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Trends in Outcomes After Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) have been shown to improve clinical outcomes among select patients presenting with peritoneal carcinomatosis. The aim of the present study was to describe temporal trends in clinical outcomes among patients undergoing CRS/HIPEC.

Materials and methods: Patients who underwent CRS/HIPEC were identified using the American College of Surgeons National Surgical Quality Improvement Program databases from 2005 to 2013. A multivariable logistic regression analysis was performed to identify risk factors associated with postoperative morbidity and mortality.

Results: A total of 889 patients were identified who met the inclusion criteria. The most common primary tumor sites were the peritoneum (59.8%), followed by the appendix (13.7%) and colon (6.4%). The median operative time for all patients was 438 min (interquartile range: 328-550); postoperative morbidity was 41.3%, and 2.0% of patients died within 30 d of surgery. Over the time evaluated, a statistically significant decrease was observed in the median operative time (2005 *versus* 2013, 600 *versus* 403 min), postoperative morbidity (50.0% *versus* 36.1%), and length of stay (13.5 *versus* 8 d; all $P < 0.05$). On multivariable analysis, age > 65 y (odds ratio [OR] = 1.51; 95% confidence interval [CI]: 1.02-2.24; $P = 0.037$), a low preoperative hematocrit (OR = 1.66; 95% CI: 1.19-2.33; $P = 0.003$), and preoperative serum albumin < 3 g/dL (OR = 2.10; 95% CI: 1.13-3.90; $P = 0.019$) were independently associated with greater odds for developing a postoperative complication and/or postoperative death.

Conclusions: Operative time, postoperative morbidity, and length of stay after CRS/HIPEC were observed to improve over the study period. Careful patient selection may result in favorable outcomes for select patients undergoing CRS/HIPEC.

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Introduction

Peritoneal carcinomatosis (PC) refers to the extensive dissemination of cancer on the surface of the abdominal cavity secondary to tumors arising from the peritoneal surface or from dissemination of tumor arising within gastrointestinal and gynecological organs.[1-3] Traditionally, PC was considered a terminal diagnosis and was treated with palliative intent by systemic chemotherapy.[2,4-6] In recent years, however, cytoreductive surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has been considered as a potential curative option among patients presenting with disease limited to the peritoneal cavity.[7-9] Large retrospective analyses as well as a limited number of phase 2 and 3 clinical trials have demonstrated an improved survival after CRS/HIPEC among a select group of patients resulting in a dramatic increase in the number of hospitals performing CRS/HIPEC in the past 2 decades.[7,8,10,11]

Although associated with improved outcomes for select patients, there is still disagreement regarding the widespread use of CRS/HIPEC given the history of postoperative morbidity and mortality associated with this procedure. Current estimates for postoperative morbidity and mortality after CRS/HIPEC range from 12% to 52% and 0.9% to 17%, respectively.[12-16] Although a limited number of single-center studies have reported improved clinical outcomes over time, it is unknown whether best practices at experienced, high-volume centers have translated to improved surgical outcomes at other institutions.[17,18] Understanding national trends is important to identifying risk factors for poor postoperative outcomes and therefore areas that can be targeted for future quality-improvement and patient-safety initiatives. Given this, using a large clinical database, the present study sought to evaluate the trends in 30-d postoperative clinical outcomes among patients undergoing CRS/HIPEC between 2005 and 2013. In addition, we sought to identify risk factors associated with adverse postoperative outcomes for patients undergoing CRS/HIPEC.

Materials and methods

Data sources and patient population

Patients who underwent CRS/HIPEC between 2005 and 2013 were identified using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). The use of intraperitoneal chemotherapy was defined using the Current Procedure Terminology (CPT) codes "77,605," "96,445," and "96,446."[15] Only patients presenting with a concomitant CPT code for a major abdominal surgery were included to ensure that only patients who underwent a CRS and received HIPEC were included in our study population. The primary site of cancer was then categorized using the International Classification of Disease, ninth Revision, Clinical Manifestation (ICD-9-CM) diagnosis codes as either colon, rectum, appendix, peritoneal, ovarian, and unspecified/other (Supplemental Table 1). For each patient, preoperative serum albumin was classified as either normal (≥3 g/dL) or low (<3 g/dL). Similarly, using sex-specific cutoffs, preoperative serum hematocrit was categorized as either normal (men: ≥38.8%, women: ≥34.9%) or low (men: <38.8%, women: <34.9%). Patients who were transferred to or from another health-care facility and patients who underwent a "nonelective" surgery were excluded from the final analysis.

Postoperative clinical outcomes

The primary outcomes of the study were 30-d postoperative morbidity and 30-d postoperative mortality. Postoperative morbidity was defined using a composite measure for postoperative complications including surgical site infection, wound dehiscence, pneumonia, prolonged ventilator use or reintubation, venous thromboembolism (deep venous thrombosis and pulmonary embolism), acute renal failure, postoperative myocardial infarction, and stroke. Other outcomes of interest included operative time, length of stay (LOS) and 30-d unplanned readmissions. Using a previously defined methodology, LOS was analyzed as a continuous as well as a binary outcome with patients demonstrating an LOS greater than the 75th percentile being categorized as demonstrating an "extended" LOS (eLOS).[19]

Comparison of temporal trends

To investigate temporal trends in postoperative outcomes for patients undergoing CRS/HIPEC, a cohort of patients undergoing an elective, pancreaticoduodenectomy for pancreatic adenocarcinoma between 2005 and 2013 was identified using relevant CPT and ICD-9-CM diagnosis codes, as previously described. For this population, postoperative outcomes including operative time, LOS, eLOS, 30-d unplanned readmission, 30-d postoperative morbidity, and 30-d postoperative mortality were examined over time.

Statistical analysis

Pearson's chi-squared test was used to compare categorical data, whereas Student's *t*-test or the Kruskal–Wallis test was used to compare continuous data, as appropriate. Multivariable logistic regression analysis was used to identify independent risk factors for 30-d morbidity and 30-d mortality. All patient and disease characteristics were included within the multivariable model, with the final selection of variables guided by statistical significance on univariable comparisons and clinical relevance. A *P* value of <0.05 was used to define statistical significance. All analyses were performed using STATA 14.0 statistical software (StataCorp, College Station, TX). As data contained within the ACS-NSQIP database are deidentified, patient consent was waived, and the study was approved by the Johns Hopkins University Institutional Review Board.

Results

Baseline patient characteristics

A total of 889 patients were identified who met inclusion criteria. Over time, the annual number of CRS/HIPEC