

Compliance to an Enhanced Recovery After Surgery Protocol for Patients Undergoing Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy: A Cross-Sectional Study

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ABSTRACT

Background: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), has improved survival and quality of life for patients with peritoneal surface malignancies. ERAS has been proven to be safe while still maintaining acceptable outcomes for these patients. In the Philippine setting, no data has reported on the outcomes and compliance rates of an ERAS protocol for patients undergoing CRS with HIPEC.

Objective: To determine compliance rates of patients and the ERAS Multidisciplinary (MDT) members in the implementation of ERAS for CRS with HIPEC.

Research Design: Cross-sectional study design.

Methods: Data of patients who underwent CRS with HIPEC were obtained from the patient information systems of the PGH. The 12-page ERAS Clinical Pathway Checklist was used. The checklist was digitally recorded in the ERAS® Interactive Audit System (EIAS), a web-based data entry and analysis system for analysis and interpretation.

Patient criteria: All patients aged 18 years old and above enrolled in ERAS who underwent CRS with HIPEC from January 1, 2019 to December 31, 2022.

Intervention: Application of the ERAS protocol components for patients undergoing CRS with HIPEC.

Outcomes: Primary outcome is compliance rates. Secondary outcomes are length of stay, length of ICU stay, post-operative course, readmission rates, and 30-day mortality and morbidity rates

Results: A total of 27 CRS HIPEC patients were enrolled under the ERAS protocol from 2019 to 2022. The team's compliance rate perioperatively for patients who underwent CRS HIPEC enrolled in ERAS was 43.9%. The median LOS was 8 days with a median ICU stay of 1 day and postoperative length of stay at a median of 6 days. Readmission rate was 11.1%. Morbidity rate was 37% and mortality rate at 3.7%.

Conclusion: ERAS is a promising adjunct in CRS with HIPEC as it has acceptable outcomes and did not increase the hospital LOS, ICU stay and complication rate.

Key words: ERAS, CRS, HIPEC, Compliance

The introduction of Enhanced Recovery After Surgery (ERAS) and its incorporation to surgical management has led to improved clinical outcomes when compared to traditional care.¹ Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), on the other hand, along with improvements in systemic chemotherapy has improved the quality of life for patients with peritoneal surface malignancies. In a study by McQuellon, 62.5% of patients rated their health following CRS with HIPEC as excellent, and 76% said life satisfaction was better after having the treatment.²

CRS with HIPEC is now being done globally, albeit with varied indications, protocols and techniques due to the possible differences in the volume of peritoneal carcinomatosis or organ involvement from one patient to another. Intraperitoneal chemotherapy also differs depending on the primary cancer diagnosis that a patient has. Likewise, some institutions prefer the closed technique, while others prefer the open or colosseum technique in doing HIPEC.³ Regardless, ERAS in patients who underwent CRS with HIPEC despite the different regimens has been proven to reduce overall intravenous fluid use, postoperative narcotic use, complication rates and hospital length of stay (LOS).⁴

CRS with HIPEC varies widely from resection of a single peritoneal nodule to complete peritonectomy along with multiple organ resections.⁵ Studies have also shown higher pain scores, higher peritoneal fluid drainage, higher risk of metabolic derangements and higher nasogastric tube outputs in patients undergoing CRS necessitating prolonged hospital and even intensive care unit (ICU) stay.^{6,7,8} In patients who undergo CRS with HIPEC, ERAS has been proven to be safe while reducing narcotic use, overall intravenous (IV) fluids use, complication rates and hospital LOS.^{4,9,10}

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Currently, the Philippine General Hospital (PGH) is the only government hospital with the distinction of being an ERAS Center of Excellence in our country. While the PGH Division of Colorectal Surgery has implemented the ERAS protocol to patients undergoing colon or rectal surgery, its introduction to patients undergoing CRS with HIPEC is still in its early stages. Certain specific components in the ERAS protocol, such as early or avoidance of peritoneal drains, early removal of urinary catheters, or early return to mobilization, have been found to be difficult to adhere to in patients who underwent CRS with HIPEC due to the procedure's complexity and known possible post-operative effects. Due to these issues, there is no data that reports on the outcomes and compliance with the implementation of an ERAS protocol for patients undergoing CRS with HIPEC.

The authors therefore aimed to determine the compliance rates of both patients and the ERAS Multidisciplinary Team (MDT) members in the implementation of an ERAS protocol for CRS with HIPEC. The study also aimed to determine the short-term outcomes among patients who underwent CRS with HIPEC in terms of total hospital LOS, length of ICU stay, post-operative LOS, readmission rates, 30-day morbidity rates and 30-day mortality rates.

General Objective

To determine the compliance rates of patients and ERAS MDT members in the implementation of an ERAS protocol for CRS with HIPEC.

Specific Objectives

1. To determine the compliance rates of patients who underwent CRS with HIPEC using the ERAS clinical pathway checklist.
2. To determine the compliance rates of the ERAS MDT members who handled CRS with HIPEC patients perioperatively using the ERAS clinical pathway checklist.
3. To assess short-term outcomes among patients who underwent CRS with HIPEC in terms of overall hospital LOS, length of ICU stay, post-operative LOS, readmission rates, 30-day morbidity rates and 30-day mortality rates.

METHODS

Through a cross-sectional study design, data of patients enrolled under the ERAS protocol pathway and underwent CRS with HIPEC were obtained from

Integrated Surgical Information System (ISIS) and patient information systems under PGH Department of Surgery and the PGH Registry of Admissions and Discharges (RADISH) from January 1, 2019 to December 31, 2022. The 12-page ERAS Clinical Pathway Checklist that was used for each patient was gathered and checked by the investigators. This checklist is an in-house form used to guide surgical trainees on the components of ERAS and how to comply with these. The checklist was then digitally recorded in ERAS® Interactive Audit System (EIAS), a web-based data entry and analysis system used to facilitate implementation and to monitor compliance with the ERAS protocols. The compliance of the patients and ERAS MDT members digitally recorded in the EIAS were collected and analyzed by the investigators.

All patients, 18 years and above enrolled in ERAS and underwent CRS with HIPEC at PGH from January 1, 2019 to December 31, 2022 were included in the study. Patients who were under 18 years old, not enrolled under the ERAS protocol, or those who did not undergo HIPEC after CRS were not included in the study. The sample size was computed based on the compliance rates of patients undergoing ERAS in our institution. The protocol was submitted to UPMREB with sample size estimation done prior to approval and implementation of the study (UPMREB CODE: 2023-0701-01).

All components, particularly 1) no oral bowel preparation unless appropriate, 2) preoperative oral carbohydrate treatment, 3) preoperative sedative medication, 4) thromboembolism prophylaxis, 5) antibiotic prophylaxis before incision, 6) postoperative nausea and vomiting (PONV) prophylaxis administered, 7) alcohol cessation, 8) smoking cessation, 9) no epidural or spinal used unless applicable, 10) spinal adjunct for general anesthesia, 11) nerve blocks or local anesthesia, 12) no long-acting systemic opioids given, 13) forced-air heating cover used, 14) no nasogastric tube (NGT) used postoperatively, 15) no resection site drainage unless applicable, 16) time to termination of urinary drainage less than 24 hours, 17) stimulation of gut motility, 18) postoperative epidural used if applicable, 19) balanced fluids day 0, 20) weight change on postoperative day 1, 21) duration of IV fluid infusion, 22) energy intake on day of surgery, 23) energy intake on postoperative day 1, 24) mobilization on postoperative days 1 to 3, and 25) 30-day follow up performed on the ERAS protocol were analyzed for compliance of the patients and ERAS MDT members.

The short-term outcome measures particularly overall hospital LOS, length of ICU stay, postoperative LOS, readmission rates, 30-day morbidity rates, and 30-day mortality rates were also obtained through EIAS.

A descriptive analysis was done based on the data gathered. The summary statistics for the study variables are reported as means and ranges for continuous variables, and as frequencies and percentages for categorical variables.

RESULTS

A total of 27 patients were enrolled under the ERAS protocol from January 1, 2019 to December 31, 2022. There were 20 female and 7 male patients. The average age of the patients was 55.2 years old, with the oldest being 72 years old. Fourteen of the 27 patients had an appendiceal neoplasm as the primary diagnosis, 7 had gynecologic malignancy, 4 had colon or rectal cancer, 1 had pancreatic malignancy, and 1 had a retroperitoneal sarcoma (Table 1).

Table 1. Demographic data and diagnoses of patients undergoing CRS with HIPEC under the ERAS protocol, UP-PGH Department of Surgery, Division of Colorectal Surgery, 2019 – 2022.

Characteristics	Result N=27
Age (Mean, Range)	55.2 years (37-72)
Gender	
Male:Female	7:20
ASA Classification	
1	0
2	18
3	9
4	0
Diagnosis	
Appendiceal neoplasm	14
Cancer of the colon or rectum	4
Gynecological malignancy	7
Others:	2
Pancreatic malignancy	1
Retroperitoneal sarcoma	1

The MDT members' compliance rate perioperatively was 43.9 percent. Compliance was highest in the preoperative phase (77.7%). Intraoperative phase compliance was 40.8 percent, while postoperative phase compliance was 30.0 percent (Table 2). There was poor compliance (<50%) with the following

components: thromboembolism prophylaxis, no epidural or spinal used unless applicable, no resection-site drainage unless applicable, postoperative epidural used if applicable, balanced fluids day 0, duration of IV fluid infusion (nights), energy intake on day of surgery, postoperatively, energy intake on postoperative day 1, mobilization on postoperative day 1, mobilization on postoperative day 2 and mobilization on postoperative day 3 (Figure 1).

Table 2. Compliance rate of patients undergoing CRS with HIPEC under the ERAS protocol, UP-PGH Department of Surgery, Division of Colorectal Surgery, 2019 – 2022.

Characteristics	Result (N=27)	
	(n)	(%)
Perioperative Compliance Rate	12/27	43.9%
Preoperative Phase	21/27	77.7%
Intraoperative Phase	11/27	40.8%
Postoperative Phase	8/27	30.0%

The median overall hospital LOS was 8 days (average = 9.6 days; range = 5 to 16 days) with a median ICU stay of 1 day (average day 0.6; range = 1 to 3 days) and postoperative LOS at a median of 6 days (average= 7.4 days; range = 4 to 14 days). ICU stay following CRS with HIPEC is not mandatory in our institution. Should patients be stable throughout the surgical procedure with good point of care laboratory results, they can be monitored in a regular room. The variation of ICU LOS is due to some patients requiring more than a day of management based on their laboratories, most notably electrolyte imbalances or a need for transfusion of blood components postoperatively. Readmission rate was 11.1 percent. Readmissions were primarily due to electrolyte abnormalities requiring intravenous correction, intravenous antibiotic treatment of pneumonia, or work-up and medical management of chemotherapy induced cardiomyopathy. The morbidity rate was 37 percent, majority of which was due to postoperative ileus (15%) and all of which were classified as Clavien-Dindo II surgical complications. There was one mortality (3.7%) due to congestive heart failure (Table 3).

DISCUSSION

Peritoneal surface malignancies have long been regarded as end-stage disease conditions which can



Figure 1. Components of the ERAS protocol with low compliance rates. The red bar is the percentage of the patients with poor compliance per component. Blue bars are those with good compliance. Grey bars are those with unknown compliance status. PGH, 2023

Table 3. Length of Stay (LOS) of patients undergoing CRS with HIPEC under the ERAS protocol, UP-PGH Department of Surgery, Division of Colorectal Surgery, 2019 – 2022.

Characteristic	Median	Mean	Range
TOTAL hospital LOS in days	8	9.6	5-16
ICU LOS in days	1	0.6	1-3
Postoperative LOS in days	6	7.4	4-14

only be treated with palliative management. However, modernization of surgical procedures along with improvement of delivery with chemotherapeutic agents in the peritoneal cavity have changed the landscape from treating these as terminal diseases into curable states.¹¹ Developed and described by Dr. Paul Sugarbaker, CRS involves removing all visible peritoneal and organ surface diseases. These may include peritonectomy, multiple organ resections such as cholecystectomy, splenectomy or bowel resections and omentectomy. Microscopic residual tumor cells will then be treated with HIPEC.^{12,13}

Professor Henrik Kehlet introduced ERAS as a multimodal evidence-based approach of care in 1997.¹⁴ It is designed to reduce perioperative stress, maintain postoperative physiologic function, and accelerate recovery most notably in colorectal cancer surgery.¹⁵ ERAS involves a multimodal, multidisciplinary approach in surgical patient care. It uses evidence-based strategies such as allowing carbohydrate drinks two hours before surgery, minimally invasive surgery rather than large midline incisions, goal-directed intraoperative fluid therapy, avoidance of peritoneal drains or NGT, early mobilization, and permitting eating or drinking right after surgery. Twenty-four elements have been identified by the ERAS Society that contribute to the faster recovery of patients.¹

In CRS with HIPEC, it has resulted in shorter overall hospital LOS, less complications and decreased narcotic use. Webb et al. in their paper, showed a mean LOS reduction from 10.3 days to 6.9 days and decreased complication rates from 24 percent to 15 percent. Martin et al. also showed improvement in their LOS from 11 days down to 9 days when using ERAS in CRS with HIPEC patients. Likewise, there was significant reduction in opioid use from Total Morphine Equivalents of 856 with non-ERAS patients down to 156 with ERAS patients.^{4,14} In our study, the mean total hospital LOS was 9.6 days. One of the reasons of the higher LOS may be due to the compliance rates in our hospital. Both articles were done in institutions with a longer experience with ERAS and with CRS with HIPEC – 8 and 16 years, respectively. This may have played a crucial role in decreasing LOS and complication rates in the two papers.

Wasif et al. in 2019 under the American College of Surgeons (ACS) described in their bulletin how they implemented ERAS in CRS with HIPEC patients and how it has shown to shorten LOS and reduce complication rates. In their paper, they also recommended other institutions to implement the protocol and gave tips on how to do so.¹⁰ A cross-sectional study done in India surveyed 136 clinicians

regarding ERAS in CRS with HIPEC; 95 percent agreed that it could be implemented in CRS with HIPEC patients, with 38.2 percent stating that the protocol was already implemented in the institution.¹⁵ While numerous studies have already proven the advantages and benefits of ERAS, especially in colorectal surgery, its implementation has not been achieved globally.¹⁶ ERAS has been shown to be complicated and resource-intensive, hence, difficult to adhere to in the long term.^{16,17} A multidisciplinary team approach with open-minded members is needed to overcome such obstacles.^{10,15}

The PGH started ERAS in the Department of Surgery, Division of Colorectal Surgery in 2014. MDT strategy for the ERAS protocol in the institution began in 2019 which improved compliance and outcomes as described by an unpublished paper by Jazon et al. in 2022. In 2020, the PGH was identified as an ERAS center of excellence. While this is so, the compliance rate of the hospital has been hovering at around 50 to 60 percent in patients undergoing CRS with HIPEC.

In conjunction with the 2019 ACS bulletin regarding ERAS in CRS with HIPEC, the authors will be utilizing and endorsing several of their recommendations.¹⁰ Finding a target physician lead who would be responsible for this group of patients is essential in implementing ERAS components in their individualized care. Each stakeholder (surgeon, anesthesiologist, nutritionist, oncologist, etc.) should be well represented and motivated in employing ERAS in CRS with HIPEC. Regular evaluation, feedback, and maintenance of a database may be a good strategy to find where improvements can be made at time-specific intervals. Finally, a patient information booklet should be distributed to manage the patients' expectations or disprove current misinformation; this should be updated regularly according to the latest evidence on ERAS specific to CRS with HIPEC.

This is the first documentation of incorporating the ERAS protocol and analyzing the compliance rates of the ERAS team in patients undergoing CRS with HIPEC locally. Based on the results, albeit a small sample size, ERAS in CRS with HIPEC patients seems to be a viable and recommendable adjunct to a complex treatment regimen. The morbidity and mortality rates when using ERAS point toward favorable outcomes and seem to have an impact in decreasing LOS. There is still room to improve the compliance rates of the ERAS team to further reduce hospital LOS and indirectly reduce hospital cost. Regular evaluation of the ERAS team compliance may help improve and develop strategies towards this goal.

LIMITATIONS AND RECOMMENDATIONS

As this is a retrospective cross-sectional research with a relatively small sample size, co-factors and possible confounders were not controlled. A larger scale prospective randomized controlled trial using ERAS in CRS with HIPEC patients may provide more information regarding its ability to decrease complication rates and to decrease hospital LOS. Its other benefits in multivisceral resections and complicated surgeries should be further investigated. Another aspect still in discussion is the cost-benefit analysis of using ERAS in these types of surgeries. Since global data have already shown decreased LOS and reduction of narcotic and IV fluid use,¹⁰ studies focusing on cost-benefit of ERAS for patients with complex surgeries must be done to further solidify its advantage over traditional approaches.

Lastly, strategies to improve compliance rates of ERAS MDT members for CRS with HIPEC must be investigated. These may improve outcomes and lessen complications for such an elaborate surgery.

CONCLUSION

This study showed that compliance rate for ERAS in patients undergoing CRS with HIPEC perioperatively is 43.9 percent, with the highest compliance at 77.7 percent during the preoperative phase and lowest during the postoperative phase at 30 percent. ERAS is a promising adjunct in CRS with HIPEC due to its acceptable outcomes; it did not increase the hospital LOS, ICU stay, and complication rate. Future studies should focus on increasing compliance with ERAS components for this type of procedure to further improve short-term and long-term outcomes.

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