





# Implementation of a Multidisciplinary Enhanced Recovery After Surgery (ERAS) Program for Cytoreductive Surgery (CRS) With Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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#### **ABSTRACT**

**Background and Objectives:** Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) can be associated with prolonged hospital stays. A novel Enhanced Recovery After Surgery (ERAS) based on ERAS Society guidelines was designed and implemented. The primary outcome was ERAS compliance. Secondary outcomes included length of stay (LOS) and postoperative complications.

**Methods:** A retrospective study on patients who underwent CRS/HIPEC between 2018 and 2022, with ERAS implementation in 2022. Health records were reviewed. Statistical analysis included descriptive statistics, Wilcoxon tests, Student *t*-test, and  $\chi^2$  and binomial negative regression. Health Ethics Research Board approval was obtained.

**Results:** Eighty patients underwent CRS/HIPEC: 59 in the pre-ERAS group and 21 in the post-ERAS group. Groups were similar in age, comorbidities, and Peritoneal Carcinomatosis Index. ERAS compliance increased from 32.8% to 70.8% (p < 0.001). Median LOS decreased from 14 to 9 days (p < 0.001). Comparing pre-ERAS to post-ERAS showed no significant difference in the major morbidity rate (13.6% vs. 9.5%) or 30-day readmission (9.4% vs. 4.8%) and no mortalities. Controlling for patient characteristics, the mean LOS decreased by 6.94 days (p < 0.001).

**Conclusion:** Implementation of an ERAS CRS/HIPEC program is safe and allows for improved compliance to ERAS protocols and a significant reduction in LOS.

#### 1 | Introduction

Enhanced Recovery After Surgery (ERAS) perioperative guidelines consist of patient-centered clinical practices implemented before, during, and after surgery. The aim of these protocols is to improve postoperative outcomes and shorten length of stay [1]. Such measures have been introduced in many different surgical fields, namely colorectal, bariatric, hepatobiliary, gynecologic, and urologic surgery [2–5]. A recent meta-analysis of 74 ERAS randomized control trials showed a decrease in hospital length of stay (LOS) by 1.88 days with a decreased risk of complications in the ERAS group [6].

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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) is a surgical treatment for peritoneal surface malignancy that combines peritoneal stripping and multivisceral resection followed by heated intra-abdominal chemotherapy [7–10]. LOS and complication rates for this procedure typically correlate with disease burden quantified by the Peritoneal Carcinoma Index (PCI). Often, a higher PCI means more extensive surgery with longer operative times, and thus higher risk of complications, slower recovery, and extended LOS. In general, major morbidity and mortality rates are estimated at 22% to 34% and 0.8% to 4.1%, respectively [11].

The introduction and feasibility of an ERAS protocol for CRS/HIPEC for non-gynecologic malignancy has been reported previously [12, 13] with a recent systematic review and meta-analysis showing improved LOS and morbidity rates amongst several studies for both gynecologic and non-gynecologic malignancies [14]. Adherence to ERAS protocols is correlated with lower postoperative complications and a reduction in LOS. In 2020, recommendations regarding perioperative care of CRS/HIPEC patients were published by the ERAS Society [15, 16].

We seek to assess the outcomes before and after the implementation of an ERAS pathway developed based on the ERAS Society guidelines for patients undergoing CRS/HIPEC. The primary objective was to measure compliance to ERAS CRS/HIPEC guidelines. The secondary objectives included assessment of LOS, 30-day morbidity and mortality, and 30-day return to emergency department.

#### 2 | Methods

#### 2.1 | Study Design

This single-center study was performed at an academic center and major referral site for CRS/HIPEC. We compared compliance to ERAS perioperative care elements before and after the introduction of ERAS guidelines in patients undergoing CRS/HIPEC. All patients underwent CRS/HIPEC between January 1, 2018 and October 31, 2022, with the introduction of the ERAS pathway on February 1, 2022. The original protocol was meant to be initiated in mid-2020, however, due to the COVID-19 pandemic it was not able to be implemented until February 2022. Patients who underwent CRS/HIPEC between January 1, 2018 and January 31, 2022 are termed "pre-ERAS," and those who underwent surgery between February 1 and October 31, 2022 are termed "post-ERAS."

The patient population included patients aged 18 years or older undergoing CRS/HIPEC at a single academic institution. Patients were excluded if no cytoreductive surgery or HIPEC was performed or if laparoscopic CRS/HIPEC was performed.

Ethics approval was obtained from the local Health Ethics Research Board (HREBA.CC-20-0450).

The reporting on ERAS compliance, outcomes, and elements research (RECOvER) check-list was used to guide the writing of this manuscript [17].

## 2.2 | Study Procedures

ERAS care principles consisted of several interventions implemented pre-admission, pre-operatively, intraoperatively and postoperatively (Figure 1).

## 2.3 | Pre-Admission

Pre-operatively, patients met with a patient educator and were given a booklet explaining CRS/HIPEC and detailing the process of preoperative to postoperative periods. Instructions were also provided for alcohol and smoking cessation, exercising, and nutritional optimization. Checkboxes were included for actionable items. Bloodwork was checked for hyperglycemia, anemia, and malnutrition. Bowel preparation was ordered for patients requiring low colorectal anastomosis.

# 2.4 | Pre-Operative

Immediately preoperatively, patients could continue a regular diet up to 6 h before surgery and received 50 g of carbohydrates 3 h before surgery. Multimodal prophylaxis for postoperative nausea and vomiting was recommended and included a corticosteroid and a selective serotonin agonist. Patients were provided with a warming gown in the preoperative holding area.

## 2.5 | Intraoperative

Parameters that were followed intraoperatively included antibiotics prophylaxis within 60 min of surgery, avoidance of hypothermia with body warmers, goal-directed fluid administration, and strict glycemic control. Due to fluid shifts and edema associated with peritoneal and diaphragmatic stripping, there was no consensus reached on the use of surgical drains in the ERAS Society Guidelines, and as such, the use of drains was left to the discretion of the surgeon [15]. Decreasing the number of drains was encouraged. Discontinuation of nasogastric (NG) tubes before transfer to the post-anesthesia care unit was encouraged but ultimately left to the discretion of the surgeon, especially in the setting of upper gastrointestinal resection.

## 2.6 | Postoperative

Postoperative principles included multimodal pain control, venous thromboembolism prophylaxis, management of foley catheter, prevention of ileus, early oral intake and mobilization. The protocol recommended thoracic epidural and multimodal analgesia using acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Venous thromboembolism prophylaxis was initiated early postoperatively and continued for 28 days postoperatively. Unless contraindicated by intraoperative interventions such as bladder resection, urinary catheters were recommended to be removed by postoperative day (POD) 2. To prevent ileus, multimodal use of epidural analgesia, laxatives (including milk of magnesium), early resuming of oral intake, and chewing gum were initiated. Clear fluids were started on

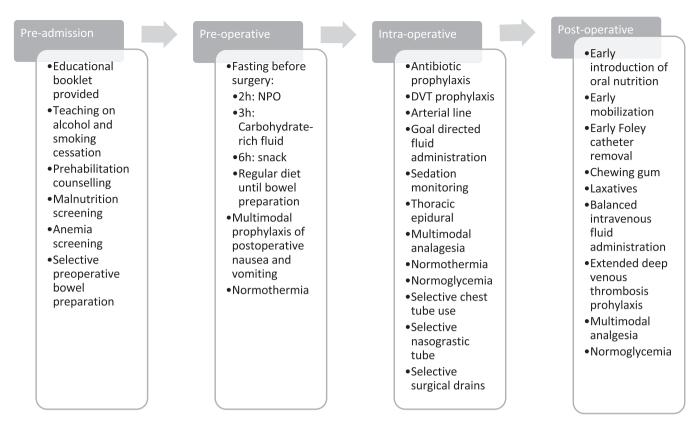


FIGURE 1 | Elements of enhanced recovery after surgery pathway for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

POD 0, and regular diet on POD 1. Incentive spirometry was encouraged to be used every hour while the patient was awake.

Box plots were created to demonstrate the difference in LOS between the two groups.

## 2.7 | Implementation

Before implementation, education was provided to healthcare providers who would be a part of the patients' care pathway. Standardized order sets were created for pre- and postoperative management of patients. A summary sheet was created for the anesthesia carts for the intra-operative measures.

## 2.8 | Data Collection

The pre-ERAS group was a retrospective group, while the post-ERAS group was a prospectively maintained group. A retrospective chart review was completed on all patients to assess for compliance with ERAS recommendations, as well as post-operative outcomes including morbidity, mortality, emergency room visits and readmissions.

# 2.9 | Statistical Methods

Descriptive statistics were used for variables, as well as for compliance to ERAS CRS/HIPEC guidelines. Wilcoxon tests were used to compare cohorts for variables with skewed distribution. For normally-distributed continuous data, Student t-test was employed.  $\chi^2$  test was used for nominal data. The two groups were compared using binomial negative regression to test for significance while controlling for confounding factors.

## 3 | Results

From January 1, 2018 to October 31, 2022 a total of 80 eligible patients underwent CRS/HIPEC with 59 in the pre-ERAS group and 21 in the post-ERAS group. The respective pre-ERAS and post-ERAS groups were comparable with the majority being female (n=33, 56% and n=15, 71%), American Society of Anesthesiologist (ASA) II or III, with mean ages of 55.7 and 53.3 years (Table 1). There were no statistically significant differences between the two groups.

Perioperatively, the compliance to ERAS protocols increased from 32.8% to 70.8% (p < 0.001) (Table 2). As intrabdominal drains were up to the discretion of the surgeon, it was not included in compliance. In the pre-ERAS group, 56 patients (95.0%) received drains, compared to 21 (100%) of the post-ERAS patients.

The outcomes of the implementation of ERAS can be seen in Table 3. There was a statistically significant decrease in LOS from a median of 14 days in the pre-ERAS group to 9 days in the post-ERAS group (IQR: 10.5-21.5 vs. 7-11, p < 0.001) (Figure 2 and Table 3). With the implementation of ERAS, there were fewer intraoperative hypoglycemia episodes. Postoperatively, there was a decrease in intravenous fluid (IVF) administration, and earlier return of bowel function in the post-ERAS group. Thoracic epidural removal and oral analgesia was started earlier in the post-ERAS group. There was no difference in the use of NG insertion postoperatively (Table 3).

**TABLE 1** | Patient characteristics of those undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy before and after implementation of enhanced recovery after surgery pathway.

Characteristic		Pre-ERAS, $n$ (%) ( $N = 59$ )	ERAS, $n$ (%), $N = 21$	<i>p</i> -value
Age (mean)		55.7	53.3	0.412
Sex	Male	26 (44.1)	6 (28.6)	0.324
	Female	33 (55.9)	15 (71.4)	
ASA Status	I	3 (5.1)	0 (0)	0.29
	II	19 (32.2)	9 (42.8)	
	III	33 (55.9)	11 (52.4)	
	IV	0 (0)	1 (4.8)	
	Missing	4 (6.8)	0 (0)	
Pathology	Appendiceal	20 (33.9)	7 (33.3)	0.7269
	Colorectal	28 (47.4)	13 (61.9)	
	Gastric	2 (3.4)	0 (0)	
	Mesothelioma	4 (6.8)	1 (4.8)	
	Other	5 (8.5)	0 (0)	
BMI (mean)		26.8	27.7	0.586
PCI (median (IQR)		11 (6–21.5)	6 (4–13)	0.129
Number of bowel anasto	omoses (median)	1	1	0.48

In terms of morbidity, the major complication rate (Clavien-Dindo  $\geq$  3) was 13.6% in the pre-ERAS group and 9.5% in the post-ERAS group (OR: 1.48, CI 95% 0.26–15.57). There were no deaths in either group at 90 days. No patients from the post-ERAS group returned to the emergency department (ED) within 30 days of surgery, while in the pre-ERAS group two returned to the ED and five patients were still admitted to hospital.

When controlling for other variables including age, BMI, ASA status and PCI through negative binomial regression, the demonstrated decrease in length of stay remained significant with an adjusted mean difference of 6.32 days (p < 0.001) (Table 4).

#### 4 | Discussion

This study aimed to evaluate the implementation an ERAS pathway for CRS/HIPEC at a single academic center and monitor subsequent outcomes. The primary objective was to assess for compliance to the ERAS protocols. We demonstrated an increased adherence to ERAS protocols from 32.8% to 70.8% (p < 0.001). When controlling for other variables, there was on average, a decrease in the LOS by 6 days in the post-ERAS group. In general, the post-ERAS group had earlier return of bowel function with comparably lower complication rates overall than the pre-ERAS group. This demonstrates that compliance to ERAS for CRS/HIPEC is safe and leads to improved LOS and postoperative outcomes.

In the recent systematic review and meta-analysis by Robella et al., there were 434 patients of 743 treated with CRS/HIPEC of which six were case-control and only one was a retrospective single cohort analysis [14]. Of the 434 patients, about half were

ovarian cancer, while the remainder were colorectal, gastric, soft tissue sarcoma, malignant peritoneal mesothelioma, primary peritoneal carcinoma, and pseudomyxoma peritonei [14]. This shows that the topic of CRS/HIPEC for non-gynecologic malignancy is still an area that requires further investigation to provide evidence for ERAS pathways in this heterogeneous population. This study is the first to our knowledge that is based on the ERAS Society guidelines and shows meaningful improvements in patient outcomes post-implementation.

ERAS pathways were created and implemented to allow for a patient-centered approach to perioperative care that ultimately led to improved outcomes and LOS. On review of a recent systematic review of ERAS for CRS/HIPEC, ERAS programs were associated with, on average, a 1-4-day reduction in LOS [14]. A feasibility study on ERAS for CRS/HIPEC by Lu et al. demonstrated a decrease in LOS from 9 to 6 days (p < 0.001) and no statistically significant differences in or mortality [13]. This study showed similar results, with a decrease in LOS of 6 days. To see major improvements in LOS and postoperative morbidity, adherence to ERAS protocols is recommended to be 70%-90% [18, 19]. This study's success in lowering the LOS by more than has been reported in the literature may be linked to the previous low compliance to ERAS protocols of 31.8%, which significantly increased to 70.8% post-implementation. Historically, the LOS has been quite long, which would be even more obvious and pronounced after the implementation of these ERAS protocols aimed at getting patients home sooner. As suggested by Bhandoria et al., compliance with some parameters should be nearly 100%, such as smoking cessation, shorter duration fasting, carbohydrate loading, multimodal analgesia, and early ambulation [19]. Preoperative carbohydrate loading was only done by six patients in the post-ERAS group showing that while the results have been excellent, there is still room for improvement.

**TABLE 2** | Adherence to Enhanced Recovery After Surgery (ERAS) principles pre- and post-implementation of ERAS pathway for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

	Pre-ERAS, % compliance $(N = 59)$	Post-ERAS, $\%$ compliance $(N=21)$	<i>p</i> -value
Overall compliance	32.8	70.8	< 0.001
Preoperative	21.5	64.6	
Intraoperative	50.9	86.9	
Postoperative	26.0	60.8	
Preoperative compliance			
Pre-op smoking and alcohol counseling	0 (0%)	16 (76.2%)	< 0.001
Missing	50 (84.7%)	5 (23.8%)	
Pre-op exercise counseling	0 (0%)	17 (81.0%)	< 0.001
Missing	59 (100%)	2 (9.5%)	
Pre-op anemia screen	2 (3.4%)	15 (71.4%)	< 0.001
Pre-op nutrition assessment	2 (3.4%)	0 (0%)	1.00*
Education booklet provided	11 (18.6%)	16 (76.2%)	0.192
Missing	46 (78.0%)	5 (23.8%)	
Pre-op Hgb A1C	5 (8.5%)	15 (71.4%)	< 0.001
Anesthesia counseling	56 (94.9%)	20 (95.2%)	1.00**
Pre-op carb loading	0 (0%)	6 (28.6%)	< 0.001
Multimodal PONV prophylaxis	38 (64.4%)	17 (81.0%)	0.396
Intraoperative compliance			
Length of time body temperature < 36° C intraoperatively			
< 20 min	13 (22.0%)	14 (66.7%)	< 0.001
> 20 min	16 (27.1%)	7 (33.3%)	
Missing	30 (72.9%)	0 (0%)	
Use of thoracic epidural	43 (73%)	20 (95%)	0.0956
Upper body forced air warming system	45 (76.3%)	19 (90.5%)	1.00***
Missing	14 (23.7%)	2 (9.5%)	
Multimodal analgesia	19 (32.2%)	20 (95.2%)	< 0.001
Postoperative compliance			
Early removal of intraoperatively placed NG	12 (20.3%)	11 (52.4%)	0.016
Missing	2 (3.4%)	0 (0%)	
Early foley catheter removal (POD 0 or 1)	4 (6.8%)	4 (19.0%)	0.048
Day when IV saline locked for at least 24 h			
Between POD 3-5	9 (15.3%)	15 (71.4%)	< 0.001
>POD 6	50 (85.7%)	6 (28.6%)	
Received oral nutritional supplementations by POD 2	0 (0%)	13 (61.9%)	< 0.001
Solid diet started			
POD 4 or before	17 (28.8%)	11 (52.4%)	< 0.001
POD 5 and later	42 (71.2%)	10 (47.6%)	
Chewing gum	0 (0%)	21 (100%)	< 0.001
Magnesium-based laxative	0 (0%)	6 (28.6%)	< 0.001
Ambulation for > 15 min POD 1-3	46 (78.0%)	19 (90.4%)	0.73

(Continues)

	Pre-ERAS, % compliance (N = 59)	Post-ERAS, % compliance $(N = 21)$	<i>p</i> -value
Ambulation for > 15 min POD 4 and beyond	5 (8.5%)	1 (4.8%)	
Missing	8 (13.6%)	1 (4.8%)	
Early extubation	50 (84.7%)	15 (71.4%)	0.18
Missing	3 (14.3%)	6 (28.6%)	

<sup>\*</sup>p-value = 1 odds ratio, Fisher's Exact Test: OR = 0.93, 95% CI (0.017, 12.42); \*\*p-value = 1.00, Fisher's Exact Test: OR = 0.93% CI (0, 15.12); \*\*\*\*Cannot determine if missing values are "yes" or "no" as such, two groups are the same.

**TABLE 3** | Patient outcomes before and after implementation of the Enhanced Recovery After Surgery pathway for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

Outcomes		Pre-ERAS	Post-ERAS	<i>p</i> -value
Length of stay (median, IQR)		14 (10.5–21.5)	9 (7-11)	< 0.001
Number of hyperglycemia episodes intraoperatively (median)		15	9	0.009
Number of nights in ICU (median)		3	4.5	0.448
Post-op IVF (cc) (mean)		14 (12.8%)	9 (20.8%)	0.012
Maximum lactate (mean)		3.5	2.8	0.20
Intraoperative blood transfusion		11 (18.6%)	0 (0%)	0.03
Estimated blood loss	100-500cc	29 (49.1%)	12 (57.1%)	0.344
	> 500cc	26 (44.1%)	4 (19.0%)	0.217
	Missing	4 (6.8%)	5 (23.8%)	
First bowel movement	By POD 4	11 (18.6%)	14 (66.7%)	< 0.001
	POD 5 and beyond	46 (78.0%)	7 (33.3%)	
	Missing	2 (3.4%)	0 (0%)	
Post-op NG insertion		6 (10.1%)	3 (14.3%)	0.567
Removal epidural	POD 5 or earlier	27 (45.8%)	14 (66.7%)	< 0.001
	After POD 5	32 (54.2%)	7 (33.3%)	
Start of exclusive oral analgesia	POD 3-5	9 (15.3%)	12 (57.1%)	< 0.001
	POD 6 and beyond	49 (83.0%)	9 (42.9%)	
	Missing	1 (1.7%)	0 (0%)	

ERAS is a multidisciplinary, multiphase process that requires intermittent auditing for compliance to be successful [20]. Currently, our center does not have a regular audit in place. The CRS/HIPEC population is quite heterogeneous in terms of pathologic diagnosis, need for multivisceral resection, and significant inflammatory response depending on the burden of disease resected, resulting in variable fluid requirements and hemodynamics [12, 21]. Due to this heterogeneity, auditing is paramount as there are many variables that could impact compliance. The ERAS pathway was modeled after the ERAS Society Guidelines, which is the gold standard resource. However, understandably, much of the evidence is low-quality due to lack of randomized data and ultimately made through expert consensus [15, 16].

One specific example is the use of intra-abdominal drains. While ERAS guidelines typically recommend not using surgical drains, the CRS/HIPEC population can have a significant inflammatory response that creates large volume ascites and

pleural effusion in the case of diaphragmatic stripping [14]. The CRS/HIPEC ERAS guidelines suggest that it is up to the discretion of the surgeon to use surgical drains and amongst experts there was a 50/50 division on the use of drains [15]. In this study's cohort, all post-ERAS patients received a surgical drain with seemingly no effect on the LOS or postoperative complications. While limiting drains in most intraabdominal surgeries is encouraged, in the CRS/HIPEC group it may be reasonable to assess on a case-by-case basis and for the use of drains to not affect "compliance rates" overall.

CRS/HIPEC has been associated with high rates of postoperative ileus with a recent prospective study reporting ileus rates of 54% [22]. This has often led to intraoperatively placed NGs and delayed diet initiation as means to prevent the complications of ileus, including emesis and aspiration. ERAS protocols suggest that decreased IVF, early mobilization, gum chewing, early initiation of diet, and multimodal analgesia can reduce the risk of postoperative ileus [14]. In this study, we

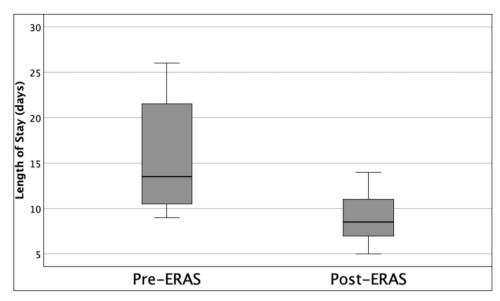


FIGURE 2 | Box plot comparing length of stay (days) before and after implementation of enhanced recovery after surgery pathway for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

**TABLE 4** | Changes in patient length of stay, readmission and complication rates (Clavien-Dindo  $\geq$  3), adjusted for significant patient characteristics after implementation of the enhanced recovery after surgery pathway for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

Measure	ERAS Pathway Rate (relative change in rate)	<i>p</i> -value
Length of stay, acute adjusted mean difference, d	−6.32 (95% CI, −9.33 to −3.32)	0.001
30-day readmission, adjusted	-0.018 (95% CI, -0.002 to 0.136)	0.807
Clavien-Dindo $\geq$ 3 complication, adjusted	0.008 (95% CI, -0.157 to 0.172)	0.926

have shown that early initiation of diet does not have an association with increased ileus or postoperative NG tube insertion. Furthermore, a bowel movement by POD 4 occurred in 66.7% of the post-ERAS group compared to 18.6% in the pre-ERAS group. This illustrates the importance of challenging pre-existing ideas on patient care with the implementation of patient-centered, evidence-based pathways.

Following the successful implementation of the ERAS program, the next step is to evaluate its sustainability. Once the initial implementation challenge is overcome, the focus shifts to maintaining these innovations and preventing a return to previous practices. Glissen et al. assessed the sustainability of an ERAS protocol in colonic surgery across 10 hospitals, revealing a common trend of decreasing compliance with the new protocols over time [23]. However, this decline doesn't necessarily correlate with poorer outcomes [23]. Thus, it's crucial to institute continuous monitoring and feedback mechanisms to sustain the improvements, while also regularly reviewing compliance [24]. Moreover, ongoing challenges must be openly addressed with all stakeholders, including floor nurses, trainees, surgeons, anesthesiologists, and other allied health professionals, to effectively adapt and uphold the protocols. This can be especially challenging once the initial phase of the quality project comes to an end.

Thus, continually auditing and re-assessing what is working (or not working) for patients is an important aspect of an ERAS

program to ensure continued success and to inform future directions. In addition to assessing current compliance with auditing, discussing challenges with and educating floor nurses, learners, surgeons, anesthesiologists, and other allied health professionals could be an effective means to addressing implementation and maintenance issues with ERAS protocols and an area of future research.

## 5 | Limitations

This is a retrospective study on a relatively small cohort of patients. Due to its retrospective nature, chart review of compliance variables had several missing data points. As the post-ERAS group was possibly more likely to record these variables in the chart, this could bias the percent compliance rate to the post-ERAS group. This retrospective setting also makes it difficult to control for all confounding variables. Lastly, due to these limitations, this data may not be generalizable to all CRS/HIPEC sites or patients.

## 6 | Conclusion

This study shows that the implementation of a patient-centered ERAS program for CRS/HIPEC is safe and can lead to significant reductions in LOS. ERAS programs require multidisciplinary involvement and compliance at all phases of care to attain the benefits of the program.

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The authors have nothing to report.

#### Disclosure

The authors have nothing to report.

#### **Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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