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Failure to rescue following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) can significantly improve the survival in selected patients with peritoneal carcinomatosis. This study aims to identify perioperative patient characteristics predictive of failure to rescue (FTR), mortality following postoperative complications from CRS/HIPEC. **Methods:** Patients suffering a complication following CRS/HIPEC between 2005 and 2013 were identified in the American College of Surgeons National Surgical Quality Improvement Program data set. FTR was defined as 30-d mortality in the setting of a complication. Patients who suffered FTR were compared against those who survived a complication (non-FTR). Predictors of FTR were identified using a multivariable logistic regression model. **Results:** A total of 915 eligible CRS/HIPEC cases were identified. In all, 382 patients (42%) developed ≥ 1 postoperative complication, and 88 patients (10%) suffered ≥ 1 major complication. Seventeen patients died following a complication, amounting to an FTR rate of 4%. FTR patients were more likely than non-FTR patients to have dependent functional status (18% versus 2%, $P = 0.01$), have American Society of Anesthesiologists (ASA) class 4 status (29% versus 8%, $P = 0.01$), develop ≥ 3 complications (65% versus 24%, $P < 0.01$), and suffer a major complication (94% versus 20%, $P < 0.01$). The following were independently associated with FTR: ASA class 4 (odds ratio [OR]: 13.4, 95% confidence interval [CI], 1.2-146.8) and major complications (OR: 66.0, 95% CI, 8.4-516.6).

Conclusions: ASA class 4, major morbidity, and likely dependent functional status are independent predictors of FTR following CRS/HIPEC to treat peritoneal carcinomatosis. Therefore, ASA class 4 and dependent functional status should be considered as contraindications for CRS/HIPEC and only offered in highly selective cases.

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Introduction

Peritoneal carcinomatosis (PC) is a malignant disease of the peritoneum that is primarily of peritoneal origin or secondary to abdominal metastatic spread. Although patients with

extraperitoneal metastases (i.e., liver and lung) undergoing curative intent surgeries now have acceptable survival rates, PC has been historically considered an incurable entity with variable survival rates and prognoses depending on the primary site of cancer.^{1,2} For instance, PC secondary to colorectal

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cancer portends a poor prognosis with a survival of months,³ whereas the survival for pseudomyxoma peritonei from appendiceal neoplasms could reach a few years. Patients with peritoneal malignancies often develop ascites, bowel obstruction, malnutrition, failure to thrive, and ultimately death.

With the advent of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), selected patients with PC have benefited from improved survival, better symptom control, and an improved quality of life.⁴⁻⁹ CRS/HIPEC is an aggressive surgical treatment that involves the complete resection or cytoreduction of visible tumors within the peritoneal cavity followed by a perfusion of the peritoneum with a heated chemotherapy solution. Thus, CRS/HIPEC is associated with morbidity and short-term mortality rates comparable to other major abdominal surgeries.¹⁰ In single-institution retrospective studies, morbidity and mortality rates range from 0%-52% and 0%-17%, respectively.^{11,12} A French retrospective multi-institutional study found morbidity and mortality rates of 33.6% and 4.1%.¹³ Similarly, recent reports of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database reported morbidity and mortality rates of 31%-33% and 2.3%, respectively.^{10,14}

Patients who sustain a complication following major abdominal surgery are at an increased risk for mortality. Given that approximately one-third of patients suffer a complication after undergoing CRS/HIPEC, it is important to distinguish factors related to mortality following morbidity. Failure to rescue (FTR), defined as death following a complication from surgery, has been proposed as an important metric to assess hospital-level variation in postoperative mortality.¹⁵⁻¹⁷ Although FTR is a useful metric for hospital quality, it is apparent that patient factors can influence the risk of FTR.^{18,19} Therefore, it is important to identify patient risk factors that could lead to FTR to improve patient selection criteria for this procedure. Using a national cohort of patients, this study aims to define the perioperative and patient risk factors that are associated with an increased risk of FTR following CRS/HIPEC.

Methods

Database and study population

Records of surgeries conducted between 2005 and 2013 were retrospectively abstracted from the ACS NSQIP data set using American Medical Association current procedure terminology codes. As previously reported in a study utilizing the NSQIP data set, cases including HIPEC were found using current procedure terminology codes 77605, 96445, and 96,446.¹⁰ Cases including hyperthermic intrathoracic chemotherapy for pulmonary cancers were excluded. Patients who suffered a complication within 30 d of undergoing CRS/HIPEC were identified. To capture the largest proportion of mortalities and maximize reliability and validity, any complication following surgery was included in the final data analysis.¹⁶

The NSQIP database provided preoperative characteristics including demographics, histories of comorbidities, American Society of Anesthesiologists (ASA) class, functional status, and laboratory values. The Charlson comorbidity index was

calculated using available data as previously reported.²⁰ Intraoperative and postoperative data include procedure type, complications, and mortality.

Definitions

Patients were grouped into FTR and non-FTR cohorts. FTR was defined as death following a complication from surgery.¹⁵ We included both major and minor complications following surgery in analyzing FTR rates in this study to improve the reliability and validity of our findings.¹⁶ Major complications were defined as those corresponding to Clavien-Dindo grades III and IV.²¹ Because NSQIP does not report complications according to the Clavien-Dindo classification scheme, we considered the following complications documented by NSQIP as Clavien-Dindo grades III and IV: reintubation, ventilator use for longer than 48 h, acute renal failure requiring dialysis, cardiac arrest, myocardial infarction, septic shock, and reoperation. Minor complications were defined as those that did not correspond to Clavien-Dindo grades III and IV. These included superficial surgical site infection (SSI), deep SSI, organ space SSI, postoperative pneumonia, dehiscence, urinary tract infection (UTI), sepsis, pulmonary embolism, deep vein thrombosis, and bleeding.

Statistical methods

Patient information, including demographics and comorbid diseases as well as other baseline information, preoperative clinical data, operative details, and postoperative complications were compared between FTR and non-FTR groups using Fisher's exact test and the Wilcoxon rank-sum test for categorical and continuous variables, respectively. A multivariable logistic regression model was used to explore for predictors of FTR. Clinically relevant variables, as well as variables with a *P* value < 0.15 on univariate analysis, were evaluated in the model. Congestive heart failure and chronic kidney disease were not included in the model as there were few cases of them. The model was selected using a forward stepwise method. All statistical tests were two-sided, and the significance level was 0.05. All statistical analyses were performed using STATA, version 14.0, (StataCorp, College Station, TX).

Results

Patients characteristics

From the NSQIP database, there were 931 patients who underwent HIPEC between 2005 and 2013 (Fig. 1). After excluding patients undergoing hyperthermic intrathoracic chemotherapy along with HIPEC for pulmonary cancer, there were 915 eligible CRS/HIPEC cases. Following CRS/HIPEC, 382 patients (42%) experienced at least one complication; those constituted the study population. Fifteen patients (4%) who suffered a complication underwent HIPEC only. Seventeen patients (5%) suffered FTR following CRS/HIPEC.

In the overall cohort of patients suffering a complication, the age distribution was as follows: 18-49 y, 104 (27%); 50-69 y, 234 (61%); ≥70 y, 44 (12%). (Table 1). When divided between

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