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Extreme cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: Outcomes from a single tertiary center☆

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ABSTRACT

Background: Multivisceral resection as part of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) may be required in order to achieve optimal debulking. This study aimed to assess perioperative and long-term outcomes of the most extensive CRS/HIPEC procedures.
Methods: All patients who underwent CRS/HIPEC at our institution between March 2007 and July 2014 were retrospectively reviewed. Patients undergoing extreme cytoreduction (n = 50), defined as a resection of ≥5 organs or ≥3 bowel anastomoses, were compared with patients who underwent less extensive procedures (n = 219).
Results: Complete cytoreduction (CC score ≤1) was achieved in 76% of the extreme CRS/HIPEC group, which included patients with colorectal cancer (CRC, n = 17), appendiceal adenocarcinoma (n = 20), gastric cancer (n = 6), and low-grade appendiceal neoplasm (n = 3). When compared with other patients undergoing CRS/HIPEC, the extreme CRS/HIPEC group had higher median PCI score, increased intra-operative blood loss, longer duration of surgery and longer hospital stay (all p values < 0.001). Major 30-day morbidity was significantly higher among the extreme CRS/HIPEC group (34% vs. 17.4%, p = 0.008) and there was also a trend towards higher 90-day mortality (12% vs. 5.1%, p = 0.07). Median disease free survival and overall survival in CRC patients undergoing extreme CRS/HIPEC was poorer (4.1 vs. 14.3 months, p = 0.01 and 10.1 vs. 43.8 months, p < 0.001, respectively). Extreme CRS/HIPEC was found to independently predict decreased overall survival in CRC patients.
Conclusions: Extreme multivisceral resection as part of CRS/HIPEC is associated with higher major morbidity and inferior oncologic outcomes; therefore CRS/HIPEC provides the best outcomes in patients with fewer organs involved.

1. Introduction

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is emerging as an effective locoregional treatment for peritoneal carcinomatosis (PC) and appears to offer a survival benefit in selected patients with colorectal cancer (CRC), appendiceal adenocarcinoma (AAC), low-grade appendiceal neoplasm and other types of cancer, as previously demonstrated by multiple phase II studies [1–6] and one prospective randomized controlled trial [7].

The primary therapeutic goal of CRS is complete tumor debulking, which has been recognized as one of the most important prognostic predictors following CRS/HIPEC in numerous studies [2,6,8,9], as well as in our institutional experience [10]. However, in order to achieve this, extensive and technically demanding CRS/HIPEC procedures may sometimes be required, occasionally necessitating resection of multiple visceral organs.

The association between the extent of CRS and postoperative morbidity has been demonstrated in multiple studies [5,11–14]. However, there is a paucity of published literature on the impact of multivisceral resection as part of CRS/HIPEC procedures on short- and long-term outcomes. In the few studies that have directly addressed this issue [15,16], multivisceral resection was not found

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to correlate with perioperative morbidity, mortality or oncologic outcomes.

We hypothesized that multi-organ resection as part of CRS/HIPEC may be associated with higher perioperative morbidity and mortality, as well as poorer long-term survival, since the resection of multiple organs may be a marker of higher carcinomatosis burden. Therefore, our study aimed to assess the short- and long-term outcomes of the most extensive CRS/HIPEC procedures performed at our tertiary center.

2. Materials and methods

Data were obtained from a prospectively collected database after receiving approval from the Institutional Review Board. All patients undergoing CRS/HIPEC with curative intent at our institution from March 2007 to July 2014 were retrospectively reviewed to identify patients who underwent extreme cytoreduction, defined as a resection of ≥5 major organs or creation of ≥3 bowel anastomoses. Major organs were considered as any of the following: small bowel, colon/rectum, spleen, pancreas, gallbladder, stomach, diaphragm (full thickness resection), liver (parenchymal resection ≥ one segment), uterus/ovaries and urinary bladder/ureter/kidney. Omentum, peritoneum, capsular liver resection and superficial diaphragmatic resection were excluded. Patients undergoing extreme CRS/HIPEC were compared with a reference group of patients who underwent less extensive procedures in terms of perioperative and long term results.

Our preoperative planning and operative technique have been previously described [10,17]. Briefly, diagnostic laparoscopy was performed routinely when feasible; when a complete cytoreduction was deemed possible, the procedure was converted to laparotomy and the abdominopelvic cavity was explored. The peritoneal cancer index (PCI) was recorded according to the Sugarbaker classification [18]. Cytoreduction was then performed, which consisted of resection of the primary tumor (if not previously resected), omentectomy, resection of involved intra-abdominal organs and stripping of involved parietal peritoneum surfaces.

Following cytoreduction, the completeness of cytoreduction (CC) score was recorded according to the Sugarbaker classification [18]; complete cytoreduction was defined as CC score ≤ 1. HIPEC was then delivered via the closed abdomen technique, using Mitomycin C as the most common chemotherapeutic agent (88%). Following the administration of HIPEC, gastrointestinal anastomoses were created.

Major morbidity was defined as Clavien-Dindo classification III–V [19]. In-hospital mortality was defined as death occurring during the same hospitalization in which CRS/HIPEC was performed. Data were analyzed with SPSS version 22 (Chicago, IL). Categorical variables, expressed as percentages, were compared by the χ^2 test or Fisher's exact test. Continuous variables, expressed as mean ± standard deviation, were compared by the Student *t*-test and Mann–Whitney test. Overall survival (OS) and disease free survival (DFS) analyses, measured from the date of CRS/HIPEC, were calculated using the Kaplan–Meier method and were restricted to patients with CRC or AAC, the two most common diagnoses among our cohort; subgroups were compared with the log-rank test. Incomplete cytoreduction (CC score > 1) was considered as immediate disease recurrence. In order to identify independent risk factors for major morbidity, all variables found to correlate with major morbidity in univariate analysis were entered into a multivariate logistic regression model; the least significant variables were removed from the model in a stepwise fashion. A Cox regression model to identify predictors of survival, restricted to only CRC patients, was executed by entering all clinical and procedural variables into the model. A *p* value of less than 0.05 was defined as significant.

3. Results

Between March 2007 and July 2014, a total of 257 patients underwent 269 CRS/HIPEC procedures. The extreme CRS/HIPEC group consisted of 50 patients who underwent 50 CRS/HIPEC procedures and was composed of patients with CRC (n = 17), AAC (n = 20), gastric cancer (n = 6), low-grade appendiceal neoplasm (n = 3), ovarian cancer (n = 2), small bowel adenocarcinoma (n = 1) and cholangiocarcinoma (n = 1). 41 patients (82%) in the extreme group had undergone resection of ≥5 major organs (5 organs: n = 26; 6 organs: n = 9; 7 organs: n = 6), whereas 9 patients (18%) had undergone resection of <5 major organs but underwent ≥3 bowel anastomoses.

The reference group consisted of 207 patients who underwent 219 CRS/HIPEC procedures. Preoperative and intra-operative characteristics of both groups are presented in Table 1. Most preoperative variables did not differ significantly between the groups. However, previous abdominal surgery was significantly less prevalent among the extreme group (50% vs. 78.1%, p < 0.001). Regarding intraoperative variables, the extreme group had higher median PCI score (21 vs. 10), increased intraoperative blood loss and longer duration of surgery (all p values < 0.001). The median number of major organs resected and gastrointestinal anastomoses created in the reference group was significantly lower as expected, due to the design of this study. Complete cytoreduction was achieved in 76% of the extreme group and 85.8% of the reference group (p = 0.09).

The prevalence of different surgical procedures performed as part of cytoreduction is presented in Fig. 1. The most common organs resected in the extreme group were the colon/rectum (84%), spleen (66%) and small bowel (56%). Gastrointestinal anastomoses were created in 90% of the extreme group and 44.3% of the reference group. Again, by virtue of the study methodology, the prevalence rates of all surgical procedures were significantly higher among the extreme group (all p values ≤ 0.001), except for the rate of liver resection which was not significantly different (10% vs. 8.7%, p = 0.77).

Postoperative outcomes are presented in Table 1. The median length of hospital stay and ICU stay were significantly higher in the extreme group. The most common postoperative complications among the extreme group were wound complications (20%, ranging from simple cellulitis to necrotizing fasciitis or wound dehiscence), intra-abdominal abscess/gastrointestinal leak (20%), paralytic ileus (12%), transient neutropenia (12%) and respiratory failure (12%). The extreme group had significantly higher incidence of overall (74% vs. 47%, p = 0.001) and major (34% vs. 17.4%, p = 0.008) 30-day morbidity when compared with the reference group. The incidence rates of wound complications (20% vs. 7.8%, p = 0.009) and intra-abdominal abscess/leak (20% vs. 8.2%, p = 0.014) were significantly higher among the extreme group; other specific postoperative complications did not differ significantly between groups. There was a trend, which did not reach statistical significance, towards higher in-hospital mortality (6% vs. 1.8%, p = 0.094) and 90-day mortality (12% vs. 5.1%, p = 0.07) in the extreme group. There was no significant difference between groups in the rate of 90-day re-operation.

In addition to extreme CRS/HIPEC, the following risk factors were found to correlate with major 30-day morbidity on univariate analysis: PCI (p = 0.004), number of major organs resected (p < 0.001), number of blood transfusions given (p < 0.001), duration of surgery (p < 0.001), ASA score (p = 0.03) and creation of gastrointestinal anastomoses (p = 0.003). On multivariate logistic regression analysis only the number of blood transfusions given (p < 0.001) and creation of anastomosis (p = 0.014) were independent predictors of major morbidity.