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# Factors associated with failure of enhanced recovery programs after laparoscopic colon cancer surgery: a single-center retrospective study

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**Abstract**

*Background* Although enhanced recovery programs (ERPs) have been proven to be beneficial after laparoscopic colon surgery, they may result in adverse clinical outcomes following failure. This study analyzed risk factors associated with ERP failure after laparoscopic colon cancer surgery.

*Methods* We analyzed the outcomes of 208 patients who underwent ERPs following laparoscopic colon cancer surgery between June 2007 and April 2013. The ERP included early oral feeding, early ambulation, and regular laxative administration. ERP failure was defined as postoperative hospital stay of more than 5 days related to postoperative complications, unplanned readmission within 30 days of surgery, or death.

*Results* Surgical procedures included anterior resection ($n = 101$), right hemicolectomy ($n = 90$), and left hemicolectomy ($n = 17$). The mean postoperative hospital stay was $6.5 \pm 2.3$ days (range 3–24 days). ERP failure occurred in 36 patients (17.3 %), with no mortality; reasons included ileus ($n = 14$), wound infection ($n = 4$), chylous drainage ($n = 3$), anastomotic bleeding ($n = 3$), pneumonia ($n = 1$), or readmission ($n = 11$) owing to delayed complications. Univariable analysis showed that ERP failure was associated with proximal colon cancer, side-to-side anastomosis, longer operation time, increased blood loss, and longer resected specimen length. Multivariable analysis showed that side-to-side anastomosis [odds ratio (OR) 4.534; 95 % confidence interval (CI) 1.902–10.811; $P = 0.001$] and increased blood loss (OR 1.004; 95 % CI 1.001–1.008; $P = 0.041$) were independent risk factors for ERP failure.

*Conclusions* We showed that increased blood loss and side-to-side anastomosis in comparison with end-to-end anastomosis were independent risk factors associated with ERP failure after laparoscopic colon cancer surgery. This suggests that intraoperative elements may be important determinants to obtain successful postoperative recovery in the era of ERP.

**Keywords** Enhanced recovery program · Early rehabilitation · Fast-track · Laparoscopy · Enhanced recovery after surgery · ERAS · Colon cancer

An enhanced recovery program (ERP) after surgery, also known as fast-track pathways or enhanced recovery after surgery (ERAS), is a multimodal approach to the perioperative management of patients undergoing colorectal surgery designed to improve the overall quality of care [1]. ERPs have been originally focused on colorectal surgery, and this specialty still dominates the literature [2, 3], but in practice, all surgical specialties are being encouraged to develop and apply such programs [4]. Their main aim is to improve patient clinical outcomes and to accelerate recovery after surgery, with benefits to patients, staff, and healthcare systems, as more patients are treated with the available resources [5].

Recently, a meta-analysis of the impact of ERPs on surgical outcomes, including 38 studies across a range of

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surgical specialties, demonstrated that use of an ERP leads to a reduction in primary hospital stay and a 30 % reduction in the risk of complications 30 days postoperatively [6]. Several prospective randomized studies, including our trial [7], showed that an ERP after laparoscopic colectomy can produce synergistic effects on enhanced recovery [8, 9].

However, many patients have failed to recover owing to significant postoperative morbidity and, consequently, have been unable to participate in an ERP after laparoscopic colectomy. Postoperative complications have also adverse effects on long-term quality of life after curative colorectal surgery [10]. There are only a few reports regarding laparoscopic colorectal surgery under ERPs and postoperative morbidity [11, 12]. Recently, a single institutional study, regarding short-term outcomes of laparoscopic rectal resection under an ERP, indicated that the main reason for prolonged hospital stay was postoperative morbidity, and unplanned readmission within 30 days occurred in 8.1 % of patients [12]. To the best of our knowledge, no report has yet elucidated the determinants of clinical deterioration after ERP using well-defined measures. This study aimed to evaluate clinical predictors in patients who might fail to fully recover despite an ERP. We hypothesized that clinically modifiable variables associated with clinical deterioration after an ERP could be addressed and optimized to improve patient outcomes.

## Materials and methods

### Patients and study design

A retrospective review of a prospective colorectal cancer database was performed to identify all major elective laparoscopic colectomies performed with an ERP in colon cancer patients. The study period for the analysis was from June 2007 to April 2013. Patients who were converted from laparoscopy to open surgery were excluded from the analysis, as these conversion cases tend to have increased complications. In addition, we intended to focus specifically on laparoscopic-only operations. Additional demographic and clinical information was obtained from electronic medical records. Data fields evaluated included age, sex, body mass index, American Society of Anesthesiologists grade, operation history, preoperative serum albumin level, tumor location, operation method, anastomotic type, combined resection, operation time, estimated blood loss (EBL), intraoperative fluid infusion, pathologic data, postoperative morbidity, length of postoperative hospital stay, and unplanned readmission.

### ERP protocol

All cases followed our standardized ERP and discharge criteria [7]. In 2007, our institution developed, refined, and established its own standardized ERP and discharge criteria that incorporate pre- and postoperative patient information, early feeding, early ambulation, active pain control, unnecessary medical tube indwelling avoidance, and promotion of patient autonomy. All patients underwent standard bowel preparation with polyethylene glycol 3350 electrolyte solution (Colyte-F powder, Tae Joon Pharm Inc., Seoul, Korea) in the evening 2 days before surgery. No nasogastric tubes were inserted, and patients were allowed to drink water (<1 L) immediately postoperatively and commenced a semifluid diet on the first postoperative day. The patients sat in a chair for more than 1 h on the day of the operation. Patients also ambulated more than 400 m (assisted or unassisted), and the urinary catheter was removed on the first postoperative day. All patients received morphine- or fentanyl-based intravenous patient-controlled analgesia. Neither epidural anesthesia nor local infiltrative anesthesia of the wound was used. Our usual protocol of intravenous patient-controlled analgesia included 1500 mcg (in patients less than 70 years old) or 1200 mcg of fentanyl (in patients more than 70 years old) as a single dose. Intraoperative goal-directed fluid resuscitation using pulmonary artery catheter or esophageal Doppler was not implemented, but conventional restrictive fluid therapy was conducted by the specialized anesthesiologists. The main goal of our ERP was not to discharge patients earlier, but to accelerate the patients' postoperative recovery with less complications resulting in a shorter hospital stay.

### Surgical procedures

The laparoscopic colectomy procedure was performed in a standard fashion, as described previously [13]. We used a midline umbilical incision to obtain specimens from patients with right-sided colon cancer and a transverse incision for left-sided colon cancer. In cases of hemicolectomy, side-to-side anastomosis with two linear staplers was used until June 2011, but from July 2011, end-to-side anastomosis with a circular stapler was performed extracorporeally. In cases of anterior resection, intracorporeal end-to-end anastomosis was performed using a circular stapler.

### ERP failure

ERP failure was defined as a prolonged postoperative hospital stay (>5 days) due to postoperative complications,

unplanned readmission within 30 postoperative days, or death. Duplication in failure events was treated as one. Complications were assessed where possible using the Clavien–Dindo classification [14], based on information available in the prospectively collected database. Complications were classified into all nonfatal events (grade I–IV): minor (I–II) and major (III–IV). Minor complications were not life-threatening and could be treated nonsurgically, such as wound infections, ileus, and urinary tract infections. Major complications included any complications requiring reoperation or radiological intervention, such as anastomotic leakage, intraabdominal abscess, or respiratory failure.

### Statistical analysis

Univariable analysis was performed first to assess the relationship between each factor and the outcome variables. Associations between categorical variables and ERP failure were analyzed using the Chi-square test or Fisher exact test, as appropriate. Continuous variables were compared using the Student unpaired *t* test or the Mann–Whitney *U* test. Multivariable analysis, the use of stepwise selection to identify the independent risk factor for ERP failure, using binary logistic regression for categorical variables and linear regression of log-transformed continuous variables, was then performed for all variables with a significant or near-significant difference ($P < 0.150$) in univariable analysis. On multivariable analysis, nonsignificant factors were excluded sequentially, and the model was run again. Continuous variables are presented as the mean ± standard deviation or the median and interquartile range (IQR). Categorical variables are presented as the percentages of patients. All reported *P* values are two-tailed, with a *P* value of 0.05 indicating statistical significance. Analyses were conducted using SPSS version 18.0 (IBM Inc., Armonk, NY, USA) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

### Ethical approval

The institutional review board of Seoul National University Hospital approved this study prior to commencement of the data collection and analysis (IRB No.: B-1407-258-112) and waived the informed consent requirement.

## Results

### Demographics

We performed the ERP after laparoscopic colectomy in 208 patients. Patient characteristics are shown in Table 1. Except for one patient with unresectable hepatic metastasis, all patients underwent curative colectomy and had no distant metastasis.

**Table 1** Patient characteristics ($n = 208$)

| Variables | *n* | % |
|---|---|---|
| Median age (years, range) | 62 (28–85) | |
| Sex | | |
| Female | 83 | 39.9 |
| Male | 125 | 60.1 |
| Body mass index (kg/m$^2$, mean ± SD) | 23.2 ± 2.6 | |
| ASA grade | | |
| I | 85 | 40.9 |
| II | 112 | 53.8 |
| III | 11 | 5.3 |
| Tumor locations | | |
| Cecum | 9 | 4.3 |
| Ascending | 60 | 28.8 |
| Transverse | 22 | 10.6 |
| Descending | 17 | 8.2 |
| Sigmoid | 100 | 48.1 |
| Operative procedures | | |
| Right hemicolectomy | 90 | 43.3 |
| Left hemicolectomy | 17 | 8.2 |
| Anterior resection | 101 | 48.5 |

*ASA* American Society of Anesthesiologists

### Operative outcomes

The median operative time was 140 min (range 70–290 min), and the median EBL was 60.0 mL (range 30–500 mL). The median length of postoperative hospital stay was 6.0 days (range 3–24 days). During admission, 31 (14.9 %) patients experienced one or more complications. Intestinal obstruction ($n = 16$) was the most frequent complication, followed by wound infection ($n = 6$), chylous drainage ($n = 4$), bleeding from the anastomotic site ($n = 3$), pneumonia ($n = 1$), and intraabdominal abscess ($n = 1$). Among these cases, two (1.0 %) patients underwent reoperation for wound dehiscence. The median time to development of complications was three postoperative days (range 2–7 days). Eleven (5.3 %) patients had unplanned readmission within 30 days for a median period of 13 days (range 9–24 days). Reasons for readmission included intestinal obstruction ($n = 6$), wound infection ($n = 4$), and intraabdominal abscess ($n = 1$). No patient died within 30 postoperative days.

### Risk factors for ERP failure

Eventually, ERP failure occurred in 36 (17.3 %) patients (Table 2). Among the remaining 172 patients who

**Table 2** Enhanced recovery program failure in the 208 patients who underwent laparoscopic colectomy

| Category | *n* | % |
|---|---|---|
| Prolonged hospital stay with complications[a] | 29 | 13.9 |
| Grade I | 8 | |
| Grade II | 19 | |
| Grade III | 2 | |
| Grade IV | 0 | |
| Unplanned readmission[b] | 11 | 5.3 |
| Postoperative mortality | 0 | 0 |
| Total[c] | 36 | 17.3 |

Grade: Clavien–Dindo classification complication grade

[a] More than 5 postoperative days due to postoperative complications

[b] Unplanned readmission within 30 postoperative days

[c] Eventual number of patients who presented enhanced recovery program failure, excluding four cases, simultaneously indexed in two categories (a) and (b)

experienced successful recovery, two patients presented minor complications consisting of wound infection and chylous drainage, without prolonged hospital stay. Clinical variables presumably associated with ERP failure were analyzed, and the results are summarized in Table 3. Univariable analysis revealed that ERP failure was associated with proximal colon cancer, side-to-side anastomosis, longer operation time, greater blood loss, and longer resected specimen length. Multivariable analysis showed that side-to-side anastomosis [odds ratio (OR) 4.534; 95 % confidence interval (CI) 1.902–10.811; $P = 0.001$] and increased blood loss (OR 1.004; 95 % CI 1.001–1.008; $P = 0.041$) were independent risk factors for ERP failure (Table 4). Overall postoperative hospital stay including unplanned readmission period within 30 postoperative days was significantly longer in the ERP failure group than in the ERP success group [8 days (IQR 7–9) vs. 6 days (IQR 5–7), $P < 0.001$] (Fig. 1).

## Discussion

To the best of our knowledge, this study is the first report to define factors for clinical deterioration after ERPs using well-defined, prospective measures. We found that anastomotic configuration and intraoperative blood loss were clinically relevant and modifiable predictors for ERP failure after laparoscopic colectomy for colon cancer. The majority of postoperative morbidity in this prospective cohort of colon cancer patients undergoing laparoscopic surgery followed by ERPs could be attributable to operative elements.

The major challenge in evaluating ERPs is determination of the effect of the program on stress response and total recovery [15]. Many studies have focused on length of hospital stay to evaluate ERPs [6, 16]. Although length of hospital stay can reflect short-term recovery, the impact of biological changes associated with short-term recovery on longer-term outcomes is not clear [17]. Furthermore, from the patient's perspective, the postoperative recovery period continues long after the patient has been discharged, and may take weeks to months [18]. Because postoperative morbidity remains a significant concern in conjunction with ERP, even with experienced surgeons performing the procedure, we analyzed areas of possible progress to reduce perioperative risk and morbidity, instead of focusing on length of stay as the primary outcome. Thus, in this study, to address and overcome these multifactorial and problematic definitions, we defined ERP failure as a prolonged postoperative hospital stay (more than 5 days) specifically associated with postoperative complications, unplanned readmission within 30 postoperative days, or death.

Hospital readmission has been targeted both as an important quality measure in the effort to reduce healthcare costs and as a surrogate marker of superior patient care [19]. Among general surgeries, colectomies have been associated with some of the highest readmission rates [20]. As such, determining the factors contributing to readmission after ERP in addition to identifying factors prolonging hospital stay after colectomy and areas for targeted intervention may have important implications for improving patient care.

In this study, univariable analysis revealed that ERP failure was associated with proximal colon cancer, longer operation time, longer resected specimen length, greater blood loss, and side-to-side anastomosis configuration. Radical resection of the proximal colon might affect postoperative ileus events, but statistical significance in multivariable analysis was not shown because of potential association with side-to-side anastomotic methods. Longer operation time, longer resected bowel, and greater intraoperative blood loss may also indicate extended surgery, technical difficulty, and/or a heightened inflammatory response, any of which may directly cause a prolonged ileus.

Blood loss and side-to-side anastomosis were considered independent risk factors for ERP failure on multivariable analysis. Blood loss during surgery is an important operative complication in patients undergoing major noncardiac surgery and may increase postoperative morbidity and mortality [21]. Anemia and hypovolemia, combined with excessive opioid use, may induce postoperative nausea and vomiting, dizziness, and orthostatic hypotension [22]. The relationship between intraoperative blood loss and postoperative ileus is not fully understood, but increased blood loss can potentially lead to a greater traumatic sympathetic

**Table 3** Risk factors for enhanced recovery program failure (univariable analysis)

| Variables | Success ($n = 172$) | Failure ($n = 36$) | $P$ value |
|---|---|---|---|
| Age (years) | | | |
| <75 | 135 (85.4) | 23 (14.6) | 0.053 |
| ≥75 | 37 (74.0) | 13 (26.0) | |
| Sex | | | |
| Female | 69 (83.1) | 14 (16.9) | 0.891 |
| Male | 103 (82.4) | 22 (17.6) | |
| ASA grade | | | |
| 1 | 72 (84.7) | 13 (15.3) | 0.553 |
| 2 | 90 (80.4) | 22 (19.6) | |
| 3 | 10 (90.9) | 1 (9.1) | |
| Operation history | | | |
| No | 136 (81.9) | 30 (18.1) | 0.562 |
| Yes | 36 (85.7) | 6 (14.3) | |
| Tumor location | | | |
| Proximal colon[a] | 68 (74.7) | 23 (25.3) | 0.007 |
| Distal colon[b] | 104 (88.9) | 13 (11.1) | |
| Operative procedures | | | |
| Right hemicolectomy | 68 (75.6) | 22 (24.4) | 0.047 |
| Left hemicolectomy | 14 (82.4) | 3 (17.6) | |
| Anterior resection | 90 (89.1) | 11 (10.9) | |
| Anastomotic type | | | |
| End-to-end | 104 (89.7) | 12 (10.3) | 0.001 |
| End-to-side | 40 (83.3) | 8 (16.7) | |
| Side-to-side | 28 (63.6) | 16 (36.4) | |
| Combined operation | | | |
| No | 161 (83.0) | 33 (17.0) | 0.714 |
| Yes | 11 (78.6) | 3 (21.4) | |
| Operation time (min) | 135.0 (115.0–160.0) | 150.0 (125.0–177.0) | 0.016 |
| EBL (mL) | 50.0 (30.0–100.0) | 80.0 (50.0–150.0) | 0.022 |
| Intraoperative fluid (mL) | 900.0 (700.0–1100.0) | 900.0 (800.0–1100.0) | 0.310 |
| Tumor size (cm) | 3.1 (2.0–4.5) | 4.0 (2.8–5.5) | 0.064 |
| Number of harvested LN | 39.0 (29.3–51.8) | 37.0 (25.0–58.0) | 0.805 |
| Specimen length (cm) | 22.3 (16.0–33.0) | 29.0 (20.8–34.0) | 0.026 |
| TNM stage | | | |
| 0/1/2 | 110 (79.7) | 28 (20.3) | 0.110 |
| 3/4 | 62 (88.6) | 8 (11.4) | |

Data are presented as median (interquartile rage) or number of patients (percentage) unless otherwise stated

*ASA* American Society of Anesthesiologists, *EBL* estimated blood loss, *IQR* interquartile range, *LN* lymph nodes

[a] Proximal colon: cecum, ascending colon, and transverse colon

[b] Distal colon: descending colon and sigmoid colon

and endocrine stress response [23]. This may in turn inhibit gastrointestinal transit.

Enteric anastomosis is essential for restoring the integrity of the gastrointestinal tract following resection of the diseased bowel segment [24], but possible associations between anastomotic type and surgical outcome are controversial [25]. A side-to-side (also called functional end-to-end) anastomosis is constructed by passing a linear cutter stapler through the target enterotomies to create an anastomosis [26, 27]. Side-to-side anastomosis has been considered more effective than end-to-end anastomosis because of its larger luminal diameter; however, side-to-

**Table 4** Independent risk factors for enhanced recovery program failure (multivariable analysis)

| Variables | aOR | 95 % CI | *P* value |
|---|---|---|---|
| EBL | 1.004 | 1.001–1.008 | 0.041 |
| Anastomotic type | | | |
| End-to-end | 1 (ref) | | |
| End-to-side | 1.554 | 0.564–4.285 | 0.394 |
| Side-to-side | 4.543 | 1.902–10.811 | 0.001 |

Variables ($P < 0.015$ on univariable analysis) including age, tumor location, anastomotic type, EBL, operation type, tumor size, and specimen length were entered on the initial step. Operative procedures were initially excluded because of collinearity with tumor location (Chi-square test, $P < 0.001$)

*aOR* adjusted odds ratio, *CI* confidence interval, *EBL* estimated blood loss (mL)

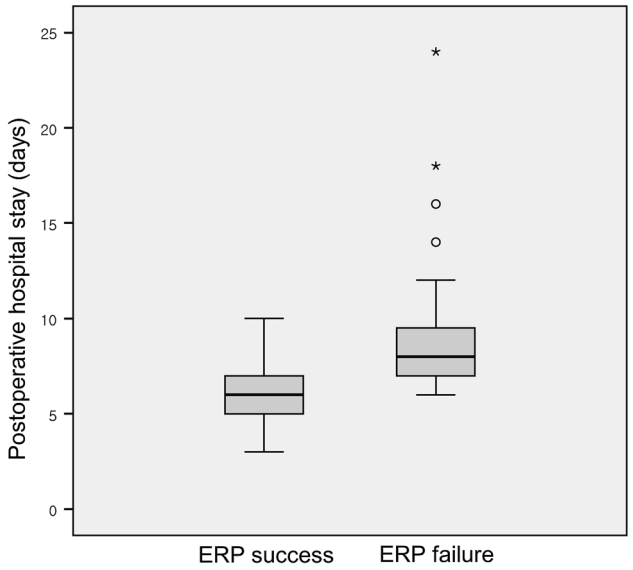


**Fig. 1** Comparison of postoperative hospital stay according to the enhanced recovery program (ERP) outcomes. Overall postoperative hospital stay including unplanned readmission period within 30 postoperative days was significantly longer in the ERP failure group than in the ERP success group [8 days (interquartile range 7–9) versus 6 days (interquartile range 5–7), $P < 0.001$] (Fig. 1)

side anastomosis is a physiologically unnatural configuration, and many complications have been reported, including intestinal pouch formation, ulceration, and anemia [28–31]. Dysmotility or chronic pseudoobstruction secondary to side-to-side intestinal anastomosis has been reported [32, 33]. Recently, in an ex vivo study of outcomes following a side-to-side partial bypass anastomosis in mouse ilea, changes in the direction and contractile activity within the bypass loop were noted [34]. These changes in the migrating motor complex after side-to-side anastomosis may account for the development of static luminal contents and postoperative ileus. Considering these findings, the postresection anastomotic technique, especially when accompanied by a planned ERP, should receive more attention. In accordance with the present results, we believe that end-to-side or end-to-end anastomosis would be a more physiologic configuration than side-to-side anastomosis and may have advantages in early postoperative recovery.

This study had several limitations. First, this ERP did not incorporate several recommended ERP components, as they have only recently been reported. These components include oral carbohydrate loading [35], perioperative intravenous fluid restriction [36], epidural analgesia [37], and avoidance of mechanical bowel preparation (MBP) [38]. The goal-directed fluid management using pulmonary artery catheter or esophageal Doppler was not used in this study. Our conventional intraoperative fluid infusion protocol conducted by the anesthesiologists is as follows: maintenance volume (1 mL/kg/h), insensible loss (2 mL/kg/h), urine output, blood loss, and preoperative fluid deficit. Crystalloid (Hartmann's solution) fluid was routinely used. In the preoperative period, the patients were allowed to receive sips of water and intravenous maintenance fluid, which was composed of an electrolyte-balanced solution of 5 % dextrose in water and Hartmann's solution with a volume of around 80–100 mL/h adjusted to the patient's weight and volume status. Although the routine use of MBP is not part of a standard ERP, it makes laparoscopic surgery technically easier. Because randomized controlled trials on MBP have included patients undergoing open colorectal surgery, the direct extrapolation to laparoscopic surgery might be questionable [39]. Interestingly, a recent observational analysis within a randomized controlled trial evaluating the long-term effect of MBP after colon cancer surgery revealed a reduction in cancer recurrence, a better cancer-specific survival, and an overall survival benefit for patients randomized to MBP [40]. The oncologic safety of MBP in patients with colorectal cancer was not yet proved. We have since gradually adopted the recent guidelines for perioperative care in elective colonic surgery proposed by the ERAS Society [39]. Second, this was a retrospective, single-center study with a small number of enrolled patients. We recognize that the results may not be generalizable to a significantly larger, more variable population. In addition, retrospective review results are inherently subject to bias; therefore, we performed stepwise selection multivariable logistic regression without overfitting to reduce statistical bias. The adverse effects of side-to-side anastomosis and increased blood loss in this somewhat limited patient population could serve as a foundation for studies on prospective validation and analysis of these findings. In particular, the

effects of the anastomotic method after colonic resection on ERP results should be specifically and strictly assessed in future clinical trials.

In conclusion, we showed that increased blood loss and side-to-side anastomosis in comparison with end-to-end anastomosis may be independent risk factors associated with ERP failure after laparoscopic colon cancer surgery. This suggests that intraoperative elements may be important determinants to obtain uneventful postoperative recovery in the era of ERPs, and the refinement of operative factors could improve the course of patients.

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