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Review

Outcomes for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the elderly

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ABSTRACT

Background: Cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) has gained acceptance in the treatment of peritoneal carcinomatosis (PC) with reported morbidity and mortality rates of 27–56% and 0–11% respectively. The safety and outcome of such major operation in the elderly remains unclear. We report our experience at a high volume tertiary center.

Method: A total of 170 consecutive patients underwent CRS-HIPEC for peritoneal carcinomatosis between March 2007 and July 2012. Mitomycin C (88.8%) was administered intraperitoneally at 42 °C for 90 min. Patients were categorized into two groups according to the age at the time of surgery: Group 1 (≤65 years-old) and Group 2 (>65 years-old). Differences between the groups were analyzed. Univariate and multivariate analyses were performed to identify variables associated with major morbidity.

Results: Of the 170 patients, 35 were older than 65 years. The two most common tumor sites were colorectal and appendiceal cancer. The perioperative morbidity and mortality rates in the elderly were 18.8% and 8.6% respectively. Gender, tumor type, estimated blood loss >400 mL, intraoperative blood transfusion, operative time >6 h, bowel anastomosis, intraoperative PCI >16, and extent of cytoreduction (Δ PCI) were not associated with major morbidity in the older group ($p > 0.05$). At a median follow-up of 15.7 months (0.2–53.5 months), recurrence rate for colorectal/appendiceal PC at 1 year was 48.0% in Group 1 and 44.3% in Group 2 (p = NS). Median survival for the colorectal/appendiceal carcinomatosis patients in Group 1 ($n = 81$) was 29.79 (SE 4.7) months and in Group 2 ($n = 20$) was 21.2 (SE 3.0) months, ($p = 0.06$, NS).

Conclusion: CRS-HIPEC procedures for peritoneal carcinomatosis in the elderly demonstrate comparable perioperative outcome in well-selected patients. Optimal cytoreduction was achieved in the majority of cases and survival was not significantly different from that of the younger group.

Contents

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Introduction

Cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) has gained acceptance in the treatment of select cases of peritoneal carcinomatosis (PC) [1–3]. For PC of colorectal cancer origin specifically, this treatment has been shown to be efficacious in multiple Phase II studies [4,5]. Further, it has been proven superior to systemic chemotherapy alone with regards to overall survival in one randomized controlled trial [3]. The procedure, however, is labor intensive, technically demanding, and rife with potential complications. The majority of authors report morbidity and mortality rates of 27–56% and 0–11% respectively [6–12] (Table 1).

As the median age of patients increases, the benefit of such an aggressive approach in the elderly remains unclear. There is a paucity of literature on the effect of age on the outcome of CRS and HIPEC in the treatment of PC.

Presented in this study are results from a tertiary medical center in the United States performing a high volume of CRS and HIPEC for PC. The specific aim of this analysis was to investigate the outcomes of this approach in patients >65 years of age. These results will help better understand the safety and feasibility of this treatment modality in the elderly population.

Methods

Study design

The records of all patients receiving CRS and HIPEC for PC from a multitude of primary tumor sites between March 2007 and July 2012 were reviewed. The procedures were performed at a single tertiary center by two different surgical oncologists. Data for this analysis were retrieved from a prospectively maintained database. The analysis focused on the subgroup of patients >65 years of age, and had as its endpoints length of stay, perioperative major morbidity and 90-day mortality. Institutional review board (IRB) approval was obtained for this study.

Co-morbidities

Diabetes mellitus was defined as a fasting blood glucose ≥120 mg/dl on two occasions or current treatment with insulin or oral hypoglycemic agent(s). Hypertension (HTN) was defined as a resting blood pressure of ≥140/90 mmHg on two separate occasions or current treatment with anti-hypertensive medication(s). Cardiovascular disease comprised any previous coronary artery stenosis/occlusion treated with angiographic or surgical revascularization, current treatment with one or more antiarrhythmic agent(s), and/or a diagnosis of atrial fibrillation. Chronic renal insufficiency was defined by a serum creatinine ≥1.5 times the upper limit of normal, or a calculated creatinine clearance <30 mL/min.

Table 1
Existing series on CRS/HIPEC for peritoneal carcinomatosis.

Author	Year	Number (*n*)	Age (mean)	Morbidity %	Mortality %
Sugarbaker [6]	1999	155	–	27	2
Sugarbaker [7]	2006	356	Median 58	19	2
Smeenk [8]	2007	323	Median 57	49.5	5.8
Levine [9]	2007	460	53 ± 12	43	4.8
Gusani [10]	2008	122	Median 53	29.8	1.6
Saxena [11]	2009	145	53 ± 11	38	5
Elias [12]	2010	523	53 ± 12	31	3.3

Diagnosis and treatment

Patients were most often referred to our institution after a diagnosis of PC had been established at an outside hospital. After initial evaluation at our institution, a contrast-enhanced cross-sectional imaging study (CT scan or MRI) of the chest, abdomen, and pelvis was obtained as a means of quantifying peritoneal disease burden and ruling out extra-abdominal spread. Unresectable visceral hepatic metastases or thoracic metastases were contraindications to CRS and HIPEC. If tissue had been obtained for diagnosis at the outside hospital, repeat pathological analysis was performed. All patients were evaluated by a multidisciplinary team. Treatment was then customized according to pathologic features, response to chemotherapy, tumor burden on imaging study and intraoperatively by laparoscopy, disease amenable to potential complete cytoreduction and patient's condition.

Although advanced chronological age did not preclude surgical consideration, an ECOG performance status of 0–2 was required. All patients ≥50 years of age, and select patients <50, received a pre-operative cardiology evaluation. A significant impairment in cardiac, pulmonary, hepatic, or renal function was a contraindication to surgery.

Patients with PC from colorectal cancer were initially treated with oxaliplatin- or irinotecan-based systemic chemotherapy, and a progression-free interval of at least 3 months was preferred before a recommendation of CRS and HIPEC was made. A more selective approach was applied to gastric origin PC, for which a sustained radiologic response (6 months or more) on systemic chemotherapy was generally required.

Surgery commenced with a diagnostic laparoscopy to assess the feasibility of thorough cytoreduction. If the disease burden was limited, a midline laparotomy was made and the patient was explored. The peritoneal cancer index was recorded (Fig. 1) [13]. If not previously performed, the primary tumor was resected. A greater omentectomy was usually performed, followed by tumor debulking as dictated by the distribution of disease. This included resection of all intra-abdominal organ(s) grossly involved by visceral peritoneal spread, and stripping of all parietal peritoneal surfaces affected, including those of the subdiapragmatic spaces, the paracolic recesses, and the anterior abdominal wall. The completeness of cytoreduction was then recorded using the Jacquet/Sugarbaker Classification System: CCR-0, no residual macroscopic disease; CCR-1, residual peritoneal deposits <2.5 mm; CCR-2, residual deposits between 2.5 mm and 2.5 cm; CCR-3, residual deposits >2.5 cm or confluent tumors. The aim was a complete cytoreduction, defined as eradication of all peritoneal nodules ≥2.5 mm in diameter (CCR 0–1) [13,14].

Following cytoreduction, HIPEC was performed as previously described. The closed abdomen technique was used in all cases. Mitomycin C was the most common agent used in our series and was administered over two doses for a 90-min perfusion period with a target intraperitoneal temperature of 41–43 °C. A 40 mg dose was used and split between 30 mg for the first 60 min and