.d.), and continuous values without a normal distribution are reported as median (interquartile range (i.q.r.)). Categorical variables are reported as numbers (n) and per cent with a 95 per cent confidence interval (c.i.). Patient and tumour characteristics were compared by performing the chi-squared test. In cases of continuous variables without a normal distribution the Kruskal–Wallis H test was used.

Results

In total, 142 consecutive patients with colorectal PMs who underwent CRS+HIPEC between March 2006 and October 2019 were included in this study. As mentioned previously, these patients were divided into five subgroups following their CCI score; CCI 0–9.9 (53 patients), CCI 10–19.9 (0 patients), CCI 20–29.9 (45 patients), CCI 30–39.9 (14 patients), CCI 40–49.9 (9 patients), and CCI ≥ 50 (21 patients). No patient had a CCI score between 10 and 19.9 and this group was excluded from further analysis.

Patients with a CCI score of less than 10 represent those with no or minor complications (up to one complication of Clavien–Dindo I), whereas patients with a CCI score of more than 50 represent those with severe complications (a patient with two complications of Clavien–Dindo IVA or a patient with three complications of Clavien–Dindo IIIB). These different subgroups including an illustrative example of possible postoperative complications are displayed in [Fig. 1](#).

Patient and tumour characteristics

[Table 1](#) presents the patient and tumour characteristics of the entire cohort, as well as a comparison of these between the five CCI groups in. Patients with a higher CCI score (40 or higher) were more likely to have a medical history of cardiac disease ($P < 0.010$); however, the number of patients with this type of medical history was low. Patients with a higher CCI score (40 or higher) were more often diagnosed with a T4 stage primary tumour compared with patients with a lower CCI score ($P = 0.030$). Other baseline characteristics were similar between the five groups.

Table 1 Comparison of baseline characteristics between patients with colorectal peritoneal metastases who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, according to the comprehensive complication index

	CCI 0–9.9 (n = 53)	CCI 20–29.9 (n = 45)	CCI 30–39.9 (n = 14)	CCI 40–49.9 (n = 9)	CCI ≥50 (n = 21)	P*
Patient characteristics						
Age (years) (i.q.r.)	59 (52–65)	58 (50–67)	62 (54–70)	63 (53–70)	65 (61–70)	0.108†
Sex ratio (M:F)	24:29	17:28	8:6	5:4	13:8	0.366
BMI (kg/m ²) (i.q.r.)	25.7 (23.8–28.0)	26.7 (23.0–31.2)	25.3 (23.3–29.1)	28.6 (22.7–31.2)	24.8 (22.6–29.1)	0.734†
ASA grade						0.449
I	8 (15.1)	8 (17.8)	1 (7.1)	0 (0.0)	2 (9.5)	
II	39 (73.6)	34 (75.6)	11 (78.6)	6 (66.7)	15 (71.4)	
III	6 (11.3)	3 (6.7)	2 (14.3)	3 (33.3)	4 (19.0)	
Co-morbidity						
Diabetes	4 (7.5)	4 (8.9)	0 (0.0)	0 (0.0)	2 (9.5)	0.933
Hypertension	8 (15.1)	11 (24.4)	3 (21.4)	3 (33.3)	3 (14.3)	0.487
Cardiac disease	4 (7.5)	2 (4.4)	0 (0.0)	2 (22.2)	5 (23.8)	<0.010
Pulmonary disease	7 (13.2)	4 (8.9)	3 (21.4)	0 (0.0)	2 (9.5)	0.575
Tumour characteristics						
Primary tumour						0.633
Appendix	0 (0.0)	2 (4.4)	0 (0.0)	1 (11.1)	0 (0.0)	
Right colon	20 (37.8)	12 (26.7)	7 (50.0)	2 (22.2)	7 (33.3)	
Transverse colon	4 (7.5)	3 (6.7)	1 (7.1)	0 (0.0)	1 (4.8)	
Left colon	6 (11.3)	7 (15.6)	1 (7.1)	1 (11.1)	4 (19.0)	
Sigmoid	17 (32.1)	14 (31.1)	4 (28.6)	5 (55.6)	4 (19.0)	
Rectum	6 (11.3)	7 (15.6)	1 (7.1)	0 (0.0)	5 (23.8)	
Signet cell histology	8 (15.1)	2 (4.4)	2 (14.3)	1 (11.1)	3 (14.3)	0.357
T category						
≤3	30 (56.6)	16 (35.6)	6 (42.9)	2 (22.2)	8 (38.1)	0.030
4	23 (43.4)	28 (62.2)	8 (57.1)	6 (66.7)	11 (52.4)	
x	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (9.5)	
N category						
0	14 (26.4)	14 (31.1)	4 (28.6)	3 (33.3)	3 (14.3)	0.236
1	15 (28.3)	12 (26.7)	5 (35.7)	3 (33.3)	5 (23.8)	
2	24 (45.3)	18 (40.0)	5 (35.7)	2 (22.2)	11 (52.4)	
x	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (9.5)	
M stage						
0	24 (45.2)	21 (46.7)	7 (50.0)	5 (55.6)	4 (19.0)	0.175
1	28 (52.8)	22 (48.9)	6 (42.9)	4 (44.4)	14 (66.7)	
x	1 (1.9)	1 (2.2)	1 (7.1)	0 (0.0)	3 (14.3)	
Onset of PM						
Synchronous	29 (54.7)	20 (44.4)	7 (50.0)	6 (66.7)	12 (57.1)	0.698
Metachronous	24 (45.2)	25 (55.6)	7 (50.0)	3 (33.3)	9 (42.9)	
Liver metastases						
Previous CRC surgery	4 (7.5)	4 (8.9)	2 (14.3)	0 (0.0)	2 (9.5)	0.819
Neoadjuvant chemotherapy	48 (90.6)	41 (91.1)	11 (78.6)	8 (88.9)	19 (90.5)	0.739
Neoadjuvant chemotherapy	10 (18.9)	10 (22.2)	2 (14.3)	0 (0.0)	8 (38.1)	0.578

Values are n (%) unless otherwise indicated. *Chi-squared test. †Kruskal–Wallis H test. CCI, comprehensive complication index; PM, peritoneal metastases; CRC, colorectal cancer.

Treatment characteristics

Table 2 provides an overview of all treatment characteristics of the entire cohort, as well as a comparison of these between the five CCI groups. Higher CCI scores were associated with reoperations ($P < 0.010$) and a prolonged hospital stay ($P < 0.010$). Although the number of anatomical resections performed during CRS+HIPEC was comparable between all CCI groups, a significant increase in bowel anastomoses was found in the higher CCI groups; 20 of 53 patients (37.7 per cent) in the CCI 0–9.9 group increasing to 15 of 21 patients (71.4 per cent) in the CCI 50 or higher group. As a result, anastomotic leakage or the presence of an intra-abdominal abscess occurred more frequently in patients with higher CCI scores. Table 3 shows the location of the anastomotic leakage based on CCI group. Ileocolic was the most common location of an anastomotic leakage (4 of 13 patients, 19 per cent).

Overall and disease-free survival

The mean OS and DFS for the entire cohort were 38 months (95 per cent c.i. 34 to 43) and 12 months (95 per cent c.i. 6 to 23) respectively. Twenty-three patients died within the first year

after CRS+HIPEC (CCI 0–9.9, six patients; CCI 20–29.9, four patients; CCI 30–39.9, three patients; CCI 40–49.9, one patient; and CCI 50 or higher, nine patients) consisting of two treatment-related deaths and 21 disease-related deaths. A significant decrease in OS can be observed in groups with a higher CCI score ($P = 0.019$).

Treatment costs

The majority of the treatment-related healthcare costs consist of ward admission costs (32 per cent) and surgical costs (31 per cent). More than 75 per cent of all treatment-related healthcare costs originate from surgical costs, ward admission costs, and ICU costs.

Figure 2 displays the correlation between the CCI score and the total treatment-related healthcare costs from 1 day before to 1 year after CRS+HIPEC. The total treatment-related healthcare costs increase significantly, as the CCI score increases.

Table 4 shows the treatment-related healthcare costs from 1 day before to 1 year after CRS+HIPEC for the different CCI groups. For the entire cohort, the total median treatment-related healthcare

Table 2 Comparison of treatment characteristics between patients with colorectal peritoneal metastases who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, according to the comprehensive complication index

	CCI 0–9.9 (n = 53)	CCI 20–29.9 (n = 45)	CCI 30–39.9 (n = 14)	CCI 40–49.9 (n = 9)	CCI ≥50 (n = 21)	P*
DLS performed	25 (47.2)	23 (51.1)	11 (78.6)	6 (66.7)	15 (71.4)	0.114
PCI at DLS (i.q.r.)	3 (2–7)	4 (2–5)	4 (2–9)	4 (3–15)	6 (2–8)	0.318†
PCI at HIPEC (i.q.r.)	8 (3–15)	9 (4–13)	9 (5–14)	14 (5–20)	13 (4–18)	0.391†
Operating time (min) (i.q.r.)	494 (435–559)	503 (454–603)	519 (478–621)	555 (483–650)	509 (455–641)	0.181†
No. of anastomoses						<0.010†
0	33 (62.3)	19 (42.2)	0 (0.0)	2 (22.2)	6 (28.6)	
1	15 (28.3)	15 (33.3)	11 (78.6)	5 (55.6)	8 (38.1)	
≥2	5 (9.4)	8 (17.8)	3 (21.4)	2 (22.2)	7 (33.3)	
No. of resections (i.q.r.)	5 (3–6)	4 (2–6)	5 (4–7)	5 (4–10)	6 (4–9)	0.188†
Stoma post HIPEC	30 (56.6)	27 (60.0)	11 (78.6)	5 (55.6)	12 (57.1)	0.661
Type of stoma						0.287
Double barrel ileostomy	1 (1.9)	0 (0.0)	0 (0.0)	1 (11.1)	1 (4.8)	
Ileostomy	9 (17.0)	4 (8.9)	1 (7.1)	1 (11.1)	2 (9.5)	
Double barrel colostomy	2 (3.8)	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Colostomy	18 (34.0)	21 (46.7)	10 (71.4)	3 (33.3)	9 (42.3)	
Blood loss (ml) (i.q.r.)	700 (500–1500)	700 (500–1100)	1000 (500–2100)	850 (275–1750)	1000 (500–1550)	0.779†
Resection status						0.109
CC-0	53 (100.0)	44 (97.8)	14 (100.0)	8 (89.9)	21 (100.0)	
CC-1	0 (0.0)	1 (2.2)	0 (0.0)	1 (11.1)	0 (0.0)	
Hospital stay (days) (i.q.r.)	13 (12–17)	18 (15–24)	22 (26–28)	32 (26–40)	38 (29–58)	<0.010†
Reoperation	1 (1.9)	2 (4.4)	4 (28.6)	3 (33.3)	13 (61.9)	<0.010
Hospital mortality	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	3 (14.3)	0.069
CD grade ≥3 complications						
Anastomotic leakage	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	10 (47.6)	<0.010
Intra-abdominal abscess	0 (0.0)	3 (6.7)	6 (42.9)	3 (33.3)	10 (47.6)	<0.010
Wound infection	0 (0.0)	3 (6.7)	2 (14.3)	2 (22.2)	7 (33.3)	<0.010
Wound dehiscence	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	6 (28.6)	<0.010
Pneumonia	0 (0.0)	6 (13.3)	3 (21.4)	4 (44.4)	5 (23.8)	<0.010
Bacteraemia e.c.i.	1 (1.9)	1 (2.2)	1 (7.1)	3 (33.3)	7 (33.3)	<0.010
Electrolyte disorder	1 (1.9)	3 (6.7)	3 (21.4)	4 (44.4)	14 (66.7)	<0.010
Fistula formation	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	8 (38.1)	<0.010
Urinoma	0 (0.0)	1 (2.2)	0 (0.0)	2 (22.2)	0 (0.0)	<0.010
Cardiac disease	0 (0.0)	5 (11.1)	0 (0.0)	0 (0.0)	8 (38.1)	<0.010
OS (months) (95% c.i.)	38.0 (32.3–43.7)	33.0 (27.5–38.5)	46.0 (17.7–74.3)	24.0 (18.0–30.0)	20.0 (11.6–28.4)	0.019‡
DFS (months) (95% c.i.)	13.0 (10.0–16.0)	11.0 (8.5–13.5)	12.0 (0.0–35.8)	10.0 (7.1–12.9)	9.0 (4.7–13.2)	0.750‡

Values are n (%) unless otherwise indicated. *Chi-squared test except †Kruskal–Wallis H test and ‡Kaplan–Meier test. CCI, comprehensive complication index; DLS, diagnostic laparoscopy; PCI, peritoneal cancer index; CC, completeness of cytoreduction; CD, Clavien–Dindo score; Bacteraemia e.c.i., bacteraemia of unknown cause; OS, overall survival; DFS, disease-free survival.

Table 3 Location of anastomotic leakage based on CCI score

	CCI 0–9.9 (n = 53)	CCI 20–29.9 (n = 45)	CCI 30–39.9 (n = 14)	CCI 40–49.9 (n = 9)	CCI ≥50 (n = 21)	P
Location of anastomotic leakage						<0.010
Ileocolic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (19.0)	
Ileorectal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	
Ileo-transverse	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (4.8)	
Duodeno-ileal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	
Jejuno-ileal	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (4.8)	
Colorectal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	

Values are n (%). P values obtained by chi-squared test. CCI, comprehensive complication index.

costs (€ (i.q.r.)) were €41 838 (€30 861–€57 307). The total median treatment-related healthcare costs were significantly increased in the groups with CCI 20–29.9 (€40 621 (€31 501–€58 761)), CCI 30–39.9 (€48 993 (€44 262–€84 805)), CCI 40–49.9 (€57 167 (€43 047–€67 591)), and CCI 50 or higher (€82 219 (€55 487–€145 314)) compared with the group with CCI 0–9.9 (€33 856 (€24 433–€40 779)) ($P < 0.010$). Further analyses demonstrated that these differences in total median treatment-related healthcare costs can be explained due to a significant increase in ward admission costs ($P < 0.010$), surgical costs ($P = 0.017$), ICU admission costs ($P = 0.028$), diagnostic costs ($P < 0.010$), and consulting department costs ($P = 0.029$).

Furthermore, the total median treatment-related healthcare costs were significantly increased in the groups with CCI 30–39.9, CCI 40–49.9, and CCI 50 or higher compared with the group with CCI 20–29.9 ($P = 0.018$) due to a significant increase in ward admission costs ($P = 0.022$) and diagnostic costs ($P < 0.010$). The total median treatment-related healthcare costs of the group with CCI 50 or higher was also significantly increased compared with the groups with CCI 30–39.9 and CCI 40–49.9 ($P = 0.045$), because of significantly increased ICU admission costs ($P < 0.010$) and diagnostic costs ($P = 0.040$).

Table 4 shows the median treatment-related healthcare costs per month OS and per month DFS for each CCI group.

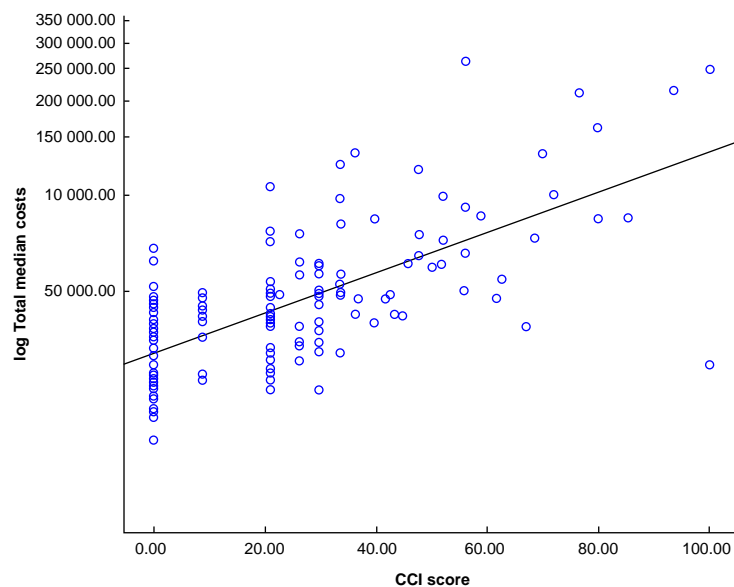


Fig. 2 Correlation between total median treatment-related healthcare costs and the comprehensive complication index score

CCI, comprehensive complication index.

Table 4 Total costs and costs of components of the combined procedure of cytoreduction and hyperthermic intraperitoneal chemotherapy 1 day before surgery to 1 year afterwards

	CCI 0–9.9 (n = 53)	CCI 20–29.9 (n = 45)	CCI 30–39.9 (n = 14)	CCI 40–49.9 (n = 9)	CCI ≥50 (n = 21)	P*
Total costs (€)	33 856 (24 433–40 779)	40 621 (31 501–58 761)	48 993 (44 262–84 805)	57 167 (43 047–67 591)	82 219 (55 487–145 314)	<0.010
Costs per month of OS (€)	1080 (605–1729)	1383 (928–2423)	1851 (954–5781)	2944 (1371–5163)	5349 (3063–12 177)	<0.010
Costs per month of DFS (€)	2151 (1063–5831)	3709 (1668–8049)	4638 (1729–24 139)	6938 (1869–10 265)	10 694 (4494–27 636)	<0.010
Items (€)						
Ward admission costs	7954 (6020–10 559)	12 407 (9031–17 933)	18 576 (13 034–34 240)	18 490 (15 152–20 593)	20 354 (15 388–35 317)	<0.010
ICU admission costs	5308 (5308–5308)	5308 (5308–7962)	5308 (5308–5971)	5308 (5308–15 923)	18 577 (9289–25 212)	<0.010
Surgical costs (€)	11 974 (8652–17 399)	15 410 (10 157–17 999)	18 125 (13 188–22 576)	15 468 (9491–23 285)	16 707 (13 895–22 444)	0.017
Diagnostics (€)						
Laboratory costs	474 (326–807)	584 (387–847)	830 (617–1844)	907 (565–2705)	1957 (659–2733)	<0.010
Radiology costs	109 (43–808)	145 (43–871)	1308 (180–2466)	820 (54–2281)	401 (46–1670)	0.096
Microbiology costs	59 (0–212)	245 (47–463)	855 (383–3080)	2491 (764–3834)	2474 (1145–8098)	<0.010
Pathology costs	832 (127–1277)	656 (212–1274)	1191 (779–1934)	571 (212–1601)	864 (287–1635)	0.134
Other costs	13 (0–376)	71 (13–814)	1012 (75–1857)	66 (33–179)	145 (33–707)	<0.010
Therapeutic costs (€)						
Blood products	0 (0–597)	0 (0–478)	239 (0–771)	478 (0–921)	1419 (379–2746)	<0.010
Consulting costs	445 (0–1450)	824 (0–1872)	1075 (568–3279)	1873 (263–4676)	2928 (1464–10 722)	0.029
Outpatient costs (€)	374 (47–796)	488 (47–886)	729 (416–1452)	868 (265–1422)	396 (158–1098)	0.077

Values are median (i.q.r) unless otherwise indicated. *Kruskal–Wallis *H* test. CCI, comprehensive complication index; i.q.r., interquartile range; OS, overall survival; DFS, disease-free survival; ICU, intensive care unit.

The median treatment-related healthcare costs per month DFS were significantly increased in the groups with CCI 30–39.9 (€4638 (€1729–€24 139)) and CCI 50 or higher (€7090 (€3292–€15 239)) compared with the group with CCI 0–9.9 (€2151 (€1063–€5831)) ($P < 0.010$). The median treatment-related healthcare costs per month OS were significantly increased in the groups with CCI 20–29.9 (€1383 (€928–€2423)), CCI 30–39.9 (€1851 (€954–€5781)), CCI 40–49.9 (€2944 (€1371–€5163)), and CCI 50 or higher (€5349 (€3063–€12 177)) compared with the group with CCI 0–9.9 (€1080 (€605–€1729)) ($P = 0.031$). The group with CCI 50 or higher also had significantly increased treatment-related healthcare costs per month OS compared with the groups with CCI 20–29.9 and CCI 30–39.9 ($P = 0.032$). Pathology costs, radiology

costs, and outpatient visit costs were similar between the different CCI groups. Rehabilitation costs were €0 among all groups and are therefore not presented.

Discussion

This study consisting of 142 consecutive patients with colorectal PMs who underwent CRS+HIPEC, shows that overall treatment-related healthcare costs up to 1 year after the procedure increase significantly and exponentially for those patients who have major postoperative complications expressed by the CCI score. This increase is caused mainly by an increase in surgical costs and ward admission costs due to reoperations,

re-interventions, and a prolonged hospital stay. Not surprisingly, in the data from this study we also note a significant decrease in survival as the CCI score increases.

The combination of minor and major postoperative complications after CRS+HIPEC not only has major consequences on survival, but also on treatment-related healthcare costs with 140 per cent increase within the first year after CRS+HIPEC. As more complications develop, survival decreases, and treatment-related healthcare costs increase. It is therefore crucial to identify patients who are at an increased risk of developing serious postoperative complications after CRS+HIPEC. There is a trend for patients with a higher CCI score to be associated with a higher PCI score although not significant. Previous studies have already illustrated that a higher PCI score is associated with increased complications and higher treatment-related healthcare costs^{31,34,35}. In more than 70 per cent of patients in the group with the highest CCI score (for example CCI 50 or higher) one or multiple anastomoses were created during CRS+HIPEC, resulting in an anastomotic leakage in two out of three patients. Patients who developed an anastomotic leakage had an increase of approximately 295 per cent of overall treatment-related healthcare costs. Those with the most serious postoperative complications after CRS+HIPEC (CCI of 40 or higher) more frequently underwent second or third surgical procedures or other re-interventions and had a significantly longer hospital stay.

To date no studies have analysed the real-time hospital costs after CRS+HIPEC in relation to the CCI score although 15 cost-effectiveness analyses and one comprehensive review have been published^{20–31,36–39}. Six of these studies focused on patients undergoing CRS+HIPEC specifically for the treatment of colorectal PMs and five studies specifically analysed the impact of postoperative complications on healthcare costs, using Clavien–Dindo^{20–31,36–39}. Simkens et al. focused on CRS+HIPEC for colorectal PM as well as the impact of postoperative complications on treatment-related healthcare costs³⁶ and demonstrated an increase in costs in patients with one or multiple severe complications; however, they did not assess surgical or outpatient costs, did not use a cumulative complication score, and only analysed costs up to 90 days after CRS+HIPEC, which explains the differences in hospital admission costs.

The results of this study demonstrate that treatment-related healthcare costs increase exponentially, and survival decreases as more complications develop. Costs per month survival increase significantly as more complications occur. Complications after CRS+HIPEC often occur in stages (anastomotic leakage can lead to intra-abdominal abscess and wound infection). These data highlight that every complication is relevant stressing the need for early detection of complications after CRS+HIPEC preventing a failure to rescue. This goal can be accomplished by improving patient selection and perioperative care. To improve patient selection before CRS+HIPEC requires evaluating our current selection protocols. To improve perioperative care and prevent failure to rescue it is essential to have a well organized care trajectory for every patient undergoing CRS+HIPEC. Staff and nurses should be trained to identify complications early and take adequate actions during the hospital stay and follow-up of these patients.

Prehabilitation science is an evolving field in colorectal surgery^{40, 41}. Optimizing modifiable patient-related risk factors before surgery not only reduces the number of patients with postoperative complications but also their impact. To our

knowledge no studies about prehabilitation in colorectal PM patients undergoing CRS+HIPEC have been published.

To reduce anastomotic leakage may require evaluating intraoperative decision-making concerning the creation of anastomoses or stoma⁴². Jacoby et al. previously showed that the creation of a protective stoma should be considered in CRS+HIPEC procedures requiring two or more anastomoses to reduce postoperative morbidity⁴³. Studies have assessed the role of indocyanine green (ICG) in predicting and preventing anastomotic leakage with variable results^{44–47}. There is a need for a prospective study in the use of ICG for the prevention of anastomotic leakage in patients with colorectal PMs undergoing CRS+HIPEC.

The main limitation of this study is that only treatment-related healthcare costs incurred in the UMCG were included. Therefore, treatment-related healthcare costs (for example, outpatient costs, rehabilitation costs, and readmission costs) incurred in other medical centres were unavailable. As rehabilitation mostly takes place outside of the UMCG, these costs are expected to be higher. For some patients' treatment-related costs are possibly increased by adjuvant chemotherapy; however, only three patients with CCI of 30 or higher have undergone adjuvant chemotherapy as a higher CCI would reduce the suitability of these treatments. Although our CRS-HIPEC surgeons are extensively trained, study results may also have been influenced by their learning curves in the beginning of this study period⁴⁸.

Funding

The authors have no funding to declare.

Acknowledgements

F.Z. and B.K. contributed equally to this work.

Disclosure

The authors declare no conflict of interest.

Supplementary material

[Supplementary material](#) is available at *BJS Open* online

Data availability statement

Data will not be made available due to patient confidentiality.

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