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

Femke A. van der Zant1, Bob J.L. Kooijman1, Judith E.K.R. Hentzen2, Wijnand Helfrich3, Emily M. Ploeg1, Robert J. van Ginkel1, Barbara L. van Leeuwen1, Lukas B. Been1, Joost M. klaase4, Patrick H.J. Hemmer3, Christian S. van der Hilst3 and Schelto Kruijff1,4

1Department of Surgery, Division of Surgical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
2Department of Surgery, Isala Hospital, Zwolle, The Netherlands
3Department of Surgery, Laboratory for Translational Surgical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
4Department of Surgery, Division of Hepatopancreatobiliary Surgery and Liver Transplantation, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

*Correspondence to: Schelto Kruijff, Department of Surgical Oncology, University Medical Center Groningen, Hanzeplein 1, Groningen, The Netherlands (e-mail: s.kruijff@umcg.nl)

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 patients; and CCI 50 or higher, 21 patients). Median (interquartile range) treatment-related healthcare costs increased significantly and exponentially for the CCI 30–39, CCI 40–49, and CCI 50 or higher groups (€48,993 (€44,262–€84,805); €57,167 (€43,047–€65,591); 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 cent1–5. 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 complications8–12. 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 is 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
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. The CCI score being cumulative and covering the range of complications is a better tool for calculating complication-related healthcare costs.

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; 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 costs. 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 costs.

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 described. 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).

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 Netherlands. 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, hospital visits to the outpatient clinic, the in-hospital rehabilitation programme, 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.
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, chemotherapy 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 dieters. 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 system. The CCI score was calculated by using the online calculator provided by www.assessurgery.com. 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 (9 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 III B). 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

| Patient characteristics | 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* |
|-------------------------|---------------------|-----------------------|----------------------|----------------------|------------------|-----|
| 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/m²) (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               | I 8 (15.1)          | 8 (17.8)              | 1 (7.1)              | 0 (0.0)              | 2 (9.5)          | 0.449 |
|                        | 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)         | 0.487 |
|                        | Cardiac disease     | 4 (7.5)               | 2 (4.4)              | 0 (0.0)              | 2 (22.2)         | <0.01 |
|                        | Pulmonary disease   | 7 (13.2)              | 4 (8.9)              | 3 (21.4)             | 0 (0.0)          | 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) |
| T category             | ≤53 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) |
|                        | Metachronous        | 24 (45.2)             | 25 (55.6)            | 7 (50.0)             | 3 (33.3)         | 9 (42.9) |
|                        | Liver metastases    | 4 (7.5)               | 4 (8.9)              | 2 (14.3)             | 0 (0.0)          | 2 (9.5)  |
|                        | Previous CRC surgery | 48 (90.6)            | 41 (91.1)            | 11 (78.6)            | 8 (88.9)         | 19 (90.5) |
|                        | Neoadjuvant          | 10 (18.9)             | 10 (22.2)            | 2 (14.3)             | 0 (0.0)          | 8 (38.1) |

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

| Characteristic                           | 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* |
|-----------------------------------------|--------------------|----------------------|----------------------|--------------------|-----------------|----|
| **Operating time (min) (i.q.r.)**       | 494 (435–559)      | 503 (454–603)        | 519 (478–621)        | 555 (483–650)     | 509 (455–641)   | 0.181† |
| **PCI at HIPEC (i.q.r.)**               | 8 (3–15)           | 9 (4–13)             | 9 (5–14)             | 14 (5–20)         | 13 (4–18)       | 0.391† |
| **Location of anastomotic leakage**    | 25 (47.2)          | 23 (51.1)            | 11 (78.6)            | 6 (66.7)          | 15 (71.4)       | 0.114 |
| **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**                   |                    |                      |                      |                   |                 |     |
| **CC-0**                               | 53 (100.0)         | 44 (97.8)            | 14 (100.0)           | 8 (89.9)          | 21 (100.0)      | 0.109 |
| **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)            | 1 (2.2)              | 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 (33.3)             | 3 (100.0)            | 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)            | 0 (0.0)              | 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 (10.0–13.5)     | 10.0 (7.1–12.9)   | 9.0 (7.4–13.2)  | 0.750† |

Values are n (%) unless otherwise indicated. *Chi-squared test except †Kruskal–Wallis 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

| Location of anastomotic leakage | 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* |
|---------------------------------|--------------------|----------------------|----------------------|--------------------|-----------------|----|
| Ileocolic                       | 0 (0.0)            | 0 (0.0)              | 0 (0.0)              | 0 (0.0)            | 4 (19.0)        | <0.010 |
| Ileo-rectal                     | 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-ileoile               | 0 (0.0)            | 0 (0.0)              | 0 (0.0)              | 0 (0.0)            | 1 (4.8)         |     |
| Jejuno-ileoile               | 0 (0.0)            | 0 (0.0)              | 0 (0.0)              | 1 (11.1)           | 2 (9.5)         |     |
| 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.

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.
The median treatment-related healthcare costs per month DFS were significantly increased in the groups with CCI 30–39.9 (€4638 (€1729–€24139)) and CCI 50 or higher (€7090 (€3292–€15239)) 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–€12177)) 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,

---

**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   | Total costs (€) | Costs per month of OS (€) | Costs per month of DFS (€) | Items (€) | Diagnostics (€) | Therapeutic costs (€) | P*   |
|-------|-----------------|---------------------------|---------------------------|----------|----------------|----------------------|------|
| 0–9.9 | 33 856 (24 433–40 779) | 1080 (605–1729) | 2151 (1063–5831) | Ward admission costs 7954 (6020–10 559) | Laboratory costs 474 (326–807) | Blood products 0 (0–597) | 0.001 |
| 20–29.9 | 40 621 (31 501–58 761) | 1383 (928–2423) | 3709 (1688–8049) | ICU admission costs 5308 (5308–5308) | Radiology costs 109 (43–847) | Consulting costs 445 (0–1450) | 0.001 |
| 30–39.9 | 48 993 (44 262–84 805) | 1851 (954–5781) | 4638 (1729–24 139) | Surgical costs 11 974 (8652–17 399) | Microbiology costs 59 (0–212) | Outpatient costs 374 (47–796) | 0.001 |
| 40–49.9 | 57 167 (43 047–67 591) | 2944 (1371–5163) | 6938 (1869–10 265) | Pathology costs 5308 (5308–5308) | Pathology costs 832 (127–1277) | Consulting costs 445 (0–1450) | 0.001 |
| ≥50 | 82 219 (55 487–145 314) | 5349 (3063–12 177) | 10 694 (4494–27 636) | Other costs 13 (0–376) | Other costs 71 (13–814) | Outpatient costs 374 (47–796) | 0.001 |

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.

---

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

CCI, comprehensive complication index.
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 costs31,34,35. 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 published20–31,36–39. 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 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 morbidity13. Studies have assessed the role of indocyanine green (ICG) in predicting and preventing anastomotic leakage with variable results44–47. 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 period46.

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.

References
1. Esquivel J, Piso P, Verwaal V, Bachleitner-Hofmann T, Glehen O, González-Moreno S et al. American Society of Peritoneal Surface Malignancies opinion statement on defining expectations from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer. J Surg Oncol 2014;110:777–778.
2. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe J-M et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009;27:681–685.
3. Van der Zant et al.
3. Elias D, Gilly F, Bouttie F, Quenet F, Bereder J-M, Mansvelt B et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63–68

4. Esquivel J, Lowy AM, Markman M, Chua T, Pelz J, Baratti D et al. The American Society of Peritoneal Surface Malignancies (ASPSM) multi-institution evaluation of the peritoneal surface disease severity score (PSDSS) in 1,013 patients with colorectal cancer with peritoneal carcinomatosis. Ann Surg Oncol 2014;21:4195–4201

5. Kuipers AM, Mirck B, Aalbers AGJ, Nienhuijs SW, de Hingh IHJT, Wiezer MJ et al. Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. Ann Surg Oncol 2013;20:4224–4230

6. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg 2009;249:900–907

7. Simkens GA, Van Oudheusden TR, Luyer MD, Nienhuijs SW, Nieuwenhuijzen GA, Rutten HJ et al. Serious postoperative complications affect early recurrence after cytoreductive surgery and HIPEC for colorectal peritoneal carcinomatosis. Ann Surg Oncol 2015;22:2656–2662

8. Slankamenac K, Slankamenac M, Schlegel A, Nocito A, Rickenbacher A, Clavien P-A et al. Impact of postoperative complications on readmission and long-term survival in patients following surgery for colorectal cancer. Int J Colorectal Dis 2017;32:805–811

9. Schneider MA, Eshmuninov D, Lehmann K. Major postoperative complications are a risk factor for impaired survival after CRS/HIPEC. Ann Surg Oncol 2017;24:2224–2232

10. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196

11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213

12. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ et al. Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 2006;244:931–937

13. Clavien PA, Vetter D, Staiger RD, Slankamenac K, Mehr T, Graf R et al. The comprehensive complication index (CCI(R)): added value and clinical perspectives 3 years “down the line”. Ann Surg 2017;265:1045–1050

14. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1–7

15. Kim TH, Suh YS, Huh YJ, Son Y-G, Park J-H, Yang J-Y et al. The comprehensive complication index (CCI) is a more sensitive complication index than the conventional Clavien–Dindo classification in radical gastric cancer surgery. Gastric Cancer 2018;21:171–181

16. Nederlof N, Slaman AE, van Hagen P, van der Gaast A, Slankamenac K, Gisbertz SS et al. Using the comprehensive complication Index to assess the impact of neoadjuvant chemoradiotherapy on complication severity after esophagectomy for cancer. Ann Surg Oncol 2016;23:3964–3971

17. Dumitra S, O’Leary M, Raoof M, Wakabayashi M, Dellinger TH, Han ES et al. The comprehensive complication Index: a new measure of the burden of complications after hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2018;25:688–693

18. Choudry MH, Shuai Y, Jones HL, Pai RK, Pingpank JF, Ahrendt SS et al. Postoperative complications independently predict cancer-related survival in peritoneal malignancies. Ann Surg Oncol 2018;25:3950–3959

19. Staiger RD, Cimino M, Javed A, Biondo S, Fondeval C, Périnel J et al. The comprehensive complication index (CCI®) is a novel cost assessment tool for surgical procedures. Ann Surg 2018;268:784–791

20. Bonastre J, Chevalier J, Elias D, Classe JM, Ferron G, Guilloit JM et al. Cost-effectiveness of intraperitoneal chemohyperthermia in the treatment of peritoneal carcinomatosis from colorectal cancer. Value Health 2008;11:347–353

21. Chua TC, Martin S, Saxena A, Liao W, Yan TD et al. Evaluation of the cost-effectiveness of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (peritonectomy) at the St. George Hospital peritoneal surface malignancy program. Ann Surg 2010;251:323–329

22. Baratti D, Scivales A, Balestra MR, Ponzi P, Di Stasi F, Kusamura S et al. Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Eur J Surg Oncol 2010;36:463–469

23. Tentes AA, Pallas N, Korakianitis O, Mavroudis C, Spiridonidou A, Zorbas G et al. The cost of cytoreductive surgery and perioperative intraperitoneal chemotherapy in the treatment of peritoneal malignancy in one Greek institute. J BUON 2012;17:776–780

24. Squires MH, Staley CA, Knechtle W, Winer JH, Russell MC, Perez S et al. Association between hospital finances, payer mix, and complications after hyperthermic intraperitoneal chemotherapy: deficiencies in the current healthcare reimbursement system and future implications. Ann Surg Oncol 2015;22:1739–1745

25. Bagnoli PF, Cananzia FCM, Brocchi A, Ardito A, Strada D, Cozzaglio L et al. Peritonectomy and hyperthermic intraperitoneal chemotherapy: cost analysis and sustainability. Eur J Surg Oncol 2015;41:386–4391

26. Naoufoue SA, O’Donoghue C, Salti G. Evaluation of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a community setting: a cost-utility analysis of a hospital’s initial experience and reflections on the health care system. J Surg Oncol 2016;113:544–547

27. Hinkle NM, MacDonald J, Sharpe JP, Dickson P, Denve J, Munene G. Cytoreduction with hyperthermic intraperitoneal chemotherapy: an appraisal of outcomes and cost at a newly established peritoneal malignancy program. Am J Surg 2016;212:413–418

28. Vanounou T, Garfinkle R. Evaluation of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin in the era of value-based medicine. Ann Surg Oncol 2016;23:2556–2561

29. Lee ZJ, Chia SL, Tan G, Soo KC, Teo CCM. Cost effectiveness of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for management of colorectal peritoneal carcinomatosis. Ann Surg Oncol 2018;25:2340–2346

30. Hamilton TD, MacNeill AJ, Lim H, Hunink MGM. Cost-effectiveness analysis of cytoreductive surgery and HIPEC compared with systemic chemotherapy in isolated peritoneal carcinomatosis from metastatic colorectal cancer. Ann Surg Oncol 2019;26:1110–1117

31. Kooijman BJL, Hentzen JKE, van der Hilst CS, Been LB, van Ginkel RJ, Hemmer PHJ et al. Impact of extent of disease on
1-year healthcare costs in patients who undergo cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: retrospective observational cohort study. BJ Open 2020;4:945–962

32. Sugarbaker PH, Averbach AM, Jacquet P, Stuart OA, Stephens AD. Hyperthermic intraoperative intreperitoneal chemotherapy (HIIC) with mitomycin C. Surg Technol Int 1996;5:245–249

33. Home of AssesSurgery. https://www.assessurgery.com/ (accessed 24 July 2021)

34. Baratti D, Kusamura S, Mingrone E, Balestra M, Laterza B, Deraco M. Identification of a subgroup of patients at highest risk for complications after surgical cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg 2012;256:334–341

35. Baratti D, Kusamura S, Íusco D, Bonomi S, Grassi A, Virzì S et al. Postoperative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: a two-center study of 101 patients. Dis Colon Rectum 2014;57:858–868

36. Simkens GA, Rovers KP, van Oudheusden TR, Nienhuijs SW, Rutten HJ, de Hingh IH. Major influence of postoperative complications on costs of cytoreductive surgery and HIPEC in patients with colorectal peritoneal metastases. Medicine 2018;97 e0042

37. McBride KE, Steffens D, Solomon MJ, Koh C, Ansari N, Young CJ et al. Cost-analysis of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal malignancy: an Australian perspective with global application. Eur J Surg Oncol 2021;47:828–833

38. Klos D, Ríško J, Kriváčková D, Loveček M, Skalický P, Neoral Č et al. Cost analysis of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and the risk factors for their increased cost in a public insurance health care system—single centre study. Euro J Surg Oncol 2020;46:607–612

39. Schwartz PB, Stahl CC, Vande Walle KA, Pokrzywa CJ, Cherney Stafford LM, Aiken T et al. What drives high costs of cytoreductive surgery and HIPEC: patient, provider or tumor? Ann Surg Oncol 2020;27:4920–4928

40. Hughes M, Hackney R, Lamb P, Wigmore S, Christopher Deans D, Skipworth R. Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. World J Surg 2019;43:1661–1668

41. van Wijk L, van der Snee L, Buis C, Hentzen J, Haveman M, Klaase J. A prospective cohort study evaluating screening and assessment of six modifiable risk factors in HPB cancer patients and compliance to recommended prehabilitation interventions. Perioper Med 2021;10:5

42. Chouliaras K, Levine E, Fino N, Shen P, Votanopoulos K. Prognostic factors and significance of gastrointestinal leak after cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 2016;24:890–897

43. Jacoby H, Berger Y, Barda L, Sharif N, Zager Y, Lebedyev A et al. Implications of stoma formation as part of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg 2018;42:2036–2042

44. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. Tech Coloproctol 2017;21:15–23

45. Mangano A, Masrur MA, Bustos R, Chen LL, Fernandes E, Giulianotti PC. Near-Infrared indocyanine green-enhanced fluorescence and minimally invasive colorectal surgery: review of the literature. Surg Technol Int 2018;33:77–83

46. Mangano A, Fernandes E, Gheza F, Bustos R, Chen LL, Masrur M et al. Near-Infrared indocyanine green-enhanced fluorescence and evaluation of the bowel microperfusion during robotic colorectal surgery: a retrospective original paper. Surg Technol Int 2019;34:93–100

47. De Nardi P, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti E et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. Surg Endosc 2019;34:53–60

48. Kuipers AM, Hauptmann M, Aalbers AG, Nienhuijs SW, de Hingh IH, Wiezer MJ et al. Cytoreduction and hyperthermic intraperitoneal chemotherapy: the learning curve reassessed. Eur J Surg Oncol 2016;42:244–250

49. Hentzen JEK, Van Wijk L, Buis CI, Viddeleer AR, De Bock GH, Van der Schans CP et al. Impact and risk factors for clinically relevant surgery-related muscle loss in patients after major abdominal cancer surgery: study protocol for a prospective observational cohort study (MUSCLE POWER). Int J Clin Trials 2019;6:138–146

50. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM et al. Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial. Ann Surg 2022;275:e299–e306