

Major influence of postoperative complications on costs of cytoreductive surgery and HIPEC in patients with colorectal peritoneal metastases

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Abstract

Complications after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) result in impaired short- and long-term outcomes. However, financial consequences of complications after CRS and HIPEC in a European health care setting are unknown. This study aims to assess the consequences of complications on hospital costs after CRS and HIPEC.

In this prospective observational cohort study, patients with colorectal peritoneal metastases treated with CRS and HIPEC were included. Financial information was collected according to the Dutch manual for costs analyses. Costs were compared between patients without complications (NC), minor complications (MC), or severe complications (SC), according to the Clavien–Dindo classification.

One hundred and sixty-one patients were included, of whom 42% experienced NC, 27% MC and 31% SC. Mean hospital costs were €9,406 ± 2,235 in NC patients, €12,471 ± 3,893 in MC patients, and €29,409 ± 22,340 in SC patients. The 31% of patients with severe complications accounted for 56% of all hospital costs. Hospital admission costs in SC patients were 320% higher compared to NC patients. Costs of complications were estimated to be 43% of all admission costs.

Severe postoperative complications have major influence on costs after CRS and HIPEC and result in a threefold increase of hospital costs in affected patients. This finding stresses the need for adequate risk assessment of developing severe complications after CRS and HIPEC.

Abbreviations: CRS = cytoreductive surgery, EPF = electronic patient file, HIPEC = hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit, IQR = interquartile range, MC = mild complications, MEC-U = medical ethical committee united, NC = no complications, PCI = peritoneal cancer index, PM = peritoneal metastases, SC = severe complications, SD = standard deviation.

Keywords: colorectal neoplasms, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, financial costs, morbidity, postoperative complications

1. Introduction

Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is standard of care in selected patients with colorectal peritoneal metastases (PM).^[1] In the last decade, a major decrease in morbidity rates has been accomplished.^[2] However, the impact of postoperative complications after CRS and HIPEC on patient outcome remains substantial.^[3] It even extends beyond the direct postoperative period and impairs long-term survival as well.^[4,5] Besides the obvious negative impact of postoperative morbidity for the individual patients and their family, the intensive in-hospital treatment of

these patients may lead to an increased consumption of financial resources.^[6]

Nowadays, healthcare costs are a major topic in political debate, increasingly influencing clinical decision-making. Consequently, several studies have investigated the cost-effectiveness of CRS and HIPEC, but the financial consequences of postoperative complications after CRS and HIPEC have never been extensively described in a European healthcare setting.^[7–9]

Therefore, the present study aims to analyse the consequences of postoperative complications after CRS and HIPEC on the costs of hospital admission after surgery in a tertiary referral centre in the Netherlands. This financial approach of morbidity may provide more insight in the impact of complications after CRS and HIPEC in colorectal PM patients.

2. Methods

2.1. Patients

All patients with colorectal PM treated with complete or near-complete CRS and HIPEC between July 2010 and January 2015 in a tertiary referral hospital in the Netherlands were included in this prospective observational cohort study. Patients with PM of appendiceal origin were excluded from this analysis, since this disease is considered a different entity.^[10] Patients with other systemic metastases besides PM, except for patients with up to three resectable liver metastases, were excluded from analysis as well. Furthermore, two patients who were transferred to the referring hospital after surgery were excluded, since the hospital costs in other hospitals could not be assessed correctly. All patient

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and treatment-related characteristics were prospectively collected in a database. Financial information for costs analyses was automatically and manually collected from the electronic patient file (EPF) system. This study was approved by the medical ethical committee (MEC-U) of the Catharina Hospital Eindhoven. All methods were carried out in accordance with the relevant guidelines and regulations. Since this was an observational study of patients treated according to standardized treatment protocols and national guidelines, no written informed consent was required.

Hospital admission costs were compared between patients with no complications (NC), minor complications (MC), or severe complications (SC). Postoperative complications were scored according to the Clavien–Dindo classification of surgical complications.^[11] MC were defined as complications with Clavien–Dindo grade 1 or 2, indicating a complication requiring pharmacological treatment, blood transfusions, or parenteral nutrition. SC were defined as complications with Clavien–Dindo grade 3 to 5, indicating a complication requiring a surgical, radiological or endoscopic intervention, admission to the intensive care, or death. Follow-up for postoperative complications was complete until 90 days after CRS and HIPEC, since postoperative complications also occur beyond the 30-day postoperative period.^[12]

2.2. Hospital admission costs

To assess the hospital admission costs after CRS and HIPEC, all components of the postoperative hospital stay, emergency department visits, and possible readmissions registered in the EPF system were collected for each patient. The costs of each component of the treatment were determined in collaboration with the financial department of the hospital and according to the Dutch manual for costs analyses, version 2010. In total, approximately 180 treatment components were scored, and several essential treatment component prices are shown in Table 1. Reoperation costs were determined by combining a fixed price for operating room use and a variable price per minute. Since the aim of the current study was to determine the additional hospital admission costs of complications after CRS and HIPEC,

Table 1
Summary of several important item prices of hospital admission costs.

Item	Price
Ward costs per day	€500
Intensive care unit per day	€2.500
Diagnosics	
Haemoglobin	€2
C-reactive protein	€4
Thoracic x-ray	€40
Abdominal ultrasound	€70
Abdominal computed tomography scan	€250
Therapeutics	
Surgical reintervention	
Fixed costs	€350
Variable costs	€12/minute
Ultrasound guided drainage	€250
Endoscopy	€200–800
Erythrocyte concentrate	€350
Consulting department visit	€10
Physiotherapy consult	€30
Dietetics consult	€30
Emergency department visit	€250

costs of the preoperative workup and the actual CRS and HIPEC procedure were not included. Since the outpatient follow-up and possible adjuvant treatment of the majority of the patients was performed elsewhere in referring hospitals, costs of the outpatient trajectory were not assessed as well.

2.3. Cytoreductive surgery and HIPEC

CRS and HIPEC were performed as described extensively elsewhere.^[13] The extent of peritoneal disease was assessed with the peritoneal cancer index (PCI) score.^[14] The completeness of cytoreduction was scored with the R-score (R1 = no macroscopic disease, R2a = macroscopic residual disease ≤ 2.5 mm). The HIPEC agent used was Mitomycin C (35 mg/m²) or Oxaliplatin (460 mg/m²). Mitomycin C was circulated for 90 minutes. Oxaliplatin was circulated for 30 minutes combined with preoperative systemic 5-FU (400 mg/m²) and Leucovorin (20 mg/m²).

2.4. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, Version 21.0 (IBM Corporation, Armonk, NY). Binary and categorical variables are expressed as n (%) and were analyzed using χ^2 or Fisher's exact test if > 20% of the cells had an expected count of < 5. Continuous variables are expressed as mean \pm standard deviation (SD) or median [interquartile range (IQR)] and were analyzed using ANOVA or Kruskal Wallis test, depending on distribution. All tests were performed two-sidedly and $P < .05$ was considered statistically significant. Total costs of complications were determined by the total hospital admission costs of 161 patients subtracted by the mean hospital costs of uncomplicated patients times 161.

3. Results

A total of 161 patients with colorectal PM were treated with CRS and HIPEC during the inclusion period. Eighty-six patients (42.2%) experienced no complications (NC) after CRS and HIPEC, 43 patients (26.7%) had minor complications (MC), and 50 patients (31.1%) had severe complications (SC). Of the patients with SC, 4 patients experienced treatment-related mortality following CRS and HIPEC. Baseline characteristics according to these complication categories are shown in Table 2. Compared to NC patients, age was higher and pulmonary comorbidity was more frequent in patients with MC and SC. Furthermore, the PCI score was higher in MC and SC patients. Procedure time, hospital stay, and intensive care unit (ICU) stay were longer in patients with complications. The percentage of SC patients treated with adjuvant chemotherapy was lower compared to NC and MC patients.

Overall mean and median hospital admission costs were €18.030 \pm 16.845 and €12.325 [10.006–18.497], respectively. Costs for ward admission (36.9%) and ICU admission (48.2%) accounted for the majority of the hospital admission costs. Patients with SC (31.1% of the patients) accounted for 55.5% of the hospital admission costs. Patients with NC (42.2%) or with MC (26.7%) accounted for 24.2% and 20.3% of the total hospital admission costs, respectively.

Mean and median hospital admission costs in NC patients were 10.340 \pm 2.455 and €10.071 [8.761–11.248], respectively (Fig. 1). In patients with MC, mean and median costs were €13.729 \pm 4.306 and €12.764 [10.654–15.097], respectively.

Table 2
Baseline characteristics of patients with colorectal peritoneal metastases treated with cytoreduction and HIPEC, stratified for postoperative complications.

Variables	NC (n=68) n (%)	MC (n=43) n (%)	SC (n=50) n (%)	P value
Male gender	27 (39.7)	26 (60.5)	28 (56.0)	.07
Age (years; median [IQR])	62 [53–67]	65 [48–73]	67 [44–71]	.04
Body mass index (median [IQR])	25.0 [23.3–28.2]	25.4 [24.1–27.7]	25.9 [22.7–29.0]	.95
Prior surgical score 2 or 3	50 (73.5)	27 (62.8)	40 (80.0)	.18
ASA score 3 or higher	3 (4.4)	6 (14.0)	4 (8.0)	.18
ECOG performance status 2 or higher	11 (16.2)	9 (20.9)	13 (26.0)	.43
Comorbidities	34 (50.0)	26 (60.5)	32 (64.0)	.28
Cardiovascular	27 (39.7)	22 (51.2)	23 (46.0)	.49
Diabetes mellitus	6 (8.8)	5 (11.6)	11 (22.0)	.11
Pulmonary	1 (1.5)	5 (11.6)	9 (18.0)	< .001
Smoking	12 (17.6)	6 (14.0)	16 (32.0)	.07
Primary tumor location				
Colon	60 (88.2)	35 (81.4)	43 (86.0)	.60
Rectum	8 (11.8)	8 (18.6)	7 (14.0)	
Synchronous peritoneal metastases	37 (54.4)	30 (69.8)	22 (44.0)	.04
PCI score (mean ± SD)	7.5 ± 4.8	8.8 ± 4.3	10.2 ± 6.0	.02
Neoadjuvant chemotherapy	16 (23.5)	13 (30.4)	11 (22.0)	.62
Number of visceral/peritoneal resections (mean ± SD)	4.1 ± 2.2	4.7 ± 2.5	5.0 ± 2.4	.07
R1 macroscopic complete resection	64 (94.1)	42 (97.7)	45 (91.8)	.56
Procedure time (minutes; median [IQR])	324 [275–379]	348 [291–427]	380 [312–422]	.02
Intraoperative blood loss (millilitres; median [IQR])	650 [450–1100]	950 [500–1500]	1000 [550–1800]	.05
Hospital stay (median [IQR])	8 [7–11]	12 [10–16]	23 [17–39]	< .001
Intensive care stay (median [IQR])	2 [2–3]	2 [2–3]	3 [2–6]	< .001
Adjuvant chemotherapy	48 (70.6)	32 (76.2)	18 (36.0)	< .001

Bold values indicate difference between groups being significant. Data are expressed as n (%) unless otherwise specified.

ASA=American Society of Anaesthesiologists, ECOG=Eastern Cooperative Oncology Group, HIPEC=hyperthermic intraperitoneal chemotherapy, IQR=interquartile range, MC=minor complications, NC=no complications, PCI=peritoneal cancer index, SC=severe complications, SD=standard deviation.

Patients with SC had mean and median hospital admission costs of €32,188 ± 24,486 and €22,941 [17,926–33,402], respectively. The hospital admission costs in NC, MC, and SC patients differed significantly among groups (*P* < .001). In patients with MC, mean hospital admission costs were €3,389 higher compared to NC patients (136% of those of NC patients). In patients with

major complications, mean hospital admission costs were €22,117 higher compared to those of NC patients, leading to 320% higher hospital admission costs.

Total hospital admission costs for 161 colorectal PM patients after treatment with CRS and HIPEC were €2,902,840. Estimated total costs of complications were €1,238,100, comprehending 42.7% of the total admission costs. A breakdown of these costs is shown in Figure 2.

The composition of hospital admission costs according to the occurrence of postoperative complications is shown in Table 3. Costs of the separate components of the hospital admission increased gradually in MC and SC patients compared to NC patients. The ward/ICU admission costs accounted for 91.4% of the hospital admission costs in NC patients, compared to 88.1% and 81.3% in MC and SC patients.

4. Discussion

Morbidity after CRS and HIPEC is common and influences both short- and long-term outcome in colorectal PM patients.^[4,5] This study revealed the major impact of complications after CRS and HIPEC on hospital admission costs in this patient group, with severe complications accounting for over 55% of total hospital admission costs. In patients with severe complications, mean hospital admission costs were 320% higher compared to patients with an uncomplicated hospital admission. This increase in hospital admission costs is mainly explained by a prolonged ICU and ward stay as well as the significantly higher costs for diagnostic and therapeutic components of the treatment.

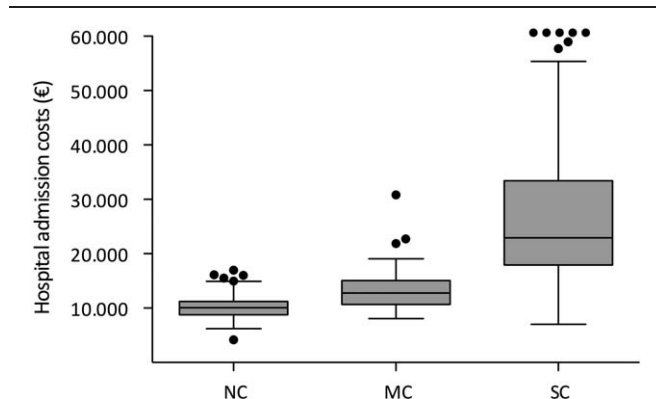


Figure 1. Hospital admission costs after CRS and HIPEC in patients with colorectal peritoneal metastases, stratified for postoperative complications. CRS=complications after cytoreductive surgery, HIPEC=hyperthermic intraperitoneal chemotherapy, NC=no complications, MC=minor complications, SC=severe complications, “•” outlier (14 in total, of which 5 > €60,000), gray box indicates median and interquartile range, whiskers are plotted according to the Tukey method. Complications after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

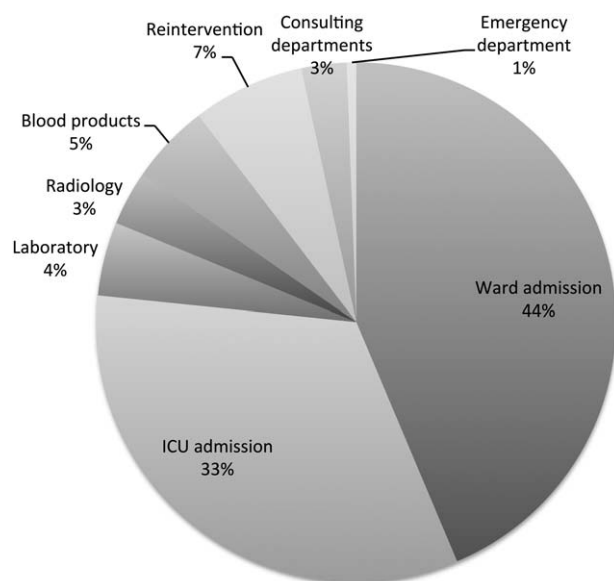


Figure 2. Breakdown of costs of complications (€1,238,100) after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

This study assessed hospital admission costs after CRS and HIPEC according to occurrence of postoperative complications. The financial impact of complications after CRS and HIPEC has been described once in the United States (US) healthcare setting.^[9] In this study, among 64 patients, severe complications were associated with 128% higher hospital costs. Although this increase was significant, it does not approach the 320% increase in costs in SC patients in the current study. In contrast with the current study, there was no increase in hospital costs in patients with minor complications in the US study. Unfortunately, the US study does not give insight in the reasons for the differences in costs between patients with and without complications. In addition to this small study, one Greek study identified morbidity after CRS and HIPEC as independent factor associated with increased treatment costs.^[15]

For major abdominal surgery in general, Straatman et al^[6] assessed the impact of postoperative complications on hospital costs in the Dutch healthcare setting. In line with the results from our study, a 180% and 340% increase in hospital costs was observed in patients with minor and major complications, respectively. Based on these results, the authors mention the importance minimizing the risk of postoperative complications.

The high hospital costs of patients with severe complications in our study are an additional argument to adequately assess the risk of developing these complications in patients treated with CRS and HIPEC. Financial consequences may not be used as the main reason to withhold patients from treatment with CRS and

Table 3

Mean + median hospital admission costs in patients with colorectal peritoneal metastases treated with cytoreduction and HIPEC, stratified for postoperative complications.

Items	NC (n=68)	MC (n=43)	SC (n=50)	P value*
Ward admission costs				< .001
Median [IQR]	€3.000 [2.000–4.500]	€5.000 [3.500–7.000]	€9.750 [7.375–16.250]	
Mean ± SD	€3.301 ± 1.531	€5.860 ± 2.973	€11.910 ± 8.598	
ICU admission costs				.03
Median [IQR]	€5.020 [5.020–7.520]	€5.020 [5.020–7.520]	€7.520 [5.015–15.025]	
Mean ± SD	€6.155 ± 2.344	€6.235 ± 2.138	€14.265 ± 19.374	
Diagnosics				
Laboratory costs				< .001
Median [IQR]	€308 [218–389]	€548 [338–776]	€926 [621–1.439]	
Mean ± SD	€331 ± 193	€601 ± 370	€1.241 ± 1.021	
Radiology costs				< .001
Median [IQR]	€80 [40–120]	€229 [80–407]	€518 [355–1.092]	
Mean ± SD	€101 ± 101	€300 ± 307	€780 ± 722	
Therapeutics				
Blood product costs				< .001
Median [IQR]	€0 [0–350]	€0 [0–350]	€700 [0–2.188]	
Mean ± SD	€247 ± 510	€269 ± 571	€1.459 ± 1.933	
Reintervention costs				–
Median [IQR]	–	–	€1.278 [770–2.037]	
Mean ± SD	–	–	€1.725 ± 1.560	
Consulting departments costs				< .001
Median [IQR]	€180 [81–257]	€270 [150–510]	€536 [247–1.034]	
Mean ± SD	€182 ± 125	€363 ± 310	€712 ± 627	
Emergency department costs				.03
Median [IQR]	€0 [0–0]	€0 [0–0]	0 [0–250]	
Mean ± SD	€22 ± 71	€99 ± 219	€95 ± 181	
Admission costs				< .001
Median [IQR]	€10.071 [8.761–11.248]	€12.764 [10.654–15.097]	€22.941 [17.926–33.402]	
Mean ± SD	€10.340 ± 2.455	€13.729 ± 4.306	€32.188 ± 24.486	

Bold values indicate difference between groups being significant.

* Kruskal Wallis test.

HIPEC = hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit, IQR = interquartile range, MC = minor complications, NC = no complications, SC = severe complications, SD = standard deviation.

HIPEC. Nevertheless, it can pose as an additional argument in individual cases with relative contra-indications like unfavorable histology, extensive peritoneal disease, and concomitant systemic metastases. To identify patients at risk of complications, several studies have investigated the impact of patient- and treatment-related factors on the occurrence of severe complications after CRS and HIPEC.^[13,16–18] Among the most frequently identified risk factors were an impaired performance status, a high PCI score and extensive cytoreductive surgery. A preoperative prediction model for severe morbidity after CRS and HIPEC was recently developed by our research group and may be of additional value in identifying patients at risk of high hospital admission costs.^[13]

Among others, Baratti et al^[7] and Chua et al^[8] stated that financial costs of the CRS and HIPEC procedure are high. With regard to hospital admission, the current study revealed that CRS and HIPEC requires similar resources as other major abdominal surgery, which is considered cost-effective and is performed on a broad scale.^[5] These results are supported by a recent study, in which CRS and HIPEC were found to be cost-effective with regard to survival gain and quality of life.^[19] Therefore, high costs of the hospital admission after surgery should not be stated as reason for limiting further implementation of this procedure in the Netherlands.

The healthcare reimbursement system in the United States and some European countries differs on many points from the single-payer government-base healthcare system in the Netherlands. These differences as well as major differences in costs calculations make comparisons between the available studies from Italy, Australia, United States, Greece, and France difficult.^[7–9,15,20] Since a comparison with these cost-effectiveness analyses is beyond the scope of this article, these results will not be further discussed.

The current study aimed to assess the impact of complications on hospital admission costs. Therefore, only costs of the initial hospital admission, emergency department costs, and readmission costs were assessed. Costs of the CRS and HIPEC procedure were not included, since these costs are regarded similar in all treated patients. Because of the tertiary character of this patient group, costs of preoperative workup, outpatient visits, and adjuvant systemic treatment were not assessed as well. As described by Chua et al^[8] in 2010, ward admission, ICU admission and clinical costs accounted for approximately 55% of the total costs for the CRS and HIPEC treatment in the Australian healthcare setting. This illustrates the current cost analysis does not comprise all healthcare costs made for the treatment of patients with colorectal PM in the Netherlands. Nevertheless, the results give more insight in the consequences of minor and severe complications on hospital admission costs of colorectal PM patients treated with CRS and HIPEC.

5. Conclusions

Severe complications after CRS and HIPEC have major consequences for hospital admission costs in colorectal PM patients. Limiting the occurrence of severe complications might lead to decreased hospital admission costs in these patients.

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