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, leading to early patient recovery and better postoperative outcomes. 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. During the study period the institutional criteria for adjuvant therapy remained unchanged and all patients were followed up for 5 years. Cox hazard regression analysis was performed per cumulative year of follow up to evaluate the association between ERAS program exposure and overall survival, cancer-related mortality, and oncologic recurrence. Subgroup analysis was performed by cancer stage (low [I/II] vs advanced [III/IV]).

Results

In total, 612 patients were included, of which 321 were pre-ERAS and 291 ERAS. Our overall median compliance rate with ERAS interventions was 90% (IQR 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), but there was no difference at 5-year follow up (73.3% vs 72.5%, P=0.82). Subgroup analysis revealed the ERAS enrollment was associated with a significantly lower risk in 5-year oncologic recurrence (aHR 0.55, 95%CI 0.33-0.94, P=0.03) and higher 4-year survival (aHR 0.59, 95%CI 0.37-0.93, P=0.02) 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. Additional prospective trials are necessary to determine causation and identify best practice principles associated with long-term recurrence and survival.

Key Points

- It is unknown whether Enhanced Recovery Programs (ERPs) are associated with cancer recurrence and survival.
- This retrospective study revealed improved survival within the first two years after colorectal cancer surgery among those who participated in an ERAS program.
- Oncological recurrence rates were significantly lower among patients with advanced colorectal cancer (III/IV) who received ERPs.

Introduction

Cancer recurrence increases patient morbidity and represents a significant economic burden for health care systems.[1] 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.[2] Literature has shown that multidisciplinary perioperative care models facilitate early recovery and hasten the return to indicated medical oncologic therapy,[3] which may reduce cancer recurrence following surgery and improve long-term survival.[4] 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.[5]

Enhanced Recovery After Surgery (ERAS) protocols involve the bundled application of evidence-based perioperative care interventions which are primarily aimed at hastening patient recovery and reducing surgical stress response.[6] In recent years, the ERAS® Society has compiled a set of guidelines across multiple surgical specialties,[7] 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.[8] As new evidence accumulates in favor of ERAS, more research is now targeting longer term outcomes, such as survival in oncologic patients.[9] 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.[10–13] Our group aimed to determine the association between an ERAS program for colorectal surgery and long-term cancer recurrence and survival.

Methods

Design

This is a retrospective, cohort study conducted in a single institution, community-based academic hospital with the same group of anesthesiologist and surgeons during the study period. The protocol for this study was approved by our institutional review board and all data was de-identified 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).

Inclusion & 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.

Variables

Demographics and clinical variables were extracted from electronic medical records. Colorectal cancer was classified based on the American Joint Committee on Cancer (AJCC) / Dukes stages,[14] as follows: Stage I (T1, T2, N0, M0), Stages II (T3, T4, N0, M0), Stage III (any T, N1, N2, M1), Stage IV (distant metastasis).

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 3 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).

Oncologic recurrence was defined as the identification of a tumor mass consistent with the primary cancer in any part of the body, after surgery or any treatment modality with curative intent. This was typically performed through an active surveillance based on the cancer stage (I – 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, annual colonoscopy were performed). The time to first recurrence was also recorded.

Statistical Analysis

An initial exploratory analysis was performed using descriptive statistics. Univariate analysis compared demographics and clinical variables between pre-ERAS and ERAS periods. Kaplan Meier curves were plotted along with log-rank P values in order 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, ASA, cancer stage, and comorbidities) were included in the multivariable survival analysis. Hazard ratios (HR) were reported along with their corresponding 95% confidence intervals (CI). 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. The initial descriptive analysis was done in Stata 14.0 (StataCorp, College Station, TX), and the survival analysis was conducted in the R Stats Package (Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

A total of 612 patients were included, 321 of which were pre-ERAS and 291 ERAS. Our overall median compliance rate with the ERAS protocol was 90% (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 minutes, P<0.01), received more total intravenous anesthetics (TIVA; 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.

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. Kaplan Meier curves of each year epoch are illustrated in Figure 1. 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 (2.3 years [1.7-3.3] ERAS vs. 2.1 years [1.1-3.8] pre-ERAS, P=0.61).

Subgroup analysis by cancer stage demonstrated an effect modification. 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. A similar association was confirmed among patients with advanced cancer stage via multivariable analysis in year 1 (aHR 0.24, 95%CI 0.09-0.62, P=0.003) through year 4 (aHR 0.59, 95%CI 0.37-0.93, P=0.02) of the study follow up period.

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 a 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), 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.

Oncologic Recurrence

Overall recurrence rates (17% ERAS vs. 21% pre-ERAS, P=0.31) as well as time to recurrence (1.56 years [0.9-2.0] ERAS vs. 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 0.55, 95%CI 0.33-0.94, P=0.03). There was no difference in recurrence rates among patients with low cancer stage (aHR 0.96, 95%CI 0.53-1.72, P=0.89).

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, 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 outcome after curative surgical resection.

Our findings align with previous studies that have showed 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.[13] Additionally, high compliance (>70%) with an ERAS program has been correlated with better 5-year survival rates in advanced stages of cancer,[12,13] but not at 3-years of study follow up.[11] Quiram et al.[10] 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.

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.[15] 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.[16] Fluid therapy optimization may also be contributing to better survival rates within ERAS according to the results presented by Asklid et al,[17] who demonstrated that restrictive perioperative fluid therapy (≤ 3000mL 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) and reduced opioid administration and subsequent cancer recurrence and rates of survival.[18] According to the PACO-RAS trial, peridural analgesia, as part of a multimodal regimen, may be associated with improved survival,[19] although similar attempts to reproduce those results have yielded conflicting results.[20] It is feasible that incremental gains provided by several interventions shown to reduce inflammation and prevent immunosuppression associated with surgical insult, 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.[21] This may have influenced survival within the first two 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 and associated

inflammation.[22] For instance, Cabellos-Olivares et al noted a reduced systemic inflammatory response as indicated by C-reactive protein (CRP) after implementing ERAS in colorectal surgery.[23] Venara 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.[24] Jaloun et al identified lower neutrophil/lymphocyte ratios in patients treated under ERAS protocols compared to conventional care.[25] 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. Though 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 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.

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 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.

Declarations

Conflicts of interest: Michael Grant receives salary support from the Agency for Healthcare Research and Quality (AHRQ; HHSP233201500020I) and serves on the Execute Board of the ERAS Cardiac Society. Gabriel 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 competing interests.

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Tables

Table 1. Patient demographics and clinical characteristics before and after institution of an ERAS program for colorectal surgery

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, $kg.m^{-2}$				
≤ 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%)	
≥ 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%)	

ASA: American Society of Anesthesiologists, COPD: chronic obstructive pulmonary disease.

Table 2. Univariate analysis of clinical variables for oncologic recurrence and 5-year survival

Variable	Disease-Free Survivors (n=239)	Affected Patients	
		Recurrence (n=123)	Deaths (n=176)
Age	71 [61-79] *	74 [63-79] †	77 [70-82] ‡
Female	64 (27.6%)	33 (26.8%)	47 (27.8%)
BMI, $kg.m^{-2}$			
≤ 18.5	0 (0%)	0 (0%)	0 (0%)
18.5 – 25	46 (12%)	20 (16.2%)	35 (19.9%)
25 – 30	76 (31.8%)	41 (33.3%)	60 (34.1%)
≥ 30	39 (16.3%)	17 (13.8%)	28 (15.9%)
Missing	78 (32.6%)	45 (36.6%)	53 (30.1%)
ASA			
I	17 (7.1%)	11 (8.9%)	7 (3.9%)
II	104 (43.5%)	64 (52.0%)	72 (40.9%)
III	106 (44.4%) *	47 (38.2%)	85 (48.3%) ‡
IV	5 (2.1%)	1 (0.8%)	5 (2.8%) ‡
Missing	7 (2.9%)	0 (0%)	7 (3.9%)
Anemia	134 (56.1%)	63 (51.2%)	106 (60.2%)
Albumin	3.8 [3.2-4.2]	4 [3.6-4.2]	3.7 [3.1-4.2]
Hypertension	149 (64.2%)	76 (61.8%)	111 (65.7%)
Diabetes mellitus	70 (30.2%) *	41 (33.3%) †	52 (30.8%)
COPD	48 (20.7%) *	18 (14.6%)	37 (21.9%) ‡
CKD	28 (12.1%) *	10 (8.1%)	24 (14.2%) ‡
Cirrhosis	24 (10.3%)	10 (8.1%)	17 (10.1%)
Surgery time	130 [104-179] *	131 [106-170]	131 [106-179] ‡
Epidural	43 (18.5%)	20 (16.3%)	32 (18.9%)
Anesthesia			
Inhaled	189 (82.3%)	104 (85.3%)	136 (80.9%)
Intravenous	41 (17.8%)	18 (14.8%)	32 (19.1%)

Fluid balance	2611 [1690-3590] *	2648 [1761-3528]	2844 [1693-3885] ‡
Conversion	12 (5.2%)	8 (6.5%)	8 (4.7%)
Stoma	59 (25.4%) *	29 (23.6%)	44 (26.0%) ‡
Cancer stage			
In-situ	23 (9.6%) *	8 (6.5%) †	18 (10.2%) ‡
I	24 (10.0%) *	9 (7.3%) †	22 (12.5%) ‡
II	54 (22.6%)	36 (29.3%)	33 (18.8%)
III	71 (29.7%) *	45 (36.6%) †	48 (27.3%) ‡
IV	53 (22.2%) *	22 (17.9%) †	43 (24.4%) ‡
Unknown	14 (5.8%)	3 (2.4%)	12 (6.8%)

ASA: American Society of Anesthesiologists, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease.

*P<0.05 comparing with patients who died or recurred.

†P<0.05 comparing with patients who recurred.

‡P<0.05 comparing with patients who survived.

Figures

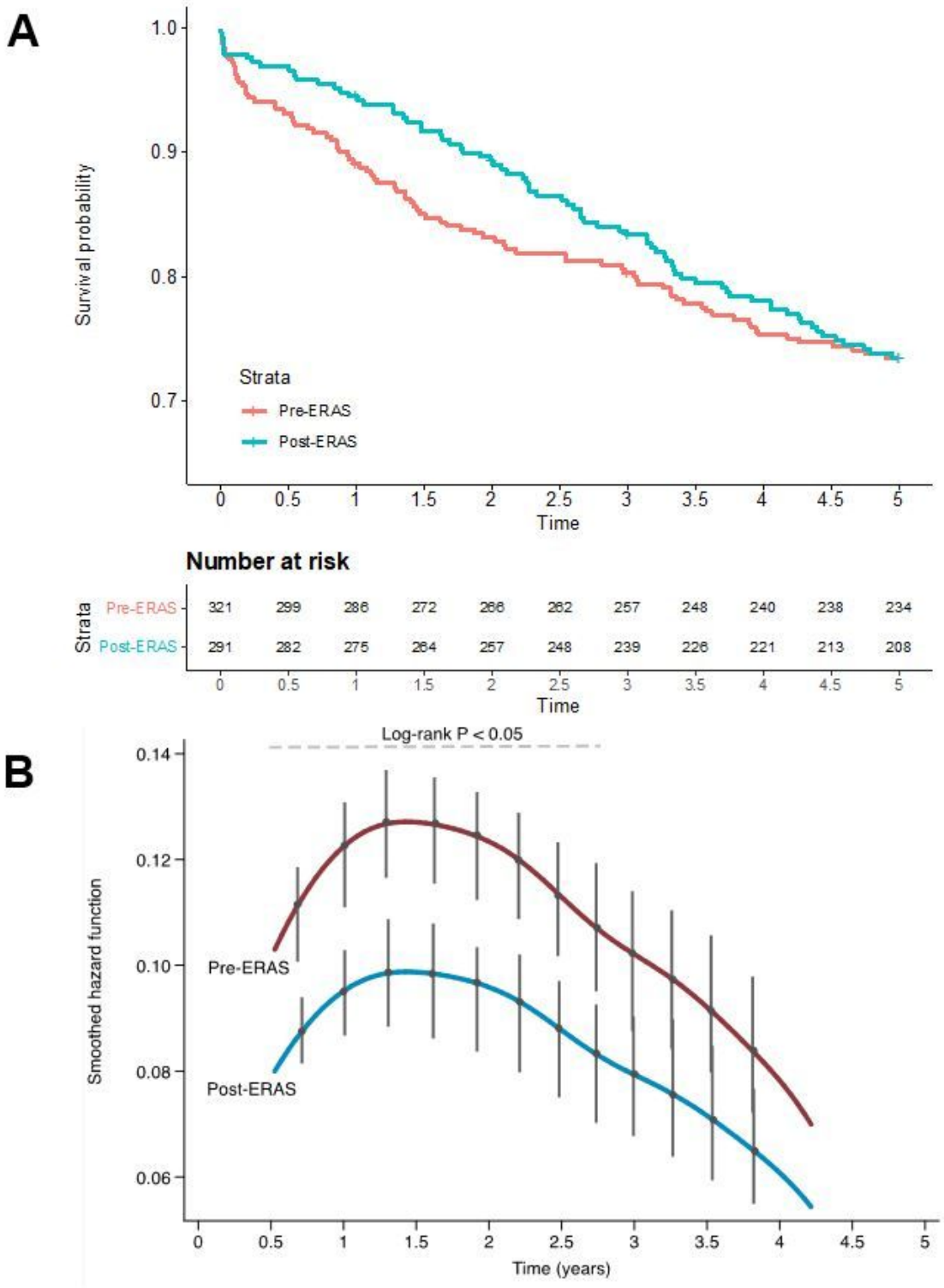

Figure 1

Survival analysis comparing pre-ERAS and ERAS. (A) Kaplan-Meier curves of each period, (B) Cox hazard function of mortality rates for each period.

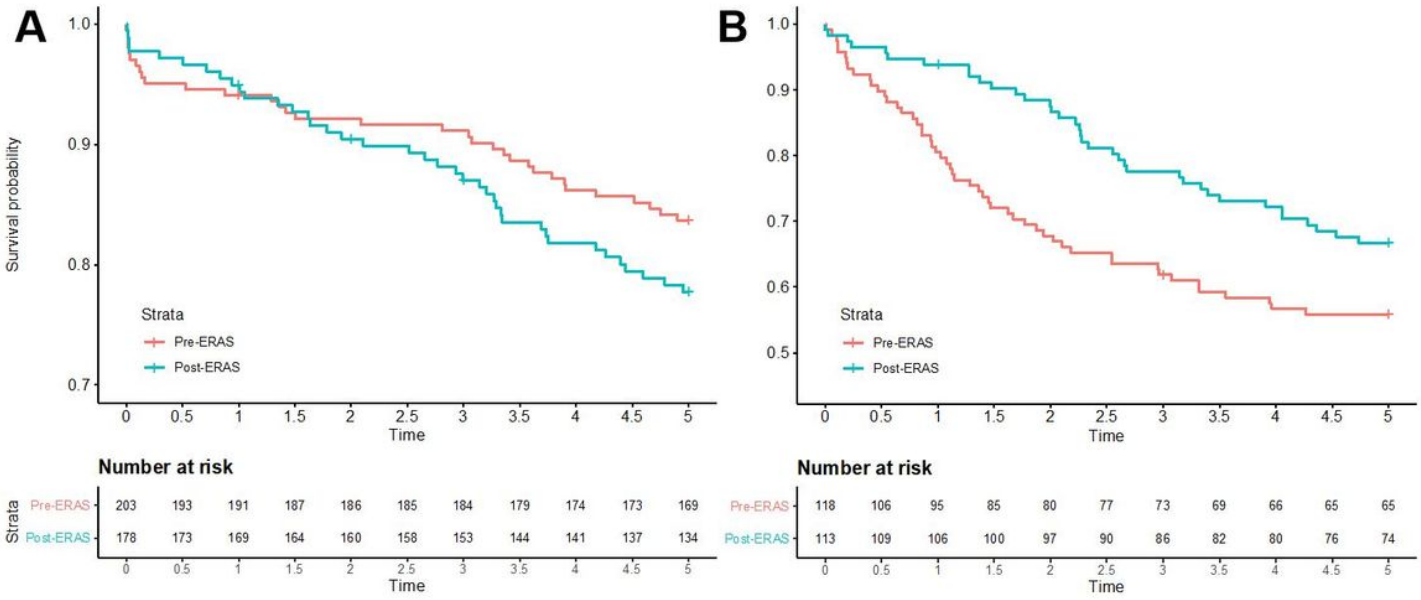

Figure 2

Subgroup analysis showing survival rates stratified based upon low cancer stage (panel A) and advanced cancer stage (panel B).