ERAS Protocol Applied to Oncological Colorectal Mini-invasive Surgery Reduces the Surgical Stress Response and Improves Long-term Cancer-specific Survival

ERAS protocol applied to oncological colorectal mini-invasive surgery reduces the surgical stress response and improves long term cancer specific survival.

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Running title

Eras decreases surgical stress response and improves cancer specific survivial

Abstract

Background

ERAS protocols are well known to reduce post-operative complications and improve short-term outcomes by minimizing the surgical stress response. Retrospective reviews of large cohorts suggest that they may also have an impact on long term oncological outcomes. In 2016, Mari et al. published a randomized trial on ERAS protocol and the impact on the SSR trough the analysis of well-known stress markers. The main finding was that IL-6 was less expresses in patients that undergo laparoscopic colorectal surgery within an ERAS protocol compared to controls. The aim of the

present study is to report the long-term oncological outcomes of oncological patients enrolled 5 years after the conclusion of the study.

Materials and methods

Patients were enrolled if they had received the indication for major colorectal surgery, aged between 18 and 80 years, with American Society of Anesthesiologists (ASA) grades I through III, autonomous for mobilization and walking, eligible for laparoscopic technique. 140 patients were enrolled and randomized into 2 groups of 70 patients each. Among these patients 52 in the EG and 53 in the SG had colorectal cancer. For them a 5-year oncological follow up according to the NCCN (16) guidelines was planned.

IL-6, C-reactive protein (CRP), prolactine, white blood cell count, albumine and prealbumine were compared between oncological patients in the EG and in the SG.

Results

EG showed lower IL-6 on postoperative day 1 (21.2 ± 9.1 vs 40.3 ±11.3; $p < 0.05$) and on day 5 (14.9 ± 6.2 vs 38.7 ± 8.9; $p < 0.05$), lower CRP on day 1 (48.3 ± 15.7 vs 89.4 ± 20.3; $p < 0.05$) and day 5 (38.3 ± 11.4 vs 74.3 ± 19.7; $p < 0.05$), and lower pre-albumine on day 5 (18.9 ± 7.2 vs 12.3 ± 6.9; $p < 0.05$) compared to SG. Median oncological follow up was 57 months [46.5-60]. There was no statistically significant difference in OS (log rank = 0.195) and DFS (Log rank = 0.089) between groups. CSS was significantly better (log rank = 0.038) in the EG compared to patients in the SG.

Conclusions

ERAS protocol applied to colorectal laparoscopic surgery for cancer is able to minimize the surgical stress response. As a possible result cancer specific survival seems to be improved in patients within enhanced protocols. However, even though there may be an association between an excess of SSR and worsen oncological outcomes, the favorable effect of ERAS protocols toward better overall and disease free survival is yet to be demonstrated.

Introduction

The phenomena that take place in the human body that undergoes a physical trauma have been studied for over 40 years(1). In particular, in response to a surgical trauma, a number of local and distant reactions compose what is known as the surgical stress response (SSR). This reaction aims to preserve and later implement the resources to help the body recover (2). The SSR follows similar pathways to a systemic inflammatory response (SIRS), with a number of up- and down-regulators that dose the response systemically. Just like SIRS, the SSR is useful yet so harmful when this mediators are overexpressed (3).

Enhanced recovery after surgery (ERAS) protocol has been established as a standard of care in colorectal surgery and is now routinely utilized in many other surgical specialties(4). ERAS protocols are well known to reduce post-operative complications and improve short-term outcomes. Retrospective reviews of large cohorts suggest that they may also have an impact on long term oncological outcomes (5-7), but the pathophysiology underneath this potential is still unknown and the level of evidence is poor.

The association between ERAS protocols and SSR has been suggested by several authors in a number of prospective trials (8-13). Even though the evidence is still low, it seems acceptable to say that ERAS protocols modulate the SSR in a way that is less harmful for a patient that undergoes surgery, (14). Nevertheless, it is still unclear which ERAS item may have an actual impact on SSR and to what extent (15), or if this modulation of the SSR provided by ERAS may have a long-term impact on oncological outcomes.

In 2016, Mari et al. published a randomized trial on ERAS protocol and the impact on the SSR trough the analysis of well-known stress markers. Their main finding was that IL-6 was less expresses in patients that undergo laparoscopic colorectal surgery within an ERAS protocol compared to controls (no ERAS)(8). The aim of the present study is to report the long-term oncological outcomes of these patients 5 years after the conclusion of the study.

Patients and Methods

In the original trial patients were enrolled if they had received the indication for major colorectal surgery, aged between 18 and 80 years, with American Society of Anesthesiologists (ASA) grades I through III, autonomous for mobilization and walking, eligible for laparoscopic technique.

Patients were randomly assigned to the ERAS group (EG) or to Standard Group (SG).

Protocol is described in supplementary materials 1. Peripheral blood and serum were collected preoperatively (baseline), 1 and 5 days after surgery for stress and nutritional parameters. Preoperative samples were collected within 4 days before surgery. All postoperative samples were collected in the morning during patients' fast. From February 2014 to December 2015, 153 patients received indication for major colorectal surgery. 140 patients were enrolled and randomized into 2 groups of 70 patients each. Among these patients 52 in the EG and 53 in the SG had colorectal cancer. For them a 5-year oncological follow up according to the NCCN (16) guidelines was planned.

IL-6, C-reactive protein (CRP), prolactine, white blood cell count, albumine and prealbumine were compared between oncological patients in the EG and in the SG.

We analyzed data including local recurrence, distant metastasis, overall survival (OS), cancer specific survival (CSS) and disease free survival (DFS) based on 105 oncological patients of the 140 patients randomized in the original trial.

Statistical analysis was performed using the SPSS software package (SPSS 16.0 for Windows; SPSS, Chicago, IL). X^2 Test, t test, Fisher exact test, and analysis of variance test were applied for group comparison when appropriate. Time-to-event Kaplan–Meier curves were determined for OS, DFS and CSS and compared with the log-rank test according to Mantel – Cox method.

Results

Patient characteristics in terms of age, body mass index (BMI), sex, ASA classification and surgical procedure were comparable between the two groups and are described in table 1.

Solid diet was tolerated on day 1 by 78% of patients. EG patients returned faster to a normal bowel function. Passage of flatus and return to a solid meal happened statistically earlier in the EG. First flatus happened at day 1.4± 0.8 in EG versus 2.2 ± 0.7 SG ($p < 0.05$). EG patients could walk at least 100 m on day 1.3± 0.7 versus 2.7 ± 0.9 in SG ($p < 0.05$). Day of discharge was 4.8± 2.2 in EG versus 7.4± 2.7 SG ($p <0.05$). EG showed lower IL-6 on postoperative day 1 (21.2 ± 9.1 vs 40.3 ±11.3; $p < 0.05$) and on day 5 (14.9 ± 6.2 vs 38.7 ± 8.9; $p < 0.05$), lower CRP on day 1 (48.3 ± 15.7 vs 89.4 ± 20.3; $p < 0.05$) and day 5 (38.3 ± 11.4 vs 74.3 ± 19.7; $p < 0.05$), and lower pre-albumine on day 5 (18.9 ± 7.2 vs 12.3 ± 6.9; $p < 0.05$) compared to SG. No significant difference was found in white blood cell count, albumin, and prolactin (table2)

Median oncological follow up was 57 months [46.5-60]. There was no statistically significant difference in OS (log rank = 0.195) and DFS (Log rank = 0.089) between groups. CSS was significantly better (log rank = 0.038) in the EG compared to patients in the SG (Figure 1,2,3).

Discussion

The present study reports 5-year oncological outcomes of patients enrolled in a randomized clinical trials comparing ERAS to standard groups. We found that ERAS protocols applied to laparoscopic oncological colorectal surgery reduces SSR lowering postoperative IL-6 and CRP, and improve 5-year cancer specific survival.

It is undisputed that ERAS items in colorectal surgery improve clinical outcomes and one of the mechanism may be through the SSR reduction.

Our previous analysis has shown that even in a subgroup of cancer patients the expression of pro-inflammatory mediators is positively affected by an ERAS protocol [8]. This could result in a preserved peri-operative immunosurveillance. Therefore, the hypothesis is whether colorectal surgery ERAS protocol lead to better long-term oncological prognosis thanks to the preservation of the peri-operative immunological activity.

Following this same intuition, a recent multicenter Spanish study was designed to support the working hypothesis that the correct implementation of an intensified recovery program in patients undergoing colorectal surgery for cancer could be related to better long-term oncological outcomes [17]. Earlier, Gustafsson et al. published a retrospective cohort study on 911 reporting a lower risk of 5-year cancer-specific death in patients with ≥70 % adherence to ERAS protocol compared to patients <70 % adherence [6].

The present results depict a superimposable OS between the two groups. However, the difference in the 5 years DFS in the two groups, although not statistically significant ($p = 0.089$), approaches a level of significance. It is possible that the sample size limited the ability to reach a statistical significant difference in OS and DFS. Indeed, the sample size of the randomized clinical trial study was calculated on the ability of an ERAS protocol to reduce the expression of IL-6. It follows that, for an oncological outcome, the study may be underpowered.

Similarly, to our findings, Quiram B.J. et al. reported that colorectal patients operated on with mini-invasive technique within an ERAS protocol had improved overall survival on univariable but not multivariable suggesting that the treatment may have had a subtle impact on overall but not disease-specific survival [5].

A recent review by Pang Q. et al. highlighted that the use of ERAS in cancer surgery can improve the on-time initiation and completion of adjuvant chemotherapy after surgery. However, they concluded that up to now it is difficult to determine whether the ERAS protocol is associated with long-term overall survival or cancer-specific survival [18].

Importantly, we found that EG had significantly improved the 5-year CSS. The better CSS detected in the EG can be attributed to a better immunosurveillance related to the ERAS protocol through the reduction of peri-operative SSR, but also to adjuvant chemotherapy started on-time . Our data show how IL-6 and CRP level are lower in the ERAS group reinforcing the idea that enhanced protocols attenuate the SSR in cancer patients. On the same line Tsuchiya et al. correlated the increased surgical stress and colon cancer metastasis using an in vivo lung metastasis model, funding an upregulation

of matrix metalloproteinase-9 and urokinase-type plasminogen activator in the metastasis target organ [19]. Similarly, Hirai et al. found that excessive surgical stress was associated to colorectal liver metastasis [20].

In conclusion, ERAS protocol applied to colorectal laparoscopic surgery for cancer is able to minimize the surgical stress response. As a possible result cancer specific survival seems to be improved in patients within enhanced protocols. However, even though there may be an association between an excess of SSR and worsen oncological outcomes, the favorable effect of ERAS protocols toward better overall and disease free survival is yet to be demonstrated.

Future ad hoc studies should be implemented to highlight the association between ERAS protocols applied to minimally invasive colorectal surgery and their impact on survival.

Table 1. Patients' characteristics

	EG (n=52)	**SG (n=53)**	**p-value**
Age	65.48 (±13)	67.75 (±12)	0.3477
Male	27 (51.9%)	30 (56.6%)	0.6302
BMI	26.86 (±5.2)	26.72 (±2.9)	0.9263
Tumor location			0.1582
Right colon Left colon Rectum	21 (40.4%) 15 (28.8%) 16 (30.8%)	24 (45.3%) 18 (18.9%) 11 (20.8%)	
TNM stage			0.5758
1 2 3 4	21 (40.4%) 18 (34.6%) 12 (23.1%) 1 (1.9%)	19 (35.8%) 15 (28.3%) 16 (30.2%) 3 (5.7%)	
ASA			0.3540
1 2 3	17 (32.7%) 27 (51.9%) 8 (15.4%)	12 (22.6%) 28 (52.8%) 13 (24.5%)	
30 days CD complication score			0.314
0 1 2 3 4	40 (76.9%) 6 (11.5%) 2 (3.8%) 1 (1.9%) 3 (5.8%)	39 (73.6%) 5 (9.4%) 7 (13.2%) 1 (1.9%) 1 (1.9%)	

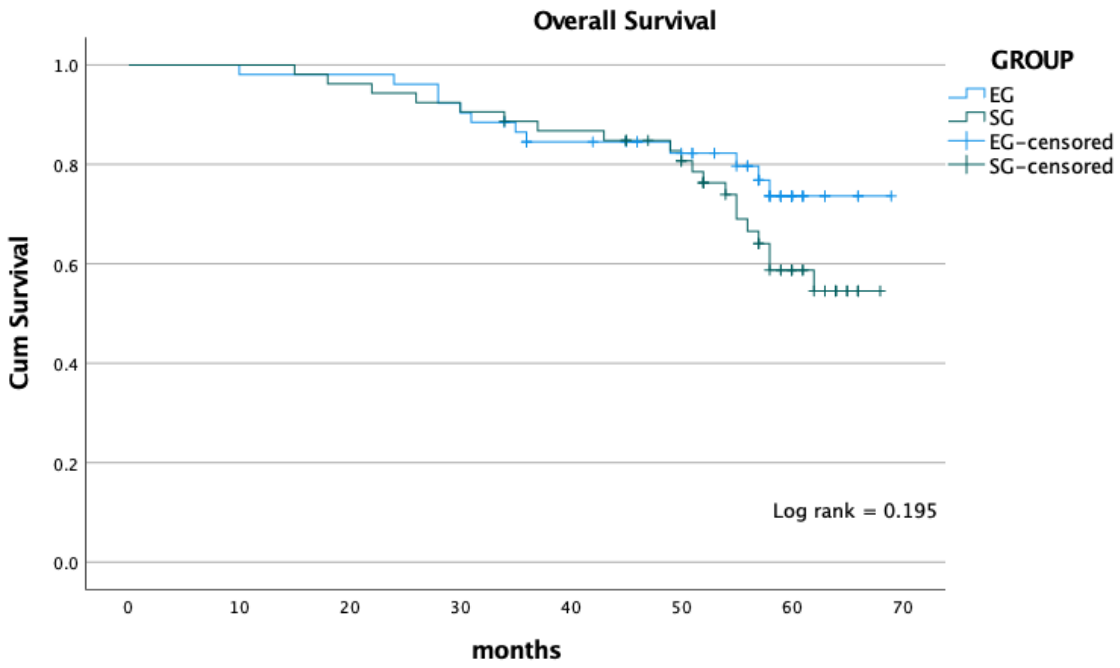
Abbreviation. EG: Enhanced Recovery After Surgery (ERAS) group; SG: standard group; BMI: body mass index; ASA: American Society of Anesthesiologists Classification; CD: Clavien-Dindo.

TNM stage according to the American Joint Committee on Cancer (AJCC)

Table 2 Surgical stress analysis

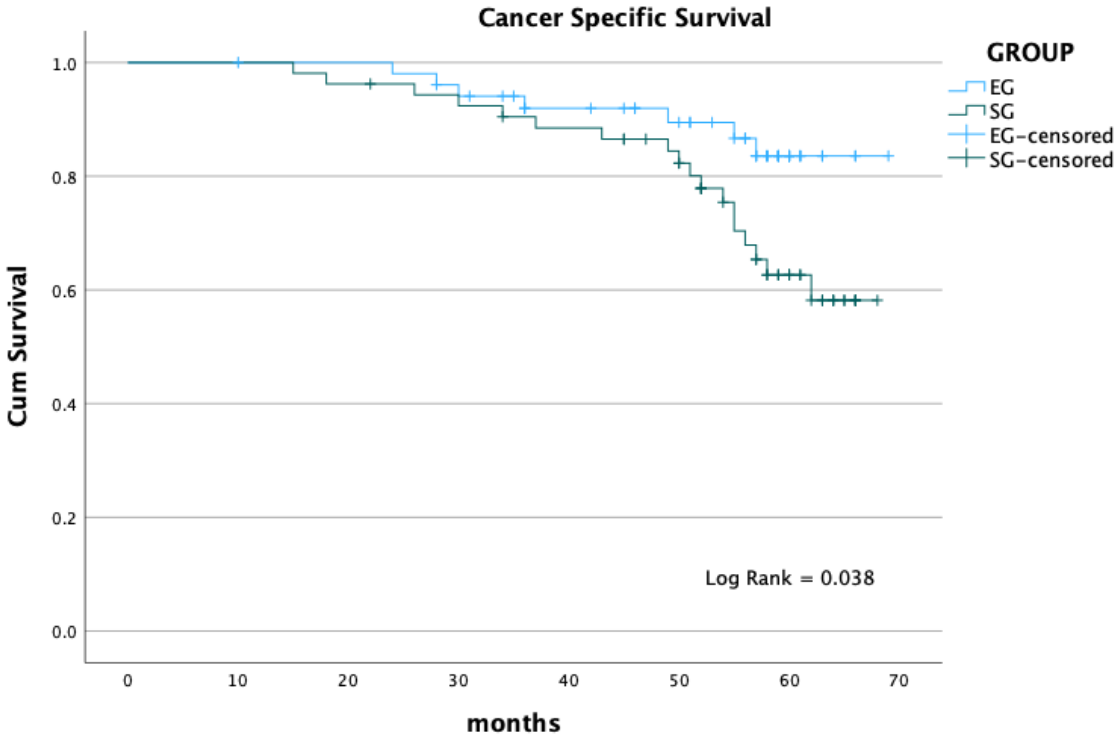
CRP (mg/L)	Pre-op	I p.o.	V p.o	p
EG	6.6 ± 6.1	48.3 ± 15.7 *	38.3 ± 11.4 *	P < 0.05
SG	11.1 ± 5.4	89.4 ± 20.3	74.3 ± 19.7	
PRL (ng/dL)				
EG	16.3 ±8.2	23.5 ± 11.7	18.9 ± 12.4	
SG	14.1 ± 7.9	22.8 ± 10.9	17.2 ± 11.3	
WBC				
EG	6420 ± 2335	10102 ± 3485	7102 ± 3210	
SG	7100 ± 3489	9892 ± 4125	8230 ± 2874	
IL-6 (pg/mL)				
EG	11.8 ± 5.9	21.2 ± 9.1 *	14.9 ± 6.2 *	P < 0.05
SG	7.2 ± 6.9	40.3 ±11.3	38.7 ± 8.9	
PRE-ALB (mg/dL)				
EG	19.1 ± 6.1	15.2 ± 5.4	18.9 ± 7.2 *	P < 0.05
SG	18.2 ± 5.7	15.1 ± 4.9	12.3 ± 6.9	
ALB (g/dL)				
EG	3.82 ± 1.1	3.33 ± 0.9	3.59 ± 1.2	
SG	3.62 ± 0.9	3.15 ± 0.8	3.19 ± 1.3	

Abbreviation. CRP: C-Reactive Protein; PRL: non so!; WBC: white blood count; IL-6: Interleukine-6; ALB: Albumine



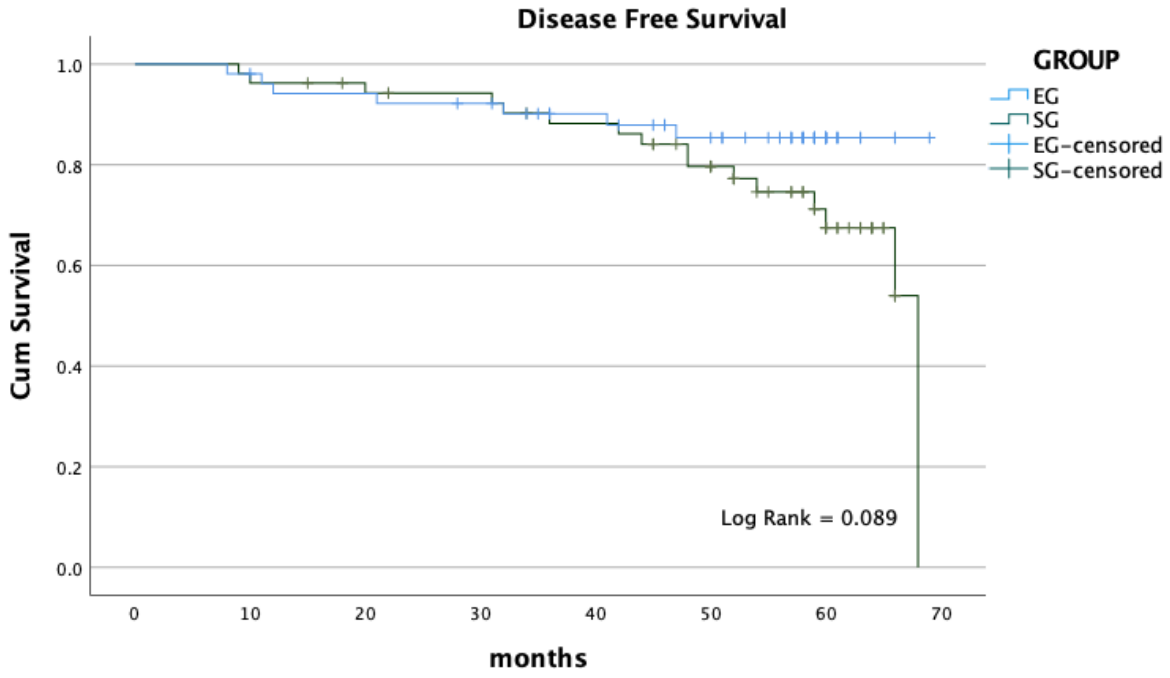
No. at risk:

EG	52	52	51	47	39	27	8
SG	53	53	51	49	44	35	10



No. at risk:

EG	52	52	51	46	39	27	8
SG	53	53	51	49	44	34	10



No. at risk:							
EG	52	51	48	44	38	25	8
SG	53	51	49	47	42	29	11

TABLE 1. Protocols Description

	EG	SG
Preoperative bowel preparation	No bowel preparation	Laxative 2 d before surgery cleaning enema 1 d before surgery
Preoperative fasting	200 mL oral maltodextrin intake 6 and 2 h before surgery	Fasting after midnight before surgery
Intraoperative fluid	5-10 mL/kg/h during surgery	No restriction in fluid management during surgery
Nasogastric tube	To remove after intubation	To keep until 24 h after surgery
Drainage	No	According to surgeon decision
Analgesia	Combined spinal analgesia with opioid and oral NSAIDs after surgery	IV opioid until 24 h after surgery then oral NSAIDs
Postoperative fluid management	1500 mL/d until 24 h after surgery	2000 mL/d until 48 h after surgery
Postoperative diet	Fluid meal 6 h after surgery then solid meal 24 h after surgery	Fluid meal 48 h after surgery then solid meal
Mobilization	Mobilization 6 h after surgery. Walk at least 100 m the day after surgery	Mobilization the day after surgery. Walk at least 100 m 48 h after surgery

EG indicates Eras group; SG, standard group.

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