Association between enrollment in an enhanced recovery program for colorectal cancer surgery and long-term recurrence and survival

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Abstract

Introduction: Enhanced Recovery After Surgery (ERAS) programs have been shown to minimize the surgical inflammatory response in colorectal cancer. Our objective was to determine the association between an ERAS program for colorectal cancer surgery and oncologic recurrence and survival.

Methods: A before-after intervention study was designed, including patients who underwent colorectal cancer surgery between November 2010 and March 2016. Cox hazard regression analysis was performed per cumulative year of follow-up to evaluate the association between ERAS program exposure and overall survival. Subgroup analysis was performed by cancer stage (low [I/II] vs. advanced [III/IV]).

Results: In total, 646 patients were included, of which 339 were pre-ERAS and 307 were ERAS. Our overall median compliance rate with ERAS interventions was 90\% (interquartile range: 85\%–95\%). Overall survival rates were higher in the ERAS group within the first 2 years after surgery (89.2\% vs. 83.2\%; \(p = 0.04\)). Multivariable analysis revealed that the ERAS enrollment was associated with a significantly lower risk in 5-year oncologic recurrence (adjusted hazard ratio [aHR]: 0.55; 95\% confidence interval [CI]: 0.33–0.94; \(p = 0.03\)) and higher 3-year survival (aHR: 0.55; 95\% CI: 0.33–0.93; \(p = 0.03\)) among patients with advanced cancer stage compared to pre-ERAS counterparts.

Conclusions: Patients with advanced colorectal cancer were less likely to suffer oncologic recurrence when managed during the ERAS period.

Keywords
anesthesiology, colorectal surgery, enhanced recovery after surgery, perioperative medicine
1 | INTRODUCTION

Cancer recurrence increases patient morbidity and represents a significant economic burden for health care systems. Although significant advancements have been made in surgical care and associated therapy, recurrence rates are still high depending on the quality of care provided during cancer surgery. Literature has shown that multidisciplinary perioperative care models facilitate early recovery and hasten the return to indicated medical oncologic therapy, which may reduce cancer recurrence following surgery and improve long-term survival. Nevertheless, there is a lack of knowledge regarding the association between specific perioperative interventions (e.g., anesthetic type, pain regimen, nutrition, rehabilitation) and long-term oncologic outcomes.

Enhanced Recovery After Surgery (ERAS) protocols involve the bundled application of evidence-based perioperative care interventions that are primarily aimed at hastening patient recovery and reducing the surgical stress response. In recent years, the ERAS Society has compiled a set of guidelines across multiple surgical specialties, all of which support the safety and efficacy of this multidisciplinary model as a standard of care to achieve better patient satisfaction, superior pain control, and lower postoperative morbidity. The current ERAS guideline for elective colorectal surgery includes a total of 24 interventions that have been shown to improve postoperative clinical outcomes. As new evidence accumulates in favor of ERAS, more research is now targeting longer term outcomes, such as survival in oncologic patients. Prior work involving patients at high risk for postoperative complications or advanced cancer stage has suggested that they benefit from care within the context of an ERAS program. Investigators have hypothesized that interventions associated with ERAS mediate this benefit by mitigating inflammation and surgical insult or through direct prevention of hospital-acquired conditions.

Unfortunately, the evidence regarding management associated with an ERAS program and cancer recurrence is still inconclusive, with a handful of studies yielding inconsistent results about the impact on survival. Our group aimed to determine the association between an ERAS program for colorectal surgery and long-term cancer recurrence and survival.

2 | METHODS

2.1 | Design

This is a retrospective, cohort study conducted in a single institution, community-based academic hospital with the same group of anesthesiologists and surgeons during the study period. The protocol for this study was approved by our institutional review board and all data were deidentified to protect confidentiality. Informed consent was waived due to the retrospective nature of this study. Two groups of patients were identified based on the period of ERAS initiation in our institution (March 2013). Patients who received conventional perioperative care underwent surgery from November 2010 through January 2013 (Pre-ERAS group). Patients who received perioperative care according to the ERAS protocol underwent surgery from March 2013 through March 2016 (ERAS group). Importantly, in the institution, we used the same guidelines, surgical techniques, and chemoradiation indications throughout the entire cohort period (from 2010 to 2016).

2.2 | Inclusion and exclusion criteria

This study included adult patients undergoing elective colorectal surgery. Emergent procedures were excluded, along with any patient who was unable or unwilling to participate in the ERAS program. In this cohort, none of the patients denied receiving perioperative care under our ERAS program.

2.3 | Variables

Demographics and clinical variables were extracted from electronic medical records. Colorectal cancer was classified based on the American Joint Committee on Cancer/Dukes stages, as follows: Stage I (T1, T2, N0, M0), Stages II (T3, T4, N0, M0), Stage III (any T, N1, N2, M1), and Stage IV (distant metastasis).

2.4 | Outcomes

Our primary outcome was overall 5-year survival, which was defined as the living or deceased status after surgical treatment. Time to death was also recorded for the purpose of the analysis. This was assessed through hospital and primary care medical records. It was classified into three categories, including postoperative causes, defined as death secondary to postoperative complications occurring in the first 30 days after surgery; oncologic causes, defined as secondary to tumor progression despite planned curative surgical treatment; and other causes, defined as those not due to tumor progression or postoperative, not related to disease (i.e., accident or other illness). Two researchers reviewed all medical records to ensure adequate follow-up.

Oncologic recurrence was defined as the identification of a tumor mass consistent with primary cancer in any part of the body after surgery or any treatment modality with curative intent. This was typically performed through active surveillance based on the cancer stage I—an annual colonoscopy; II/III/IV—clinical review at least every 6 months during the first 3 years and annually until the fifth year with carcinoembryonic antigen, chest X-ray and abdominal ultrasound, and annual colonoscopy were performed). The time to the first recurrence was also recorded.

2.5 | Statistical analysis

An initial exploratory analysis was performed using descriptive statistics. The univariate analysis compared demographics and clinical
variables between pre-ERAS and ERAS periods. Kaplan–Meier curves were plotted along with log-rank p values to identify potential differences in time to mortality events or recurrence events between both periods. Cox hazard regression analysis was performed at each year of follow-up to evaluate the association between ERAS program enrollment and overall survival, cancer-related mortality, and oncologic recurrence. Certain clinically relevant confounders (i.e., age, American Society of Anesthesiologists, cancer stage, and comorbidities) were included in the multivariable survival analysis. Hazard ratios (HRs) were reported along with their corresponding 95% confidence intervals (CIs). Kaplan–Meier curves were constructed. We performed parametric survival analysis using Weibull distribution in those cases where the Cox assumptions were violated. Survival rates and oncologic recurrence were also evaluated in subgroup analysis based on cancer stage (low [I/II] vs. advanced [III/IV]). p < 0.05 was considered significant for all analyses. Additionally, mediation analyses were conducted including factors (i.e., surgical time [>2 h, median], liberal fluid therapy [>2 L, median], type of anesthesia [propofol vs. inhaled]) that may potentially explain the effect of ERAS on mortality or cancer recurrence. This additional analysis was only performed when there was a statistically significant effect. The descriptive and mediation analyses were done in Stata 14.0 (StataCorp), and the survival analysis was conducted in the R Stats Package (Statistical Computing).

3 | RESULTS

3.1 | Patient characteristics

In total, 646 patients were included, of which 339 were pre-ERAS and 307 ERAS. Our overall median compliance rate with the ERAS protocol was 90% (interquartile range [IQR]) 85%–95%. There was a greater proportion of female patients in the ERAS period (42% vs. 32%; p = 0.03). The remainder of baseline demographic and clinical characteristics were comparable between periods (Table 1). Patients enrolled in the ERAS program had shorter surgical times (119 vs. 140 min; p < 0.01), received more total intravenous anesthetics (24.7% vs. 13.9%; p < 0.01), fewer epidurals (10.2% vs. 21.0%; p < 0.01), and less perioperative fluid (1970 vs. 2183 ml; p < 0.01) compared to pre-ERAS counterparts. None of the patients was lost over the 5-year follow-up period.

3.2 | Survival analysis

There was no difference in overall 5-year survival between groups (71.5% ERAS vs. 73.3% pre-ERAS; p = 0.31). Survival rates were greater at year 1 (94.8% ERAS vs. 89.8% pre-ERAS; p = 0.02) and year 2 (89.2% ERAS vs. 83.2% pre-ERAS; p = 0.04) in the ERAS group, but no difference was detected thereafter. Overall survival was associated with ERAS in year 1 (adjusted hazard ratio [aHR]: 0.40; 95% CI: 0.22–0.73; p = 0.003) through year 2 (aHR: 0.57; 95% CI: 0.37–0.88; p = 0.01) of the study follow-up period (see Supporting Information). Kaplan–Meier curves of each year epoch are illustrated in Figure 1. Only 616 patients were included in the survival Cox regression analysis due to missing data (323 of which were pre-ERAS and 293 were ERAS). There was no difference in the proportion of cancer-related deaths (15% ERAS vs. 17% in pre-ERAS; p = 0.35) and survival time was not statistically different (median 2.3 years [1.7–3.3] ERAS vs. median 2.1 years [1.1–3.8] pre-ERAS; p = 0.61).

Univariate analysis of patients who died, recurred, and were disease-free is presented in Table 2. Disease-free 5-year survival did not differ between groups (66% ERAS vs. 60% pre-ERAS; p = 0.14), but it was significantly higher in the ERAS group compared to conventional care among patients with advanced cancer stage (58% ERAS vs. 39% pre-ERAS; p < 0.01). While there was no difference in disease-free 5-year survival between groups among low cancer stage (aHR: 1.11; 95% CI: 0.74–1.67; p = 0.59), multivariable analysis showed that advanced cancer stage patients who were enrolled in ERAS had better disease-free 5-year survival (aHR: 0.53; 95% CI: 0.36–0.77; p < 0.01) compared to conventional care counterparts.

3.3 | Subgroup analysis

We stratified our analysis by cancer stage. Although low cancer stage did not reveal an association with survival at 5 years of follow-up (77% ERAS vs. 83% pre-ERAS; p = 0.13), patients with advanced cancer stage who were enrolled in ERAS experienced a statistically significantly higher 5-year overall survival (67% vs. 55%; p = 0.05) compared to those who received conventional care. An extended association of ERAS and lower mortality was confirmed among patients with advanced cancer stage via multivariable analysis in year 1 (aHR: 0.20; 95% CI: 0.07–0.58; p = 0.003) and year 3 (aHR: 0.53; 95% CI: 0.33–0.83; p = 0.025) of the study follow-up period (Figure 2). The results of the multivariable Cox regression model are described in detail in the Supplemental Information. It is worth mentioning that the subset of the low cancer stage violated fundamental Cox assumptions; thus, we used parametric survival analysis using Weibull distribution. There were differences in survival rates at any point among patients with low cancer stages (I/II). Subgroup analysis demonstrated an effect modification as shown in Table 3. Mediation analysis showed that a lower surgical duration (<2 h) contributed to 32.6% of the effect of ERAS on mortality at 2 years, while total intravenous anesthesia (propofol) and restrictive fluid therapy (<2 L) contributed 24.6% and 14.9%, respectively.

3.4 | Oncologic recurrence

Overall recurrence rates (17% ERAS vs. 21% pre-ERAS; p = 0.31) as well as time to recurrence (median 1.56 years [0.9–2.0] ERAS vs. median 1.15 years [0.5–2.4] pre-ERAS; p = 0.15) was similar. Subgroup analysis revealed that patients with advanced cancer stage experienced lower oncologic recurrence (22% in ERAS vs. 32% in
pre-ERAS; \( p = 0.05 \), a result that was confirmed after adjusting for potential confounders (aHR: 0.53; 95% CI: 0.32–0.89; \( p = 0.02 \)). There was no difference in recurrence rates among patients with low cancer stage (aHR: 1.02; 95% CI: 0.57–1.80; \( p = 0.95 \)). The results of the multivariable Cox regression model are described in detail in the Supporting Information. Mediation analysis for the effect in advanced cancer stages showed that a lower surgical duration (<2 h) contributed to 43.2% of the effect of ERAS on cancer recurrence, while total intravenous anesthesia and restrictive fluid therapy (<2 L) contributed 27.3% and 15.6%, respectively.

| Variables                  | Overall (n = 646) | Pre-ERAS (n = 339) | ERAS (n = 307) | \( p \) value |
|----------------------------|-------------------|-------------------|----------------|--------------|
| Age                       | 73 [63–80]        | 72 [62–79]        | 74 [64–80]     | 0.15         |
| Female                    | 233 (36.4%)       | 109 (32.5%)       | 124 (40.7%)    | 0.03         |
| BMI (kg m\(^{-2}\))       |                   |                   |                |              |
| \( \leq 18.5 \)            | 3 (0.5%)          | 2 (0.9%)          | 1 (0.5%)       | 0.24         |
| 18.5–25                   | 108 (16.7%)       | 47 (13.9%)        | 61 (19.9%)     |              |
| 25–30                     | 217 (33.6%)       | 119 (35.1%)       | 98 (31.9%)     |              |
| \( \geq 30 \)             | 123 (19.0%)       | 60 (17.7%)        | 63 (20.5%)     |              |
| Missing                   | 195 (30.2%)       | 111 (32.7%)       | 84 (27.4%)     |              |
| ASA                       |                   |                   |                | 0.08         |
| I                         | 53 (8.3%)         | 32 (9.6%)         | 21 (6.9%)      |              |
| II                        | 360 (56.3%)       | 189 (56.4%)       | 171 (56.1%)    |              |
| III                       | 217 (33.9%)       | 112 (33.4%)       | 105 (34.4%)    |              |
| IV                        | 9 (1.4%)          | 1 (0.3%)          | 8 (2.6%)       |              |
| Anemia                    | 302 (46.7%)       | 159 (46.9%)       | 143 (46.6%)    | 0.94         |
| Albumin                   | 4 [3.5–4.3]       | 4 [3.5–4.3]       | 4 [3.4–4.3]    | 0.11         |
| Hypertension              | 383 (59.8%)       | 192 (57.3%)       | 191 (62.6%)    | 0.17         |
| Diabetes                  | 163 (25.5%)       | 86 (25.7%)        | 77 (25.3%)     | 0.90         |
| COPD                      | 96 (15.0%)        | 55 (16.4%)        | 41 (13.4%)     | 0.29         |
| Kidney disease            | 58 (9.1%)         | 34 (10.2%)        | 24 (7.9%)      | 0.32         |
| Cirrhosis                 | 61 (9.5%)         | 37 (11.0%)        | 24 (7.9%)      | 0.17         |
| Surgery time              | 125 [99–167]      | 140 [110–180]     | 119 [90–145]   | <0.01        |
| Epidural                  | 101 (15.8%)       | 70 (21.0%)        | 31 (10.2%)     | <0.01        |
| Anesthesia                |                   |                   |                | <0.01        |
| Inhaled                   | 514 (80.9%)       | 285 (86.1%)       | 229 (75.3%)    |              |
| Intravenous               | 121 (19.1%)       | 46 (13.9%)        | 75 (24.7%)     |              |
| Fluid balance             | 2351 [1302–3393]  | 2783 [1687–3658]  | 1970 [1049–2873] | <0.01 |
| Conversion                | 31 (4.8%)         | 16 (4.8%)         | 15 (4.9%)      | 0.93         |
| Stoma                     | 122 (19.1%)       | 67 (20.0%)        | 55 (18.0%)     | 0.53         |
| Cancer stage              |                   |                   |                | 0.14         |
| In situ                   | 114 (18.5%)       | 68 (20.9%)        | 46 (15.8%)     |              |
| I                         | 114 (18.5%)       | 55 (16.9%)        | 59 (20.2%)     |              |
| II                        | 154 (25.0%)       | 80 (24.7%)        | 74 (25.3%)     |              |
| III                       | 160 (25.9%)       | 76 (23.5%)        | 84 (28.8%)     |              |
| IV                        | 74 (12.0%)        | 45 (13.9%)        | 29 (9.9%)      |              |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ERAS, Enhanced Recovery After Surgery.
DISCUSSION

The results of this study found several important associations between care administered through an ERAS program and survival after colorectal surgery. First, we did not detect a difference in overall survival, disease-free survival, or oncologic recurrence at 5 years. However, subgroup analysis revealed an association between ERAS program enrollment and survival, and disease-free survival and oncologic recurrence among patients with advanced cancer stage compared to those who received conventional care. These associations remained statistically significant after adjustment for a number of potential confounders. These findings suggest that care administered through an ERAS program may impact not only immediate postoperative rates of recovery as demonstrated in previous studies but potentially play a role in longer term outcomes after curative surgical resection.

Our findings align with previous studies that have shown improved survival rates associated with ERAS. Lohsiriwat et al. conducted a similar cohort study and showed ERAS was associated with improved survival among a subgroup of patients with stage III cancer. Additionally, high compliance (>70%) with an ERAS program has been correlated with better 5-year survival rates in advanced stages of cancer, but not at 3 years of study follow-up. Quiram et al. found a statistically significant association between ERAS and overall survival, but no relationship was detected for disease-free survival. As shown, our study demonstrated a significant improvement in both overall and disease-free survival rates among patients with advanced initial cancer stage.
### TABLE 2 Univariate analysis of clinical variables for oncologic recurrence and 5-year survival

| Variable | Disease-free survivors | Affected patients | Deaths |
|----------|------------------------|-------------------|--------|
|          | (n = 375)              | (n = 123)         | (n = 176) |
| Age      |                        |                   |        |
| Female   | 156 (41.6%)            | 33 (26.6%)        | 47 (27.8%) |
| BMI (< 18.5) | 3 (1.2%)             | 0 (0%)            | 0 (0%)  |
|          | 18.5–25                | 57 (21.9%)        | 20 (16.2%) |
|          | 25.1–30                | 126 (48.5%)       | 41 (33.3%) |
|          | >30                    | 74 (28.5%)        | 17 (13.8%) |
| Missing  | 115 (30.7%)            | 45 (36.6%)        | 53 (30.1%) |
| ASA      |                        |                   |        |
| I        | 36 (9.3%)              | 11 (8.9%)         | 7 (3.9%) |
| II       | 238 (63.5%)            | 64 (52.0%)        | 72 (40.9%) |
| III      | 100 (26.7%)            | 47 (38.2%)        | 85 (48.3%) |
| IV       | 1 (0.1%)               | 1 (0.8%)          | 5 (2.8%) |
| Missing  | 4 (0.1%)               | 0 (0%)            | 7 (3.9%) |
| Anemia   | 156 (41.6%)            | 63 (51.2%)        | 106 (60.2%) |
| Albumin  | 4.1 [3.7–4.4]          | 4 [3.6–4.2]       | 3.7 [3.1–4.2] |
| Hypertension | 218 (58.1%)         | 76 (61.8%)        | 111 (65.7%) |
| Diabetes mellitus | 88 (23.5%)        | 41 (33.3%)        | 52 (30.8%) |
| COPD     | 45 (12.0%)             | 18 (14.6%)        | 37 (21.9%) |
| CKD      | 26 (6.9%)              | 10 (8.1%)         | 24 (14.2%) |
| Cirrhosis| 33 (8.8%)              | 10 (8.1%)         | 17 (10.1%) |
| Surgery time | 122 [95–159]          | 131 [106–170]    | 131 [106–179] |
| Epidural | 50 (13.4%)             | 20 (16.3%)        | 32 (18.9%) |
| Anesthesia |                        |                   |        |
| Inhaled  | 307 (82.3%)            | 104 (85.3%)       | 136 (80.9%) |
| Intravenous | 66 (17.7%)            | 18 (14.8%)        | 32 (19.1%) |
| Missing  | 2 (1.0%)               | 1 (0.8%)          | 8 (4.5%) |
| Fluid balance (ml) | 2226 [1245–32-69] | 2648 [1761–3-528] | 2844 [1693–38-85] |
| Conversion | 17 (4.5%)             | 8 (6.5%)          | 8 (4.7%) |
| Stoma    | 57 (15.2%)             | 29 (23.6%)        | 44 (26.0%) |
| Cancer stage |                     |                   |        |
| In situ  | 83 (23.1%)             | 8 (6.5%)          | 18 (10.2%) |
| I        | 86 (23.9%)             | 9 (7.3%)          | 22 (12.5%) |
| II       | 95 (26.5%)             | 36 (29.3%)        | 33 (18.8%) |
| III      | 77 (21.5%)             | 45 (36.6%)        | 48 (27.3%) |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

†p < 0.05 compared with patients who died or recurred.
‡p < 0.05 compared with patients who recurred.
§p < 0.05 compared with patients who survived.

There are several reasons to suspect that interventions included within an ERAS program may positively influence survival rates after surgery. In a recent trial, prehabilitation was associated with improved 5-year disease-free survival in patients undergoing colorectal surgery. Minimally invasive surgical technique, evaluated in a recent meta-analysis, was shown to yield better survival compared to an open approach following colorectal cancer resection. Fluid therapy optimization may also be contributing to better survival rates within ERAS according to the results presented by Askild et al., who demonstrated that restrictive perioperative fluid therapy (≤3000 ml on the day of surgery) is associated with a 55% increase in 5-year survival. A number of other observational trials have identified an association between certain anesthetics, analgesics (i.e., neuraxial), reduced opioid administration and subsequent cancer recurrence and rates of survival. According to the patients with colorectal cancer after surgery (PACO-RAS) trial, peridural analgesia, as part of a multimodal regimen, may be associated with improved survival, although similar attempts to reproduce those results have yielded conflicting results. It is feasible that incremental gains provided by several interventions are shown to reduce inflammation and prevent immunosuppression associated with surgical insult, with the net effect potentially being long-term reductions in cancer recurrence and improved survival.

ERAS programs are associated with fewer postoperative complications (e.g., ileus, anastomotic leak, surgical site infections), which may underpin short-term benefits. Our program previously demonstrated that interventions were associated with reduced moderate and severe complications compared to conventional care. This may have influenced survival within the first 2 years. However, our analysis also revealed an association between ERAS and lower cancer-related deaths and oncologic recurrence. As theorized previously, this can be explained either through reduced surgical insult or through associated inflammation. For instance, Cabellos Olivares et al. noted a reduced systemic inflammatory response as indicated by C-reactive protein after implementing ERAS in colorectal surgery. Venera et al. observed less expression of arachidonic acid metabolism in patients managed with ERAS protocols, particularly a reduction in microsomal prostaglandin E synthase and hematopoietic prostaglandin D synthase. Jaloun et al. identified lower...
neutrophil/lymphocyte ratios in patients treated under ERAS protocols compared to conventional care. An alternative therapy altogether may be that faster recovery leads to the hastened ability to undergo subsequent intended oncologic therapy, which may be particularly true for patients with advanced cancer stage (III/IV), who experienced the greatest improvement in survival with ERAS implementation.

This study has several important limitations, including its retrospective design, which obviously precludes establishing causality. Although we attempt to address relevant confounders, we cannot exclude the potential for unmeasured or uncaptured variables that may impact the analysis. Unfortunately, data regarding metastatic disease and relevant neoadjuvant therapy is not available, which prevents us from evaluating for an association between subsequent oncological therapy and overall rates of recurrence and survival. However, the selection criteria for adjuvant and neoadjuvant therapy did not differ between study periods, and with the exception of gender, the patients had comparable demographic and clinical characteristics.

### 5 | CONCLUSION

Although enrollment was not associated with a difference in survival at 5 years after surgery, patients who received perioperative care within an ERAS program with advanced colorectal cancer did have improved survival and a lower likelihood of oncologic recurrence compared to conventional care. These findings should be considered hypothesis-generating and large, prospective trials designed to assess for cancer recurrence and long-term survival are necessary to confirm these results.

### CONFLICT OF INTERESTS

Michael C. Grant receives salary support from the Agency for Healthcare Research and Quality (AHRQ; HHSP233201500020I) and serves on the Executive Board of the ERAS Cardiac Society. Gabriel E. Mena has an academic grant from Pacira Pharmaceuticals. Javier Ripolles-Melchor receives honoraria as a consultant for Edwards Lifesciences and Fresenius Kabi. All other authors have no conflict of interests.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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