Morbidity after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with carboplatin used for ovarian, tubal, and primary peritoneal cancer

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Title: Morbidity after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy with Carboplatin used for Ovarian, Tubal and Primary Peritoneal Cancer

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Running head

Ovarian cancer and HIPEC

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Disclosures

All authors have no conflicts of interest regarding this article.

Synopsis

The aim of the study was to evaluate short-term morbidity after treatment of primary advanced-stage ovarian, tubal or primary peritoneal cancer with cytoreductive surgery and carboplatin HIPEC. In our prospective feasibility study with 25 patients, we found an acceptable rate of grade 3 adverse events within 30 days and no grade 4 adverse events and deaths were observed.
Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abstract

Background and Objectives

Hypertherm intraperitoneal chemotherapy (HIPEC) is increasingly used in treatment of ovarian, tubal and primary peritoneal cancer (OC). The aim was to evaluate short-term morbidity of cytoreductive surgery (CRS) and carboplatin HIPEC.

Methods

Prospective feasibility study performed from January 2016 to December 2017. Twenty-five patients with primary OC (FIGO III-IV) received upfront or interval CRS combined with carboplatin HIPEC at dose 800 mg/m². Primary outcome measurements: grade 3-5 adverse events within 30 days according to Common Terminology Criteria for Adverse Events (CTCAE). Secondary outcome measurements: reoperation rate, length of hospital stay, readmission rate and time from surgery to systemic chemotherapy administration.

Results

No deaths (grade 5) or grade 4 adverse events were observed. Eleven patients (44.0%) experienced at least one grade 3 adverse event, the most common being infection (28.0%) and neutropenia (12.0%). Reoperation rate was 8.0%. Median hospital stay was 14 days (range 9-25 days), and five patients (25.0%) were readmitted within 30 days.
after surgery. Median time from surgery to administration of first dose of systemic chemotherapy was 41 days (range 24-81 days).

Conclusion

Our small-scale prospective study supports that CRS and carboplatin HIPEC used for primary advanced-stage OC is feasible with acceptable morbidity.

Key words
Ovarian cancer, hyperthermic intraperitoneal chemotherapy, cytoreductive surgery, complications.

Main text

Introduction

Epithelial ovarian, tubal, and primary peritoneal cancer (OC) is considered as an entity of malignant gynecological disease for which identical treatment strategies are used. OC is associated with fatal outcome with more than 150,000 annual deaths worldwide.¹ Seventy-five percent of women with OC present with advanced disease.² Advanced-stage OC, corresponding to International Federation of Gynecology and Obstetrics stages III–IV (FIGO III–IV), is often characterized by diffuse peritoneal metastases.

The current standard treatment of primary OC is ‘upfront’ cytoreductive surgery (CRS) combined with adjuvant chemotherapy with paclitaxel and carboplatin postoperatively. Upfront CRS is sometimes unfeasible due to excessive tumor burden or poor general condition. In such cases, ‘interval’ CRS may be applied. Interval CRS involves that patients receive three series of neoadjuvant chemotherapy to downsize intraabdominal...
tumor masses before the CRS procedure, which is followed by another three chemotherapy series. A surgical outcome with complete resection, i.e. no visible tumor nodules after surgery, is an important positive prognostic factor for both progression-free and overall survival. Unfortunately, even if complete resection is achieved, recurrence risk is high. Hence, median overall survival ranges from 38 to 81 months for patients with FIGO stage IIIC-IV disease with complete resection upfront or following interval CRS.\textsuperscript{3,4}

Survival may be improved by use of hyperthermic intraperitoneal chemotherapy (HIPEC), which consists of intra-operative perfusion of the peritoneal cavity with a solution of cytotoxic agents heated to 41–43°C for 30–90 minutes depending on the drugs used. Administration of chemotherapy into the peritoneal cavity allows use of a high intraperitoneal concentration of cytotoxic agent compared with systemic administration. The aim of HIPEC is to eliminate microscopic intraabdominal disease after CRS and thereby reduce the risk of recurrence. CRS combined with HIPEC is associated with a more favorable outcome than CRS alone when used for other peritoneal surface malignancies such as pseudomyxoma peritonei,\textsuperscript{5} peritoneal spreading from colorectal and appendiceal cancer,\textsuperscript{6} and malignant peritoneal mesothelioma.\textsuperscript{7} Moreover, morbidity has been reported to be acceptable. Whether the same applies to OC with peritoneal metastases remains controversial.\textsuperscript{8-11}

Carboplatin is part of the standard systemic chemotherapy regimen used for primary OC and has a favorable toxicity profile compared with cisplatin. Carboplatin used for HIPEC in doses 800–1000 mg/m\textsuperscript{2} has been reported to be safe, with an acceptable level of bone marrow toxicity.\textsuperscript{12-14} However, most published studies evaluating morbidity associated

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with CRS with carboplatin HIPEC are retrospective and/or patients received carboplatin HIPEC as consolidation or for recurrent disease.\textsuperscript{14-16}

The aim of our prospective study was to evaluate morbidity and mortality within 30 days in patients treated for primary advanced-stage OC with CRS combined with carboplatin HIPEC.

**Material and methods**

**Patients and setting**

In January 2016, CRS combined with HIPEC with carboplatin 800 mg/m\(^2\) was introduced at the Department of Gynecology, Aarhus University Hospital, Aarhus, Denmark. This prospective feasibility study reports the results of the first 25 patients with primary OC. Our catchment area was the Central Denmark Region with 1.3 million citizens. Approximately 110 women with primary OC are referred to our department annually. The study period was January 2016 through December 2017. The inclusion criteria were: 1) patients with FIGO stages III–IV epithelial ovarian, tubal, or primary peritoneal cancer scheduled for upfront or interval CRS; 2) age 18–75 years; 3) completeness of cytoreduction score 0 (CC–0), defined as no macroscopic tumor nodules remained after surgery; 4) American Society of Anesthesiologists scores I–II (ASA scores I–II); 5) normal hematologic values and biochemical tests of kidney and liver function; and 6) no psychiatric illness or social conditions making patients unable to abide by study requirements and/or give informed consent. Regarding FIGO stage IV, only patients with resectable distant metastases or with complete remission of extra-abdominal metastatic disease after three series of neoadjuvant chemotherapy with paclitaxel and/or carboplatin were included. All OC patients were discussed on
multidisciplinary team conferences. Eligible candidates were invited to participate. The flowchart for patient selection is presented in Figure 1.

**CRS and HIPEC**

All patients had a midline incisional laparotomy. At commencement of the surgical procedure, the extent of peritoneal metastases was evaluated using the Peritoneal Cancer Index (PCI) described by Jaquet and Sugarbaker. Three gynecologic oncologists and one colorectal surgeon were included in the CRS team. The colorectal surgeon had 10 years’ experience with CRS and HIPEC for other peritoneal surface malignancies.

The HIPEC procedure was performed immediately after the CRS procedure using an open abdominal technique with The Performer HT® system from RAND (Medolla, Italy). Carboplatin 800 mg/m² was added to 5 l 0.9% isotonic sodium chloride to create the perfusion solution. The solution was heated to 41–42 °C and circulated into the peritoneal cavity for 90 minutes. Two inflow and three outflow tubing catheters were used for perfusion.

**Postoperative management**

Postoperatively, patients were closely monitored clinically as well as biochemically to detect any signs of complications promptly. Relevant imaging, e.g. chest x-ray, thoracic or abdominal CT scan, or electrocardiogram was performed if clinical signs of complication occurred.

When discharged from hospital, patients were instructed to contact the department if they experienced fever (rectal temperature > 38.0 °C), compromised bowel or bladder function, or major discomfort in general. Furthermore, a clinical evaluation was performed approximately four weeks after surgery.
Blood samples evaluating hemoglobin, white blood cell count with differential count, platelets, C-reactive protein (CRP), creatinine, and liver function were taken daily on days 1–7, and on day 14, 21, and 30 postoperatively to assess hematological, renal, and hepatic toxicity related to HIPEC.

Outcome measures

The primary outcome measure was perioperative and postoperative complications within 30 days according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Only grades 3–5 adverse events are reported here. Grade 3 adverse events are defined as severe or medically significant events that are not immediately life-threatening events that warrant hospitalization or prolongation of hospitalization. Grade 4 adverse events are life-threatening and require urgent intervention. Grade 5 is death related to adverse events. We excluded grade 3–4 anemia and thrombocytopenia registered during and 24 hours after surgery to discriminate the HIPEC-related bone marrow suppression from decreased levels of hemoglobin and platelets caused by perioperative bleeding associated with the CRS procedure.

Secondary outcome measures were length of hospital stay, reoperation rate, type of reoperation, readmission rate, and time from surgery to administration of first dose of adjuvant systemic chemotherapy.

Statistical analyses

Demographic and clinical data regarding each study participant were collected prospectively and analyzed with descriptive statistics using Stata/IC version 14. Categorical variables were described with frequency and percentage, and continuous variables with median and range.
Approvals

The Ethical Committee in Central Denmark Region approved the study. Project ID: 1-10-72-384-14. The Danish Data Protection Agency approved collection and storage of data in RedCap. Project ID: 1-16-02-20-15. Informed written consent was obtained from all study participants and the study was performed in accordance with the ethical standards of the Helsinki Declaration.

Results

In total, 14 patients had upfront CRS, and 11 patients underwent interval CRS. Median PCI (all patients) was 11 (range 5-32). Patient characteristics are outlined in Table 1.

Extensive surgery with upper abdominal peritonectomy (peritonectomy of the subhepatic space, and/or excision of the hepatic falciform ligament, and/or resection of liver capsule, and/or lesser sac peritonectomy, and/or peritoneal stripping from beneath the hemidiaphragm(s)) was performed in 13 patients (52.0%, eight in upfront CRS group and five in interval CRS group). Nine patients (36.0%, seven in upfront CRS group and two in interval CRS group) had en bloc pelvic resection of uterus, adnexae, pelvic peritoneum, and rectosigmoid resection with a colostomy. Cytoreductive surgery details are outlined in Table 2.

Complications and secondary outcomes within 30 days are outlined in Table 3. No deaths or grade 4 adverse events were observed within 30 days. Eleven patients (44.0%) experienced at least one grade 3 adverse event within 30 days. In total, 13 grade 3 adverse events were identified. The most common grade 3 adverse event was infection (28.0%, six patients in upfront CRS group and one patient in interval CRS group). Three patients received treatment with drainage and/or antibiotics for abdominal abscess/peritonitis, and one patient was diagnosed with pneumonia. Three patients in the upfront CRS group were diagnosed with infection of unknown origin. They presented
with fever, increasing CRP, and no focus of infection was found with supplemental paraclinical tests and relevant imaging. They all recovered within few days to one week after treatment with broad-spectrum antibiotics. Grade 3 neutropenia was identified in three patients around day 14-21 after surgery (12.0%, two patients in upfront CRS group and one patient in interval CRS group). Two patients (8.0%, one in each group) had a prolonged recovery due to grade 3 paralytic ileus, which postponed adjuvant chemotherapy administration.

Reoperation within 30 days was necessary in two patients (8.0%). One patient had prolonged postoperative ileus, and abdominal CT scan revealed a pelvic abscess, which was drained 15 days after surgery. Bowel function was still insufficient, and the patient had a local operative procedure with stoma revision on day 27 after surgery due to suspicion of stoma stenosis. Another patient had intraabdominal hemorrhage after removal of a drainage tube three days postoperatively.

Median hospital stay was 14 days (range 9–25 days). Five patients (25.0%), all in the upfront CRS group, were readmitted within 30 days after surgery. The most frequent causes for readmission were fever and compromised bowel function. The patient with pelvic abscess and stoma stenosis was one of the readmitted patients, and length of rehospitalization was 15 days. All other readmitted patients were discharged within one further week of hospitalization with no need for further surgery.

All patients started postoperative chemotherapy. The median time from surgery to administration of the first dose of systemic chemotherapy was 41 days (range 24–81 days).
Discussion

We introduced carboplatin HIPEC as supplement to CRS in patients with advanced-stage primary OC at our department in January 2016 and included twenty-five patients in our feasibility study. As patient safety was an important factor in the process of introducing a new procedure, we chose to use carboplatin in dose 800 mg/m². Addition of carboplatin HIPEC following CRS in this patient group was successful as measured by short-term outcome. Hence, no deaths and life-threatening adverse events were observed within 30 days. Furthermore, the patients’ postoperative recovery was as expected after an extensive cytoreductive procedure.\textsuperscript{19}

Huo and colleagues performed a systematic review including 451 OC patients treated with CRS and HIPEC in a primary setting.\textsuperscript{9} The pooled median 30-day mortality rate was 1.8\% (0–7.1\%), and the median pooled rate of major complications (grades 3 and 4) was 31.3\% (1.8–55.6 \%). Our grade 3 adverse event rate of 44.0\% might be considered high compared with what is reported by other centers, according to this review. Some of this may be explained by our meticulous systematic postoperative evaluation, as our patients underwent a daily clinical evaluation while hospitalized and at four weeks after surgery. In addition, blood samples evaluating sign of infection, hematological, hepatic, and renal toxicity were taken systematically up to four weeks after surgery. The true grade 3 and 4 adverse rates in our study were most likely even higher. Hence, development of grade 3 and grade 4 anemia was prevented by giving red blood cell transfusions postoperatively. Our patients received a median of two units of packed red blood cells (range 1-8) day 1-30 after surgery. It is, however, important to emphasize that no deaths or grade 4 adverse events were seen. Also, we identified no signs of hepatic and renal toxicity. We are convinced that our systematic clinical evaluation after surgery detected some complications at an early stage. Early diagnosis and timely treatment of identified grade 3 adverse events - in this case infections - may prevent deterioration to a more severe clinical condition, and thereby ensure faster recovery.

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Three patients had transient grade 3 neutropenia around day 14-21 after surgery, which could not be explained by systemic infections or other complications. Systemic uptake of carboplatin during HIPEC procedure is reported to be minimal in pharmacokinetic studies, and we do not consider chemotherapy induced myelosuppression as an isolated explanation for these delayed episodes of neutropenia. In pharmacokinetic studies evaluating carboplatin use in HIPEC, the dose-limiting hematologic toxicity is defined as grade 4 neutropenia. Most often, isolated transient grade 3 neutropenia is without clinical relevance, which our data supports. Neither of our patients with grade 3 neutropenia required supplemental treatment with e.g. Granulocyte Colony Stimulating Factor (GCSF) or had neutropenia related complications. They were monitored with blood samples according to the study protocol, and their levels of neutrophils normalized within 1-2 weeks.

One may argue that treatment with neoadjuvant chemotherapy prior to CRS would make patients more susceptible to postoperative infections after HIPEC due to suppressed bone marrow function. Still, this was not the case in our study. Surprisingly, we observed a higher frequency of grade 3 infections in the upfront CRS group (42.9%) than in the interval CRS group (9.1%). Similarly, we observed a higher readmission rate within 30 days in the upfront CRS group. These results may reflect the more extensive surgical procedures performed in the upfront CRS group than in the interval CRS group. This should, of course, be evaluated in larger studies.

Intestinal resection as part of CRS with HIPEC is associated with a higher rate of major morbidity, and not surprisingly a correlation between number of bowel anastomoses and major morbidity/anastomotic leakage has been described. The effect of HIPEC on the
anastomotic leak rate is still debated. There are plausible mechanisms which can explain diminished healing of the intestinal anastomosis after HIPEC such as bowel wall edema, increased inflammation, and higher risk of infection. However, no significant association between HIPEC and a higher anastomotic leak rate is found in clinical studies. Since anastomotic leakage is an extremely severe and often life-threatening adverse event, we decided to use a safe approach in case of rectosigmoid resection and made a colostomy instead of an anastomosis. This may contribute to the absence of grade 4 adverse events and deaths in our study. Study participants with good performance status and without any sign of early relapse (disease free survival>12 months) were candidates for stoma reversal.

When discharged, patients were instructed to contact the department by phone if they experienced fever, compromised bowel or bladder function, or any other major discomfort in general. One quarter of the patients were readmitted after a telephone contact with a nurse or a doctor. We believe that the high readmission rate reflects our cautioned approach after introducing CRS combined with HIPEC in the department. All readmitted patients were discharged within one week after readmission. Moreover, except for one readmitted patient, reoperation was not performed, which confirms that major interventions were unnecessary.

The median time from surgery to administration of first chemotherapy was 41 days, which is within the range reported by other centers after HIPEC (28–46 days). One strength of the present study is the fixed dose of carboplatin and the fixed solution volume during HIPEC perfusion. The prospective design and the systematic clinical postoperative evaluation are other important strengths. The most important limitation of
our study is the non-randomized, small-scale observational cohort study design, which prevents us from drawing solid conclusions.

Three ongoing randomized studies evaluating treatment of OC with CRS and carboplatin HIPEC are registered on ClinicalTrials.gov (Identifier: NCT02124421, NCT01767675 and NCT03188432). Our small-scale study supports that CRS and HIPEC with carboplatin used in treatment of advanced-stage primary OC is feasible with an acceptable rate of severe complications.

The effect of CRS and HIPEC in terms of progression-free and overall survival at different time points in OC treatment remains unclear. To date only two randomized controlled studies have evaluated this endpoint, with one evaluating HIPEC used for interval surgery and the other evaluating HIPEC for recurrent disease.²⁵,²⁶ Van Driel and colleagues randomized 245 patients to either interval CRS without HIPEC (n=123) or interval CRS with HIPEC (n=122).²⁵ Median progression-free survival and median overall survival was 10.7 months and 33.9 months in the surgery group without HIPEC and 14.2 months and 45.7 months in the surgery group with HIPEC, respectively. Grade 3/4 adverse event rates were similar in the two groups (25% in surgery group without HIPEC, and 27% in surgery group with HIPEC, p=0.76). However, cisplatin 100 mg/m² was used for HIPEC in contrast to carboplatin as in our study. Thus, further results from ongoing and upcoming randomized studies are needed, and most authors recommend using HIPEC only in clinical trials.²⁸,¹⁰,²⁷ Therefore, we posit that it is still reasonable to consider HIPEC as a promising yet experimental supplement to standard OC treatment.
References


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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Figures

**Figure 1** Flowchart for patient selection

OC, epithelial ovarian, tubal and primary peritoneal cancer; n, number of patients; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; ASA, American Society of Anaesthesiologists score; NAC, neoadjuvant chemotherapy; CC-0, completeness of cytoreduction score 0.
## Tables

**Table 1** Patient characteristics, n=25

<table>
<thead>
<tr>
<th></th>
<th>Upfront CRS n=14</th>
<th>Interval CRS n=11</th>
<th>Total n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>54</td>
<td>54 (39-73)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24</td>
<td>24</td>
<td>24 (19-35)</td>
</tr>
<tr>
<td>PCI</td>
<td>14</td>
<td>8</td>
<td>11 (5-32)</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ASA I</td>
<td>8</td>
<td>7</td>
<td>10 (40.0)</td>
</tr>
<tr>
<td>ASA II</td>
<td></td>
<td>15</td>
<td>(60.0)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fallopian tube</td>
<td>9</td>
<td>4</td>
<td>13 (52.0)</td>
</tr>
<tr>
<td>ovary</td>
<td>4</td>
<td>5</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>primary peritoneal</td>
<td>1</td>
<td>2</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Histology</td>
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<td></td>
<td></td>
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<tr>
<td>high grade serous</td>
<td>11</td>
<td>10</td>
<td>21 (84.0)</td>
</tr>
<tr>
<td>clear cell</td>
<td>2</td>
<td>1</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>carcinosarcoma</td>
<td>1</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGO IIa</td>
<td>1</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>FIGO III</td>
<td>6</td>
<td>4</td>
<td>10 (40.0)</td>
</tr>
</tbody>
</table>
N/n, number of patients; CRS, cytoreductive surgery; BMI, body mass index; PCI, peritoneal cancer index; ASA, American Society of Anaesthesiologists score; FIGO, International Federation of Gynecology and Obstetrics.

\(^a\): One patient initially assessed with FIGO stage III was diagnosed with FIGO stage II after the postoperative histopathological evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Upfront CRS</th>
<th></th>
<th>Interval CRS</th>
<th></th>
<th>Total</th>
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<td>n=25</td>
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<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
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<tr>
<td>Hysterectomy</td>
<td>13 (92.9)</td>
<td>11 (100.0)</td>
<td>24 (96.0)</td>
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<tr>
<td>Bilateral/unilateral salpingo-oophorectomy</td>
<td>14 (100.0)</td>
<td>9 (81.8)</td>
<td>23 (92.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater omentectomy</td>
<td>14 (100.0)</td>
<td>10 (90.9)</td>
<td>24 (96.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical pelvic lymphadenectomy</td>
<td>14 (100.0)</td>
<td>10 (90.9)</td>
<td>24 (96.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical para-aortic lymphadenectomy</td>
<td>14 (100.0)</td>
<td>10 (90.9)</td>
<td>24 (96.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonectomy upper abdomen/diaphragm(^a)</td>
<td>8 (57.1)</td>
<td>5 (45.5)</td>
<td>13 (52.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonectomy lower abdomen/pelvis</td>
<td>6 (42.9)</td>
<td>3 (27.3)</td>
<td>9 (36.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>En bloc pelvic resection with colostomy(^b)</td>
<td>7 (50.0)</td>
<td>2 (18.2)</td>
<td>9 (36.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel resection with anastomosis</td>
<td>1 (7.1)</td>
<td>1 (9.1)</td>
<td>2 (8.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmental colectomy with anastomosis</td>
<td>0</td>
<td>1 (9.1)</td>
<td>1 (4.0)</td>
<td></td>
<td></td>
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<tr>
<td>Splenectomy</td>
<td>3 (21.4)</td>
<td>0</td>
<td>3 (12.0)</td>
<td></td>
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</tr>
</tbody>
</table>
Duration of surgery (including HIPEC) (min) & 342 (285-539) & 321 (247-450) & 335 (247-539) \\
Intraoperative bleeding (ml) & 1000 (550-4500) & 1000 (400-3000) & 1000 (400-4500) \\
RBC transfusions intraoperative (units) & 1 (0-8) & 1 (0-5) & 1 (0-8) \\

N/n, number of patients; CRS, cytoreductive surgery; CC-0, completeness of cytoreduction score 0; HIPEC, hyperthermic intraperitoneal chemotherapy; RBC, red blood cell.

*a*: Peritonectomy upper abdomen/diaphragm: peritonectomy of the subhepatic space, and/or excision of the hepatic falciform ligament, and/or resection of liver capsule, and/or lesser sac peritonectomy, and/or peritoneal stripping from beneath the hemidiaphragm(s).

*b*: En bloc pelvic resection: removal of uterus, adnexae, pelvic peritoneum and rectosigmoid colon as one single excision.

**Table 3** Postoperative complications graded by Common Terminology Criteria for Adverse Events (CTCAE) and secondary outcomes within 30 days

<table>
<thead>
<tr>
<th></th>
<th>Upfront CRS n=14</th>
<th>Interval CRS n=11</th>
<th>Total n=25</th>
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<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>≥1 grade 3 adverse event</td>
<td>7 (50.0)</td>
<td>4 (36.4)</td>
<td>11 (44.0)</td>
</tr>
<tr>
<td>≥1 grade 4 adverse event</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Mortality (grade 5 adverse event)</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 infection (total number)</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>(28.0)</td>
</tr>
<tr>
<td>unknown origin (fever and increasing CRP)</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>(12.0)</td>
</tr>
<tr>
<td>peritonitis/abdominal abscess</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>(12.0)</td>
</tr>
<tr>
<td>pneumonia</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>(4.0)</td>
</tr>
<tr>
<td>Grade 3 hematologic (total number)</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>(12.0)</td>
</tr>
<tr>
<td>neutropenia (0.5x10^9/L &lt; neutrophil count &lt; 1.0x10^9/L)</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>(12.0)</td>
</tr>
<tr>
<td>anemia day 1-30 (hemoglobin &lt; 4.9 mmol/L)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>thrombocytopenia day 1-30 (25.0x10^9/L &lt; platelet count &lt; 50.0x10^9/L)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Grade 3 ileus</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>(8.0)</td>
</tr>
<tr>
<td>(severely altered GI function, TPN indicated &gt;1 week postoperatively)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 postoperative haemorrhage</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>(4.0)</td>
</tr>
<tr>
<td>(operative intervention indicated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reoperation</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>(8.0)</td>
</tr>
<tr>
<td>Readmission</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>(25.0)</td>
</tr>
<tr>
<td>Started postoperative systemic chemotherapy</td>
<td>14</td>
<td>11</td>
<td>25</td>
<td>(100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (range) Length of hospital stay (days)</th>
<th>14 (10-25)</th>
<th>13 (9-18)</th>
<th>14 (9-25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) Time from surgery to first chemotherapy administration (days)</td>
<td>43 (24-81)</td>
<td>38 (31-52)</td>
<td>41 (24-81)</td>
</tr>
</tbody>
</table>

N/n, number of patients; CRS, cytoreductive surgery; NA, not applicable; CRP, C-reactive protein; GI, gastrointestinal; TPN, total parenteral nutrition.