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Enhanced recovery after surgery is safe for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

Robert CG. Martin II *, Bryce M. Marshall, Prejesh Philips, Michael Egger, Kelly M. McMasters, Charles R. Scoggins

Department of Surgery, Division of Surgical Oncology, University of Louisville School of Medicine, USA

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ABSTRACT

Introduction: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is an effective, aggressive approach to treating intraperitoneal carcinomatosis. This study aimed to test the efficacy/safety of an enhanced recovery (ERAS) program after CRS-HIPEC surgery.
Methods: Review of an IRB-approved prospectively maintained HIPEC database from 2003 to 2019. Adverse events and outcomes related to the primary operation were noted.
Results: 125 HIPEC procedures performed met inclusion criteria, with 20 treated through ERAS. There was an improvement in LOS (ERAS: 9, 6.0–28.0; non-ERAS: 11.0, 6.0–45.1, P = 0.5), a significant reduction in opioid use during hospitalization (ERAS Total Morphine Equivalents 156 vs Non-ERAS of 856, $p < 0.001$), and a significant reduction in discharge opioid requirements (ERAS 55% of patients, non-ERAS 97%, $p < 0.02$).
Conclusion: ERAS for CRS-HIPEC is safe, while maintaining quality outcomes, and leads to significant reductions in hospital opioid use and discharge narcotic usage. Our experience supports the full implementation of an ERAS protocol for HIPEC.

Introduction

Peritoneal carcinomatosis (PC) is a manifestation of primary peritoneal cancer or metastasis from a gastrointestinal tract (appendix, colon, stomach, other), ovary or lung cancer to the peritoneal surface. PC can be based on disease histology can be rapidly fatal with survival rates as low as 4 months when left untreated.[1]

First proposed in the 1980s and more widely adopted in the early 2000s, CRS-HIPEC is an aggressive procedure that offers the best prognosis for treatment of PC of Pseudomyxoma peritonei from appendiceal primary or colorectal origin.[2–4] The cytoreductive portion of the procedure focuses on resecting visible metastases, often with the addition of the gallbladder and omentum due to their ability to harbor residual disease. Following CRS, a peritoneal perfusion circuit is initiated and heated peritoneal chemotherapeutic lavage is initiated to treat remaining microscopic peritoneal disease[5]. Despite its efficacy, CRS-HIPEC is a highly invasive procedure associated with significant morbidity, which makes patient selection and management all that much more critical.[6,7]

In an effort to improve the patient management aspect of care, there has been a growing push to standardize perioperative protocols. A Dutch investigation into standardized therapy showed improved patient selection and decreased morbidity.[5] Despite these data being reported in 2015, a 2017 survey of the American Society of Peritoneal Surface Malignancies reported that only 68% of respondents followed a set preoperative protocol; 26% of respondents followed an established enhanced recovery after surgery (ERAS) protocol; and 76% implemented at least one ERAS principle.[8]

ERAS is a set of perioperative guidelines that emphasizes a multimodal, team-based approach to recovery after surgery in an effort to minimize postoperative metabolic and neuroendocrine trauma.[9] ERAS guidelines incorporate evidence-based practices into the preoperative, perioperative and postoperative management of patients.[10] Specifically, ERAS focuses on core tenets of patient education, opiate-sparing, early feeding, early ambulation, goal-directed fluid therapy and early removal of tubes and drains, with additional guidelines depending on the type of surgery. In many subsets of GI operations, ERAS has become standard of care, yet it has been hesitantly applied to CRS-HIPEC.[11] The reason for

* Corresponding author. University of Louisville School of Medicine, Professor of Surgery Director, Division of Surgical Oncology Director, Upper Gastrointestinal and Hepato-Pancreatico-Biliary Clinic, 315 E. Broadway - # 311, Louisville, KY 40202, USA.
E-mail address: Robert.Martin@louisville.edu (R.CG. Martin).

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low ERAS implementation is not evidently clear but may be related to fear over increased morbidity or just lack of reporting.

The goal of this study is to report one institution's initial use of an established ERAS protocol for CRS-HIPEC, outlining the protocol, safety and challenges.

Methods

Patient population

A review of our University of Louisville IRB-approved prospective database was conducted for patients undergoing cytoreductive surgery and HIPEC with Enhanced Recovery After Surgery (ERAS) protocol from July 2007 to May 2019. Starting in 2016, ERAS protocol was adopted for patients undergoing HIPEC procedures. An enhanced recovery protocol was also initiated in January 2013 with previous results presented from this protocol for a subset of gastroesophageal and hepatopancreatobiliary patients.[9] After implementation of ERAS protocol for HIPEC in 2016, all subsequent surgeries followed the ERAS guidelines. This ERAS protocol included goal directed fluid management with an opioid free anesthesia when possible. This protocol included, Gabapentin, Tylenol, Celebrex and Pepcid pre-operatively. Intra-operatively this included Precedex, Magnesium, and Ketamine. Post-operatively patients were manages with thoracic epidurals for at least 5 days duration.

Peritoneal disease surface severity scoring was then used for patient selection, induction chemotherapy, operative planning, and additional adjuvant systemic therapy.[8,12] The standard imaging criteria for our patients include CT chest with contrast, and triple-phase, thin-cut CT of the abdomen and pelvis at the time of diagnosis and within at least 2–3 weeks prior to surgery. PET scanning is also utilized in select patients to assess for extra-abdominal disease and for more extensive lymph node disease.[13] We utilize the following clinical and radiographic variables to best predict the ability of achieving a complete removal of all tumor greater than 2.5 mm:[1]: ECOG performance status 2 or less[2]; no evidence of extra-abdominal disease[3]; up to 3 small, resectable parenchymal hepatic metastases[4]; no evidence of biliary obstruction[5]; no evidence of ureteral obstruction[6]; no evidence of intestinal obstruction at more than one site[7]; no evidence of gross disease in the small bowel mesentery with several segmental sites of partial obstruction[8]; small volume disease in the gastro-hepatic ligament.

We have recently evaluated the core 15 components to our ERAS protocol, which are predictive of improved ERAS outcomes. There are preoperative ERAS education, smoking cessation education, prehabilitation education, nutritional optimization, clear liquids before surgery, appropriate bowel prep, preoperative pain management education, time hypothermic (defined as <35 °C (<95 °F), intraoperative opioid-sparing, goal-directed fluid therapy, appropriate Foley catheter use, riddance of NGT, post-operative nausea and vomiting (PONV) management, early nutrition, and early mobilization[9].

Standard demographic and clinicopathologic variables were collected including patient gender, BMI, tobacco and alcohol use, preoperative Karnofsky performance status, comorbidities and previous surgery. Diagnostic parameters were also reported and included response to chemotherapy, degree of differentiation, TNM staging, CEA at initial diagnosis, location of solid-organ metastases, preoperative chemotherapy, mucinous or signet ring pathology, as well as total lymph nodes resected at initial operation and total lymph nodes positive for disease.[12,14]

Patients were grouped into two categories based on those who followed ERAS protocol and those who did not. All patients underwent a closed HIPEC technique at a single institution as described previously[12,14]. Outcomes examined included length of stay, readmission (30 day), survival, recurrence, time to recurrence, and complications. All complications (90 day) were graded using the Clavien-Dindo complication scale[15]. The decision to utilize an ERAS protocol was based on the physicians' discretion during this evaluation period with this type of surgical procedure. Post-operative wound complications and type of SSI were recorded non-infectious and septic wound complications were divided into two groups comprising superficial (superficial or deep incisional) infection and organ space infection (OSI), respectively, according to Centers for Disease Control and Prevention (CDC) criteria[16].

Statistical analysis

Contingency analysis was performed on all categorical variables, which were reported as n (%). Logistic analysis was performed on all continuous variables and were reported as mean ± standard deviation or median and range. Univariate analysis was performed using two-tailed student's t-test for continuous variables and Fisher's exact test or Chi-square test as appropriate for categorical variables. Multivariable analysis was performed using logistic regression. Statistical significance was defined as a p-value of < 0.05. Statistics were calculated using MedCalc software (MedCalc, Inc., Ostend, Belgium).

Results

This study identified 125 patients who underwent CRS-HIPEC between 2003 and 2019, with the 20 most recent patients enrolled in our ERAS protocol. Patient demographics were similar across groups including both medical and surgical histories (Table 1). Additionally, primary tumor type showed no statistically significant variation (Table 1). While operative data were similar in regard to EBL, number of organs resected and total pre-operative PCI score, there were variations in both total anastomoses and chemotherapeutic drug used (Table 2). ERAS patients were equally treated with oxaliplatin and mitomycin as to non-ERAS patients. ERAS also had an increased number of anastomoses at 1.5 with a range of 0–4 compared to 1 with a range of 0–5 ($P = 0.0309$).

ERAS Compliance was successful in 7 out of the 15 factors (Table 2). The single largest deviations from ERAS was, early NGT removal and early nutrition in the entire group. All other factors improved over the last 10 patients evaluated for this protocol with continued education of all staff involved. Nine patients did have hypothermia (<35°) for a time period of median 25 min (range 10–65 min) in attempt to cool the patient prior to hyperthermia to avoid core hyperthermia during the 90 min perfusion.

Post-operative data were also similar across groups (Table 2), except for intra-operative fluid administration when the ERAS patients followed a goal directed administration. The time to gastrointestinal function was significantly better in the ERAS patients (median 4, range 4–8) than the non-ERAS patients (median 8, range 6–12) ($p = 0.02$).

While not statistically significant, readmission rates were higher in ERAS patients compared to non-ERAS patients (ERAS 30.0%; non-ERAS 18.63%, $P = 0.2561$) and length of stay was also decreased in ERAS (ERAS 9.0, 6.0–28.0 days; non-ERAS 11.0, 6.0–111.1 days, $P = 0.4965$). When three times intervals for this study were evaluated for the non-ERAS patients there was an improvement in length of stay: 2003–2012 (median LOS 14(9–111)); 2012–2016 (median 11[6–22]; 2016–2019 (median 10(5–16)).

The cause for readmission for these six patients were delayed anastomotic leak ($n = 1$), exacerbation of chronic renal failure ($n = 1$), hyponatremia ($n = 1$), hospital/community acquired pneumonia ($n = 3$). All 6 of these patients recovered with a

Table 1
Clinicopathologic characteristics of HIPEC treated with ERAS and Non-ERAS.

	ERAS[20]	Non-ERAS (105)	p-value
Male Gender	8 (40%)	62 (59.0%)	0.2518
Age	51.7, 34.5–71.2	58.7, 25.1–80.0	0.7151
BMI	26.8, 19.0–36.9	26.5, 17.1–53.4	0.9675
Past Medical History			
Cardiac	2 (10.0%)	16 (16.2%)	0.4465
Pulmonary	0	7 (7.1%)	0.1979
Diabetes	3 (15.0%)	9 (9.1%)	0.4399
Alcohol	4 (20.0%)	23 (23.2%)	0.5959
Tobacco	9 (45.0%)	30 (30.3%)	0.4333
Hepatic	0	6 (6.1%)	0.2344
HTN	5 (25.0%)	49 (49.5%)	0.0999
Surgical History			
TAH	2 (10.0%)	23 (23.2%)	0.5959
Cholecystectomy	5 (25.0%)	18 (18.2%)	0.8965
Colorectal	6 (30.0%)	38 (38.4%)	0.3518
Appendectomy	5 (25.0%)	22 (22.2%)	0.6501
Other Major Abdominal Surgery	2 (10.0%)	17 (16.2%)	0.4438
Primary Tumor Type			
Primary Tumor Type			0.4449
Appendiceal	9 (45.0%)	35 (35.4%)	
Metastatic Colorectal	8 (40.0%)	42 (42.4%)	
Gastric	1 (5.0%)	3 (2.9%)	
Primary Peritoneal	1 (5.0%)	7 (7.1%)	
*Other**	1 (5.0%)	10 (10.1%)	

Other includes small bowel adenocarcinoma, mesothelioma, GIST, papillary serous adenocarcinoma and ovarian.

readmission length of median 4 days (range 2–9) and none of these 6 had 90-day mortality.

There was a significant reduction in opioid use during hospitalization (ERAS Total Morphine Equivalents 156 mg vs non-ERAS of 856 mg, $p < 0.001$), and a significant reduction in discharge opioid requirements (ERAS 55% of patients, non-ERAS 97%, $p < 0.02$).

Discussion

The results of this study demonstrate that ERAS protocols can be implemented safely in patients undergoing CRS-HIPEC. The implementation of this protocol is associated with decreased opiate use and decreased length of hospital stay without increasing overall complication rates, severity of complications, or rate of re-operation.

Reporting of ERAS for HIPEC has been minimal, but there have been two very recent reports coming from academic institutions.[17,18] In the report by Webb et al., LOS was reduced from 10.3 ± 8.9 days to 6.9 ± 5.0 days ($p = 0.007$), and Siddharthan et al. showed a reduction from 11 to 7 days ($p < 0.05$).[17,18] Both of these are similar to our reported reduction of LOS from 11 to 9 days; however, ours was not found to be statistically significant. Our report echoes those findings in that ERAS is safe for CRS-HIPEC despite it being a long, invasive procedure. Decreased rates of opioid use are another commonality as both our report and Webb et al. showed decreased dependence on post-operative opioids.

While it is important to always be mindful of evidence-based practice and ERAS guidelines, there were certain scenarios in which ERAS principles were not practical. For example, patients that required esophageal anastomoses necessitated use of nasal-gastric tubes for feeding and took longer to return to nutrition by mouth. Additionally, a subset of patients were not good candidates for thoracic epidurals, which meant that opioid-sparing techniques were not practical due to increased sensation of pain. While these are just two examples of necessary deviations from ERAS protocol, each patient must be evaluated individually. Even when a patient does not fully comply with an ERAS protocol, previous work has demonstrated there is inherent benefit from the implementation of standardized perioperative care pathways in surgical oncology.[19,20] This benefit may also be explained by the overall improved quality of care due to ERAS protocol and continuous internal auditing; educating all parties engaged in the recovery process, from nurses and physicians to patients themselves, has been shown to improve the quality of care for patients across the board.[21]

NGT tube use, Foley catheter use, and early nutrition are obvious ERAS components that are not possible to control is many/most CRS-HIPEC patients. However, the remaining components were all implemented with good compliance and no change in safety/complication rates. Clearly the pre-operative factors can be implemented universally with ease with more complete education and screening. Surgeons, individually need to decide if they will continue to operate on patients who refuse to stop smoking. We have begun to check serum continine levels at pre-admission testing and day of surgery, with the patient's surgery being cancelled if positive. Should pulmonary complications continue to be accepted if they can be mitigated with optimal ERAS implementation and patient compliance? For this study, no patients were excluded based on smoking status. In fact, there was a higher rate of tobacco use in the ERAS group compared to the non-ERAS group. In the future, smoking status will be more closely monitored to check patient compliance to smoking cessation.

The intra-operative factors require a greater amount of collaboration and communication with anesthesia. A complete opioid-sparing anesthetic management is possible with regional catheter use and the use of alternative medications. The degree/extent and the duration of hypothermia should be discussed at the initiation of surgery with the goal of not exposing the patient to unnecessary extended periods of hypothermia. Similarly, with the ability to actively cool during HIPEC, a patient can remain below <38 °C, but this takes multiple active cooling points (i.e. cooling blanket, reduced room temp, and ice packs for example).

We have found that the critical post-operative components are the hardest to implement from an institutional standpoint. Opioid reduction or avoidance will remain difficult if the institution continues to use the outdated verbal numerical rating scale (VNRS) (0 no pain; 1–3 mild pain; 4–7, moderate pain; and 8–10, severe

Table 2
Operative and postoperative factors for ERAS and Non-ERAS patients.

	ERAS[20]	Non-ERAS (105)	p-value
EBL	250, 150-450	225, 0-2500	0.395
Total Anastomoses	1.5, 0-4	1, 0-5	0.031
Total Organs Resected	4.5, 3-7	4, 0-11	0.42
Total Pre-Op PCI Score	3.0, 0–23.0	5.5, 0–39.0	0.32
Overall Operative Time (median; range)	4.5 (3.4–8) hours	5 (3.5–8.5) hours	ns
ICU Use	0%	19 (18%)	
Days in ICU (median, range)	N/A	2[1–5] days	
Perfusion Chemotherapy Drug			
Cis-Adriamycin	0	3 (2.9%)	
Cisplatin	1 (5%)	2 (1.9%)	
Irinotecan	2 (10%)	1 (1.0%)	
Mitomycin	11 (55%)	55 (52.4%)	0.8
Ox/IRI	0	11 (10.5%)	
Oxaliplatin	6 (30%)	27 (25.7%)	0.9
Other	0	6 (5.7%)	
Intra-Operative Volume Given(Median, Range)	1850 (1500–4235)cc	2950 (2300–5600)	0.03
ERAS Compliance Factors	20/20 (100%)	Not Applicable	
Pre-Op Smoke Cessation	16/20 (80%)		
Pre-Habilitation	20/20 (100%)		
Nutritional Supplement	18/20 (90%)		
Clear Liquids Before No Bowel Prep	10/20 (50%)		
Pre-op Pain Education	20/20 (0%)		
Time Hypothermia	9/20 (45%)		
Intra-Op Opioid Spare	13/20 (65%)		
Goal Directed Fluid	8/20 (40%)		
Foley D/C < 24 h	5/20 (25%)		
NGT D/C < 24 h	13/20 (65%)		
PONV Management	14/20 (70%)		
Early Nutrition	3/20 (15%)		
Early Mobilization	20/20 (100%)		
Postoperative Factors			
Final PCI Score Post CRS and HIPEC	0, 0	0, 0-16	0.056
Re-Operation	1 (5.0%)	7 (7.1%)	0.84
Total Number of Complications (Range)	1, 0-5	1, 0-8	0.9
Highest Complication Score (Range)	1, 0-3	1, 0-5	0.95
Types of Complication(Grade)			
Pancreatitis	0	3	
Leak	2 (Grade 2,3)	18	
PE	0	2	
Pleural Effusion	0	17	
DVT	0	1	
Surgical Site Infection:	1 (Grade 1)	18	
Superficial	1 (Grade 3)	19	
Deep	1 (Grade 1)	1	
Mental Status Change	1	4	
Pneumonia			
Readmission	6 (30.0%)	19 (18.6%)	0.26
LOS	9, 6.0–28.0	11, 6.0–45.1	0.5

pain). This type of pain scale has been demonstrated by the American College of Surgeons to be inadequate and inaccurate (FACS.org/SafePainControl) for opioid reduction or avoidance. It is not uncommon for a patient to report their pain as a "13" when they are watching television or having a conversation with their care provider. However, this type of pain scale score is a deficiency for the institutional nursing quality assessment and pain comfort plan. Thus utilizing a more functional and educational pain assessment is the key foundation for opioid reduction. The remaining factors that may cause ERAS protocol to deviate are based on the clinical care and presentation of the patient. NGT removal and early nutrition are two factors that can be delayed without impacting the short term benefits of the ERAS protocol, as demonstrated by our reduction in overall length of stay.

ERAS has improved the quality of care among surgical patients, thus reducing complications and readmission rates. However, we did see higher readmission rates our initial ERAS patients. This is possibly related to a smaller sample size, patient education at the time of discharge and lack of daily phone follow up in the first 3–5 days which can help in early readmissions most commonly for dehydration and failure to thrive. In a recent review of 2017 US HIPEC cases, there was a 15.9% rate of readmission within 30 days following CRS-HIPEC.[22] According to these data, our readmission rate of 18.6% for non-ERAS is already slightly high, and the 30.0% rate for ERAS is nearly double related to our current ERAS numbers. This is mostly likely related to the small sample size of our ERAS cohort mixed with added re-admit precaution while the safety of ERAS for HIPEC is being worked out. None of the readmitted patients had protracted stays in the hospital upon readmission.

This initial review of our ERAS protocol with CRS-HIPEC has limitations. The smaller number of patients limits us in identifying predictive pre-operative factors that may lead to better ERAS outcomes. Similarly the diversity of CRS-HIPEC patients in relation to the type of resections that are required do not allow complete matching of all cases.

However, we do conclude that an ERAS protocol can be safely implemented in patients undergoing CRS-HIPEC. Standardization of therapy has a number of benefits, but this study demonstrated both a significant reduction in hospital opioid use and the need for discharge narcotic usage. Our experience supports the full

implementation of an ERAS protocol for CRS-HIPEC patients.

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Declaration of competing interest

Bryce M Marshall, Prejesh Philips, Michael Egger, Kelly M McMasters, Charles Scoggins, and Robert C.G. Martin declare no conflicts of interest regarding the article "Enhanced Recovery After Surgery is Safe for Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy," submitted to American Journal of Surgery on 3/25/2020.

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