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Authors

Jafari, Mehraneh D
Halabi, Wissam J
Stamos, Michael J
et al.

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Surgical Outcomes of Hyperthermic Intraperitoneal Chemotherapy Analysis of the American College of Surgeons National Surgical Quality Improvement Program

Mehraneh D. Jafari, MD; Wissam J. Halabi, MD; Michael J. Stamos, MD; Vinh Q. Nguyen, PhD; Joseph C. Carmichael, MD; Steven D. Mills, MD; Alessio Pigazzi, MD, PhD

IMPORTANCE Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery have been shown to benefit selected patients with peritoneal carcinomatosis. However, these procedures are associated with high morbidity and mortality. Available data investigating the outcomes of HIPEC are mostly limited to single-center studies. To date, there have been few large-scale studies investigating the postoperative outcomes of HIPEC.

OBJECTIVE To determine the associated 30-day morbidity and mortality of cytoreductive surgery–HIPEC in the treatment of metastatic and primary peritoneal cancer in American College of Surgeons National Surgical Quality Improvement Program centers.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review of HIPEC cases performed for primary and metastatic peritoneal cancer diagnoses was conducted. The cytoreductive surgical procedures were sampled, and disease processes were identified. Patient demographics, intraoperative occurrences, and postoperative complications were reviewed from the American College of Surgeons National Surgical Quality Improvement Program from 2005-2011.

MAIN OUTCOMES AND MEASURES Thirty-day mortality and morbidity.

RESULTS Of the cancers identified among the 694 sampled cases, 14%of patients had appendiceal cancer, 11% had primary peritoneal cancer, and 8%had colorectal cancer. The American Society of Anesthesiologists classification was 3 for 70%of patients. The average operative time was 7.6 hours, with 15%of patients requiring intraoperative transfusions. Postoperative bleeding (17%), septic shock (16%), pulmonary complications (15%), and organ-space infections (9%) were the most prevalent postoperative complications. The average length of stay was 13 days, with a 30-day readmission rate of 11%. The rate of reoperation was 10%, with an overall mortality rate of 2%.

CONCLUSIONS AND RELEVANCE American College of Surgeons National Surgical Quality Improvement Program hospitals performing HIPEC have acceptable rates of morbidity and mortality.

Peritoneal carcinomatosis (PC) is defined as tumor dissemination inside the abdominal cavity secondary to tumors arising from the peritoneal surface or from visceral organs. Dissemination is a result of uncontrolled proliferation of the primary tumor, which allows the tumor cells to exfoliate and circulate within the peritoneal fluid, allowing for an exponential progression of disease given the lack of growth inhibition in the newly implanted peritoneal metastases. Tumor cell implantation on other visceral organs and bowel, mesentery, and peritoneal surfaces ultimately leads to malnutrition, bowel obstruction, and death.[1,2]

Peritoneal carcinomatosis from gastrointestinal cancers has traditionally been viewed as not amenable to surgical treatment. It has been considered the terminal stage of disease, and median survival has been reported as 6 to 12 months with systemic chemotherapy.[3-6] In fact, palliative systemic chemotherapy has shown good tumor response but without improvement insurvival.[7] Surgical options for the treatment of PC were popularized in the 1990s by Sugarbaker,8 who advocated the use of cytoreductive surgery (CRS), including peritonectomy, in combination with hyperthermic intraperitoneal chemotherapy (HIPEC), to treat peritoneal surface neoplasms. Cytoreductive surgery–HIPEC has been shown to increase survival in selected patients with colorectal, appendiceal, and primary peritoneal cancers[5,9-12] in phase 2 and 3 trials.[12-14]

Cytoreductive surgery, in combination with perioperative HIPEC, is an aggressive form of locoregional therapy.[15] Cytoreduction involves leaving no or only minimal residual tumor volume within the abdomen. Following surgery, HIPEC is used to bathe the peritoneal cavity with a heated solution containing high chemotherapeutic drug concentrations. The pharmacokinetic advantages of the intraperitoneal route of chemotherapy permit increased drug concentrations and locally dosed intensive therapy, in addition to its synergistic effects with hyperthermia.[7,12] Hyperthermia exerts its own cytotoxicity against malignant cells and facilitates greater tissue penetration of antineoplastic agents.[16,17] For these reasons, HIPEC, in combination with CRS, is believed to achieve macroscopic and microscopic disease clearance and hence possibly improve survival.[7,12]

Despite the promise of improved survival in patients with PC, HIPEC is associated with significant morbidity and mortality. Although there exists a growing body of literature regarding survival benefits, to our knowledge, specific morbidity and mortality data are only reported in a few publications. In this study, we present a review of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) cases of CRS-HIPEC, and their associated morbidity and mortality in the treatment of metastatic and primary peritoneal cancer.

Methods

The ACS NSQIP is the first nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care. The program provides more than 500 participating hospitalswith data on preoperative risk factors, intraoperative Intraoperative variables, and 30-day postoperative mortality and morbidity for patients undergoing major surgical procedures in both the inpatient and outpatient settings. Each participating hospital has a dedicated surgical clinical nurse reviewer who captures these

data using a variety of methods including medical record abstraction. Full description of the ACS NSQIP is available on the NSQIP website.18 Approval for the use of the ACS NSQIP database for this study was obtained from the institutional review board of the University of California, Irvine, and the ACS NSQIP. Patient data were deidentified; therefore, exempt institutional review board approval was granted.

Case Selection

The ACS NSQIP was retrospectively reviewed for all cases of HIPEC between January 1, 2005, and December 31, 2011, using the appropriate American Medical Association Current Procedure Terminology codes. We analyzed the available data on all patients who underwent HIPEC with concurrent cytoreductive cases. The ACS NSQIP only provides data on procedures occurring under the same anesthesia. Therefore, all cases reviewed underwent HIPEC concurrently with an associated cytoreductive procedure. To ensure that we captured concurrent cases, patients were selected only if they had undergone HIPEC and another specified procedural code. Patients who underwent HIPEC (codes 77605, 96445, and 96446) were selected. The number of patients who underwent tumor debulking (codes 49203 and 49204), colectomy (codes 44204, 44210, and 45216), pelvic exenteration (code 45126), peritonectomy (code 39560), splenectomy (code 38100), gastrectomy (codes 43611, 43620, 43621, 43631, and 43633), omentectomy (code 49255), small-bowel resection (codes 44120 and 44121), and small-bowel biopsy (code 44110) were analyzed. The appropriate diagnostic code as specified by the International Classification of Diseases, Ninth Revision, Clinical Modification was used to select the percentage of patients with rectal cancer (codes 154.0, 154.1, 154.8, 197.5, 209.17, and 230.4), colon cancer (codes 153.0, 153.1, 153.2, 153.3, 153.4, 153.6, 153.7, 153.8, and 153.9), and appendiceal cancer (code 153.5). Pathologies were selected based on recent literature validating the use of HIPEC and CRS.[7,12]

Variables

The variables used were provided by the NSQIP database and included patient demographics (age and sex), American Society of Anesthesiologists (ASA) class, functional status, and comorbid conditions. Body mass index was calculated based on the available data points of weight and height. The operative variables available included intraoperative transfusion, wound classification, operative time, anesthesia time, and intraoperative occurrences. Intraoperative occurrences included cardiac arrest, myocardial infarction, and unplanned intubation. Variables with a high percentage of missing data were excluded from the analysis.

Outcomes

The primary aim of our study was to provide the latest description of outcomes of patients undergoing HIPEC. Our primary end points were overall 30-day morbidity and mortality. We also reported the outcomes with respect to length of stay and postoperative complications, which included cerebrovascular accidents, myocardial infarction, pneumonia, superficial surgical site infections, deep surgical site infections, organ/space

surgical site infections, wound disruption, urinary tract infections, progressive renal insufficiency, acute renal failure, deep venous thrombosis, sepsis, septic shock, return to the operating room within 30 days of the index operation, and readmission rates. Progressive renal insufficiency was defined in the ACS NSQIP as an increase in creatinine of more than 2mg/dL from preoperative value. Acute renal failure was defined as patients who require dialysis postoperatively and did not do so prior to admission. Readmission rates are available in the 2011 data set only and capture readmission to a surgical service within 30 days of the index operation.

Statistical Analysis

Data extraction and statistical analyses were performed using SAS version 9.3 and the R Statistical Environment. Predictive models for respiratory complications, septic shock, and return to the operating room were built based on Lasso algorithm.19 Predictive and protective variables were selected from the training data set and 10-fold cross-validation along with the 1-SE rule were used on the validation set to select for model size and control for over fitting. Receiver operating characteristic curve with area under the curve statistic was used on the validation set.

Results

Demographics

A total of 694cases of patients who under went HIPEC with CRS were sampled. Pathological type was identified in 226 patients (32.6%). Of the pathologies sampled, appendiceal cancer was noted in 43% of patients, primary peritoneal cancer in 32%, and colorectal cancer in 24%.Themeanpatient age was 55 years, and females comprised 54% of patients. Most patients were ASA class 3 (70%) and ASA class 2 (24%).Most patients had independent functional status (49%);however,50% of caseswere missing this variable (Table 1).Cytoreductive surgery was identified in82% of patients,with omentectomy and small-bowel resections coded as the most often concomitant procedures (Table 2). Patient comorbidities are listed in Table 3.

Table 1. Demographics of Patients Who Underwent HIPEC-CRS at ACS NSQIP Hospitals During 2005-2011

Demographic	No. (%)
Age, mean (SD), y	55 (10)
Sex	
Female	377 (54.3)
Male	316 (45.5)
ASA class	
1-No disturbances	2 (0.3)
2-Mild disturbances	166 (23.9)
3-Severe disturbances	483 (69.6)
4-Life threatening	43 (6.2)
BMI	
≤18	12 (1.7)
19-25	234 (33.7)
26-30	229 (33.0)
>30	214 (30.8)
Functional health status before surgery	
Independent	342 (49.3)
Partially dependent	7 (1.0)
Totally dependent	1 (0.1)
Missing	344 (49.6)
Cancer type	
Appendiceal	97 (14.0)
Primary peritoneal	73 (10.5)
Colorectal	39 (8.0)
Unspecified pathology	468 (67.4)

Abbreviations: ACS, American College of Surgeons; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; NSQIP, National Surgical Quality Improvement Program.

Table 2. Cytoreductive Procedures Performed During HIPEC-CRS at ACS NSQIP Hospitals During 2005-2011

Procedure Type	No. (%)
Omentectomy	153 (21.6)
Small-bowel resection	90 (12.7)
Tumor debulking, cm	
5	75 (10.6)
5-10	21 (3.0)
>10	58 (8.2)
Unspecified size	42 (5.9)
Peritonectomy	50 (7.1)
Splenectomy	50 (7.1)
Gastrectomy	11 (1.6)
Small-bowel biopsy	11 (1.6)
Pelvic exoneration	4 (0.6)
Colectomy	3 (0.4)
Other	140 (19.8)

Abbreviations: ACS, American College of Surgeons; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; NSQIP, National Surgical Quality Improvement Program.

Table 3. Comorbidities of Patients Who Underwent HIPEC-CRS at ACS NSQIP Hospitals During 2005-2011

Comorbidity	No. (%)
History of smoking	90 (13.0)
Diabetes mellitus	53 (7.6)
Obesity	214 (30.8)
Respiratory disease	129 (18.6)
Ascites	98 (14.1)
Hypertension	257 (37.0)
Acute renal failure	1 (0.1)
Bleeding disorder	19 (2.7)
Steroid use for chronic condition	10 (1.4)
Weight loss in last 6 mo	46 (6.6)
Malnutrition, albumin <3.5 g/dL	126 (18.2)
Chemotherapy in the last 30 d	65 (9.4)
Radiotherapy in the last 90 d	1 (0.1)

Abbreviations: ACS, American College of Surgeons; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; NSQIP, National Surgical Quality Improvement Program.
SI conversion factor: To convert albumin to grams per liter, multiply by 10.

Outcomes

Postoperative bleeding requiring transfusion (17%), sepsis/septic shock (16%), and respiratory complications (15%) were the most prevalent complications (Table 4). Average operative time was 455minutes, and anesthesia time was 547minutes. There was 1 intraoperative occurrence (unplanned intubation), and 15% of patients required an intraoperative transfusion (Table 5). Overall mortality was 2.3%, with 9.8% returning to the operating room. Mortality was most likely to occur after postoperative day 17, with the exception of 1 patient with colon cancer who died within 6 days of operation. The Lasso algorithm did not demonstrate any strong predictors of mortality and morbidity given the low number of patients with mortality.

Table 4. Outcomes of Patients Who Underwent HIPEC-CRS at ACS NSQIP Hospitals During 2005-2011

Postoperative Outcome	No. (%)
Bleeding transfusion	118 (17.0)
Sepsis/septic shock	110 (15.9)
Organ/space SSI	65 (9.4)
Superficial SSI	45 (6.5)
Deep incisional SSI	14 (2.0)
Wound disruption	13 (1.9)
On ventilator ≥48 h	36 (5.2)
Pneumonia	33 (4.8)
Unplanned intubation	32 (4.6)
Progressive renal insufficiency	16 (2.3)
Acute renal failure	10 (1.4)
DVT	14 (2.0)
Pulmonary embolism	9 (1.3)
Myocardial infarction	2 (0.3)
Overall morbidity	228 (32.9)
30-d mortality	16 (2.3)
Return to operating room in 30 d	68 (9.8)
Readmission in 30 d	79 (11.4)
Hospital length of stay, mean (SD), d	13 (16)

Abbreviations: ACS, American College of Surgeons; CRS, cytoreductive surgery; DVT, deep venous thrombosis; HIPEC, hyperthermic intraperitoneal chemotherapy; NSQIP, National Surgical Quality Improvement Program; SSI, surgical site infection.

Table 5. Intraoperative Outcomes of Patients Who Underwent HIPEC-CRS at ACS NSQIP Hospitals During 2005-2011

Intraoperative Outcome	No. (%)
Intraoperative transfusions, No.	103 (14.8)
1	19 (2.7)
2	42 (6.1)
>3	42 (6.1)
Wound classification	
1-Clean	83 (12.0)
2-Clean/contaminated	579 (83.4)
3-Contaminated	30 (4.3)
4-Dirty/infected	2 (0.3)
Anesthesia, mean (SD) [range], min	547 (507) [237-1160]
Operation, mean (SD) [range], min	455 (417) [148-1320]

Abbreviations: ACS, American College of Surgeons; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; NSQIP, National Surgical Quality Improvement Program.

Discussion

The management of PC is the subject of ongoing debate between those who support the use of an aggressive surgical intervention with intraperitoneal chemotherapy and those practitioners who favor the use of systemic chemotherapy. Cytoreductive surgery, combined with HIPEC, can offer improved long-term survival and could possibly be a curative procedure in a select group of patients with surface tumor especially those with good performance status and low volume of disease as measured by the peritoneal cancer index.[5,7] However, the oncology community continues to hesitate on the role of HIPEC because of the lack of large prospective clinical trials demonstrating improved survival compared with current systemic chemotherapeutic regimens.1 Resistance to the adoption of CRS-HIPEC is also owing to the inherently complex nature of this procedure, which results in high rates of morbidity and mortality.[1,7,12] Therefore, improved patient selection and technique for this procedure have been advocated. Although it has been hypothesized that at high-volume centers postoperative morality should be less than 1%,[15] the larger studies in the literature report an approximately 4% to 8% mortality rate.[12,17,20,21] In this study, we showed that the overall reported mortality (2.3%) and morbidity (33%) at ACS NSQIP centers were in line with, and possibly lower than, what were reported in other large institutional case series.

Possible explanations for these apparently decreased rates of mortality in the ACS NSQIP are shorter study period and participation within the ACS NSQIP. This study was conducted over 6 years as opposed to longer periods described in other publications.[17,20,21] The longer study periods do not account for change in practices,

newer generation of chemotherapeutic regimens available, and advances in surgical technique, critical care, and anesthesiology. This evolution in surgical management and technique may have influenced our reported outcomes. Participation within the ACS NSQIP may also reflect that these operations may have been performed in high volume centers with specific HIPEC programs. There may also be a bias toward hospitals with an emphasis on outcome improvement practices given their participation in the ACS NSQIP.

This snapshot into the practices of participating centers within the ACS NSQIP demonstrates the acceptable rates of mortality and morbidity associated with this complex procedure. The main cause of death after CRS-HIPEC is attributed to sepsis followed by respiratory complications.[12,20] Abdominal sepsis, anastomotic leak, and intestinal fistulas were the most commonly reported complications in most large series.[12,17,21,22] The ACS NSQIP centers also reported septic complications, respiratory complications, and rate of reoperation as the most common causes of morbidity. The overall rate of septic complications in this study was 16%, with 4% of patients exhibiting septic shock. This is higher than the organ space infection rate (9%), which may in fact more precisely capture anastomotic leaks and enteric fistulas. Respiratory complications after CRS-HIPEC are common given the resuscitation required to keep up with the hemodynamic demands of the procedure.[23] The massive fluid shifts may cause an increased incidence of reintubation, need for prolonged ventilator support, and increased incidence of pulmonary interventions. Overall, respiratory complications were the third most common cause of morbidity in our series of patients at 15%. This included a 5% rate of pneumonia, 5% rate of unplanned intubations, and 5% rate of need for prolonged ventilator support. We did not find any preoperative and intraoperative patient risk factors that may have influenced respiratory complications. In a retrospective review of 76 HIPEC cases, Arakelian et al[4] reported on specific respiratory outcomes and interventions. Their findings were consistent with our results, with a reported 15% rate of pulmonary complications. They found that PC index and ASA class correlated with the presence of pleural effusions. They also reported that only 16% of patients required intervention with thoracocentesis or chest tube. They concluded that the high rate of respiratory complications are common but do not affect postoperative recovery.

Most patients in the ACS NSQIP were younger than the age of 65 years, which has been found to be a positive prognostic indicator of survival,[7,20,21] and this is consistent with the average reported age of 55 years in the literature.[12,17,20,21] Most of the sampled patients had an ASA class 3 status, which constitutes patients with severe systemic disease. However, most of our patients were functionally independent at the time of their operation. Despite systemic disease, the members of the selected group of patients at ACS NSQIP hospitals were deemed good candidates in regard to their functional status. Patient selection is extremely important given the physiological demands of CRS-HIPE Conan individual. The morbidity and mortality of CRS-HIPEC result from the combined effects of cytoreduction and the physiological insult of the intraoperative chemotherapy. A large intra-abdominal dissection area with combination of peritonectomy can cause massive fluid losses. Systemic hyperthermia required during HIPEC can also result in hemodynamic changes that may result in moderate blood loss, peripheral vasodilation, and massive fluid shifts.[24,25] This change in the physiological demands of the patient can increase morbidity and mortality.

There are 3 large cases series and 1 randomized prospective study in the literature that reported on the postoperative outcomes of CRS-HIPEC. A prospective randomized Dutch study observed a mortality rate of 8% for colorectal PC, with enteric fistulas as the most commoncause of morbidity.[12] Despite the high reported morality rates, Verwaal et al[12] re reported an improved median survival of 21 months (by a factor of 2) when comparing HIPEC-CRS with systemic chemotherapy. Larger series have shown lower rates of mortality. In a retrospective study of 501 patients over a 15-year period, the reported morbidity and mortality rates were 43% and 4.3%, respectively.[17] This was confirmed by Glehen et al[21] in a multicenter review of 506 patients with colorectal cancer who Underwent HIPEC over a 15-year period, which found a 4% mortality rate with septic shock as the most common cause of death. They reported a 10.7%reoperation rate and a 23% major postoperative complication rate, with fistulas as the most common complication (8.3%). The authors concluded that a more extensive cytoreduction correlates with an increased risk for morbidity and mortality. This was confirmed again by a larger multi-institutional French study including 1290 patients over an18-year period. They reported 4%mortality,with enteric fistulas (9%) and pneumonia (9%) as the most common causes of morbidity. They demonstrated a reoperation rate at 14%.20 The current study showed a reoperation rate of 9.6%, with a 30-day readmission rate of 11%. Our mortality rates were lower by a factor of 2comparedwith the larger studies. We were unable to identify specific factors that predict morbidity and/or mortality given the small number of patients with morbidity and mortality and the limitations of the administrative data available.

The ACS NSQIP database restricts information to 30-day postoperative morbidity and mortality, thus complications and readmission data are unknown because repeated hospital admissions for the same patient cannot be linked. Furthermore, long-term outcomes and survival rates are not available. There is no information as to the nature of reoperation nor of the extent of cytoreduction. We were also not able to discern whether patients received postoperative intraperitoneal chemotherapy; our data only captured intraoperative chemotherapy at the time of cytoreduction. We did not have information on the chemotherapeutic agents used and/or the timing of HIPEC during the operation. The ACS NSQIP does not provide any data points with regard to hematological complications. It is also not possible to discern the exact number of centers within the participating hospitals that perform HIPEC. Nevertheless, to our knowledge, this study is one of the largest to date to analyze 30-day morbidity and mortality in patients who underwent HIPEC and CRS. In fact, it is the only large study in the literature providing this information through a short study period, which may adjust for temporal trends.

Conclusions

Given the low survival of PC,CRS, in combination with HIPEC, has been shown to offer patients a chance for long-term survival. We used a large nationwide database to demonstrate that the overall mortality and morbidity rates associated with HIPEC-CRS are acceptable. In fact, the mortality rate of 2.3% is lower than some of the larger series in literature. Although the resultant morbidity is not negligible, with good patient selection, this modality appears to be overall safe and effective in experienced hands.

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Study concept and design: Jafari, Nguyen, Pigazzi.
Acquisition of data: Jafari, Mills.
Analysis and interpretation of data: Jafari, Halabi, Stamos, Nguyen, Carmichael.
Drafting of the manuscript: Jafari, Halabi, Nguyen, Pigazzi.
Critical revision of the manuscript for important intellectual content: Jafari, Halabi, Stamos, Carmichael,Mills, Pigazzi.

Statistical analysis: Jafari, Nguyen.
Administrative, technical, or material support: Mills, Pigazzi.
Study supervision: Stamos, Carmichael, Mills, Pigazzi.

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Author Affiliations: Department of Surgery, University of California, Irvine, School of Medicine, Orange (Jafari, Halabi, Stamos, Carmichael, Mills, Pigazzi); Department of Statistics, University of California, Irvine (Nguyen).
Corresponding Author: Alessio Pigazzi,MD, PhD, Division of Colorectal Surgery, University of California, Irvine, School of Medicine, 333 City BlvdW, Ste 850, Orange, CA 92868 (apigazzi@uci.edu).