OPEN

Three-year Survival Outcomes of Patients With Enhanced Recovery After Surgery Versus Conventional Care in Laparoscopic Distal Gastrectomy

The GISSG1901 Randomized Clinical Trial

Yulong Tian, MD, PhD,† Shougen Cao, MD, PhD,*† Leping Li, MD, PhD,‡ Wenbin Yu, MD, PhD,§ Yinlu Ding, MD, PhD,‖ Guangyong Zhang, MD, PhD,¶ Lixin Jiang, MD,# Jianjun Qu, MD, PhD,** Hao Wang, MD, PhD,†† Xinjian Wang, MD,‡‡ Weizheng Mao, MD, PhD,§§ Huanhu Zhang, MD,‖‖ Xianqun Chu, MD,¶¶ Xizeng Hui, MD,## Dongfeng Zhang, MD, PhD,*** Zhaojian Niu, MD, PhD,*† Changqing Jing, MD, PhD,‡ Haitao Jiang, MD, PhD,*† Xiaodong Liu, MD,*† Zequn Li, MD,*† Henrik Kehlet, MD, PhD,†††✉ Yanbing Zhou, MD, PhD,*†✉ and on behalf of the Shandong Gastrointestinal Surgery Study Group (GISSG)*

Objective: The efficacy of enhanced recovery after surgery (ERAS) to improve the prognosis of patients who undergo laparoscopic distal gastrectomy (LDG) for gastric cancer is uncertain. This randomized study compared oncological outcomes in LDG after ERAS or conventional care.

Background: At present, randomized controlled trials have confirmed that ERAS can improve the short-term clinical outcomes of patients undergoing LDG, but whether it improves survival has not been reported yet.

Methods: A multicenter, randomized, controlled trial was performed to compare oncological outcomes of ERAS versus conventional care in LDG. Between April 4, 2019 and March 18, 2020, 527 patients with locally advanced lower gastric adenocarcinoma were recruited from 13 centers in China. The primary endpoints were 3-year overall survival (OS) and disease-free survival (DFS). The secondary endpoints were complications, mortality, recovery, time of receiving adjuvant chemotherapy, and medical expenses.

Results: The full analysis set included 186 cases in the ERAS group and 184 in the conventional group, well balanced with respect to patient demographics and baseline characteristics (published before). Postoperative hospital stay and the interval before adjuvant chemotherapy were obviously shorter in the ERAS group compared with the conventional group as reported previously and with lower medical expenses. Compared with the conventional group, the ERAS group had fewer overall complications (21.0% vs 30.4%, respectively; $P = 0.037$). The median (interquartile range) follow-up for all cases was 42.17 (range: 3.12–48.50) months. The 3-year OS and DFS in the ERAS group and conventional group were 86.56% and 80.11% (log-rank $P = 0.025$), 79.57% and 69.57% (log-rank $P = 0.027$), respectively. In a subgroup analysis of stage I and II disease patients, 3-year OS and DFS were similar between the groups ($P = 0.901$; $P = 0.859$ for stage I and $P = 0.421$;

From the *Department of Gastrointestinal Surgery, Qingdao University, Affiliated Hospital of Qingdao University, Qingdao, China; †Gastrointestinal Tumor Translational Medicine Research Institute of Qingdao University, Affiliated Hospital of Qingdao University, Qingdao, China; ‡Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China; §Department of Gastrointestinal Surgery, Qilu Hospital of Shandong University, Jinan, China; ‖Department of Gastrointestinal Surgery, The Second Hospital of Shandong University, Jinan, China; ¶Department of Gastrointestinal Surgery, The first affiliated hospital of Shandong First Medical University, Jinan, China; #Department of Gastrointestinal Surgery, Yantai Yuhuangding Hospital, Yantai, China; **Department of Gastrointestinal Surgery, Weifang People's Hospital, Weifang, China; ††Department of Gastrointestinal Surgery, Dongying People's Hospital, Dongying, China; ‡‡Department of Gastrointestinal Surgery, Weihai Central Hospital, Weihai, China; §§Department of Gastrointestinal Surgery, Qingdao Municipal Hospital, Qingdao, China; ‖‖Department of Gastrointestinal Surgery, Weihai Municipal Hospital, Weihai, China; ¶¶Department of Gastrointestinal Surgery, Jining No. 1 People's Hospital, Jining, China; ##Department of Gastrointestinal Surgery, Rizhao People's Hospital, Rizhao, China; ***Department of Epidemiology and Health Statistics, The School of Public Health of Qingdao University, Qingdao, China; and †††Section for Surgical Pathophysiology 7621, Rigshospitalet Blegdamsvej 9, DK-2100, Copenhagen, Denmark.

✉henrik.kehlet@regionh.dk; zhouyanbing@qduhospital.cn.

Yulong Tian, Shougen Cao, and Leping Li contributed equally to this work and should be considered co-first authors.

This study was supported by the Natural Science Foundation of Shandong (ZR2023QH103), China Postdoctoral Science Foundation (2024M751571), and Qingdao Postdoctoral Science Foundation (QDBSH20240101031).

Chinese Clinical Trial Registry, CHiCTR1900022438.

Y.T., S.C., C.J., W.Y., Y.D., Z.N., H.J., X.L., L.L., H.K., and Y.Z.: conception and design. W.Y., Y.D., G.Z., L.J., J.Q., H.W., X.W., W.M., H.Z., X.C., X.H., L.L., and Y.Z.: administrative support. Y.T., F.T., M.W., Y.D., G.Z., Z.Y., J.Q., H.W., X.W., W.M., H.Z., Y.K., X.H., Z.N., D.C., H.J., and X.L.: collection and assembly of data. Y.T., S.C., Z.N., H.J., X.L., L.L., and D.Z.: data analysis and interpretation. Y.T., S.C., C.J., W.Y., Y.D., Z.N., H.J., X.L., L.L., H.K., G.Z., L.J., J.Q., H.W., X.W., W.M., H.Z., X.C., X.H., D.Z., Z.L., and Y.Z.: manuscript writing, final approval of the manuscript, and accountable for all aspects of the work.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

DOI: 10.1097/SLA.0000000000006603

$P = 0.459$ for stage II). However, in the stage III disease, the ERAS group exhibited longer 3-year OS and DFS than the conventional group (79.41% vs 64.47% for OS, log-rank $P = 0.046$; 70.59% vs 53.95% for DFS, log-rank $P = 0.046$).

Conclusions: Patients undergoing ERAS LDG had fewer overall complications, shorter hospital stays, decreased medical expenses, and improved 3-year OS and DFS rates, particularly in cases with stage III gastric cancer.

Keywords: clinical outcomes, enhanced recovery after surgery, gastric cancer, laparoscopic surgery, survival

(*Ann Surg* 2025;282:46–55)

Gastric cancer is considered the most prevalent malignant neoplasm worldwide, ranking fifth in terms of morbidity and fourth in terms of mortality.[1] The prevalence of gastric cancer is notably elevated in East Asia, particularly in China, South Korea, and Japan. In 2020, China alone contributed 44% of newly diagnosed cases of gastric cancer (480,000 cases) and 49% of global fatalities (374,000 deaths).[2]

In the past few decades, advancements in surgical techniques, the introduction of chemotherapy, molecular targeted therapy, and immunotherapy have led to substantial improvements in the prognosis of gastric cancer cases.[3] Nowadays, the primary approach for the treatment of gastric cancer is radical surgery combined with comprehensive perioperative management.[4] Following the initial report by Kitano et al[5] in 1994 on laparoscopic distal gastrectomy (LDG), this surgical technique has undergone continuous refinement and development, resulting in its gradual maturation. Clinical studies, including CLASS-01, KLASS-02, and JLSSG0901, have demonstrated the safety of laparoscopic radical gastrectomy even within advanced gastric carcer. This surgical intervention yields clinical outcomes comparable to those of laparotomy while offering the added benefits of reduced surgical trauma and expedited postoperative recovery.[6–8]

Since the proposal by Kehlet[9] in 1997, enhanced recovery after surgery (ERAS) has undergone nearly 3 decades of development. ERAS is intended to optimize and integrate various aspects of perioperative care, including anesthesia, analgesia, nutrition, psychosocial support, surgical techniques, and multidisciplinary teamwork.[10–12] Consequently, ERAS has gained recognition as a key perioperative management method across procedures.[13]

However, research on whether the ERAS protocol improves the prognosis of gastrointestinal tumors is limited and controversial.[14] Although our single-center retrospective research suggested that an ERAS program may improve the 5-year overall survival (OS) of cases who undergo laparoscopic gastrectomy (LG), especially those with advanced gastric carcer,[15] there is few higher quality evidence to verify this finding. Four years ago, the Shandong Gastrointestinal Surgery Study Group (GISSG) designed a multicenter, nonblinded controlled trial to compare the prognoses of patients who underwent LDG with ERAS management (Supplemental Digital Content eTable 1, http://links.lww.com/SLA/F355).[16] Previously, we reported the outcomes of this study, which showed that the ERAS program promoted postoperative recovery, shortened hospital stays, reduced medical costs, and enabled patients to receive adjuvant chemotherapy earlier without

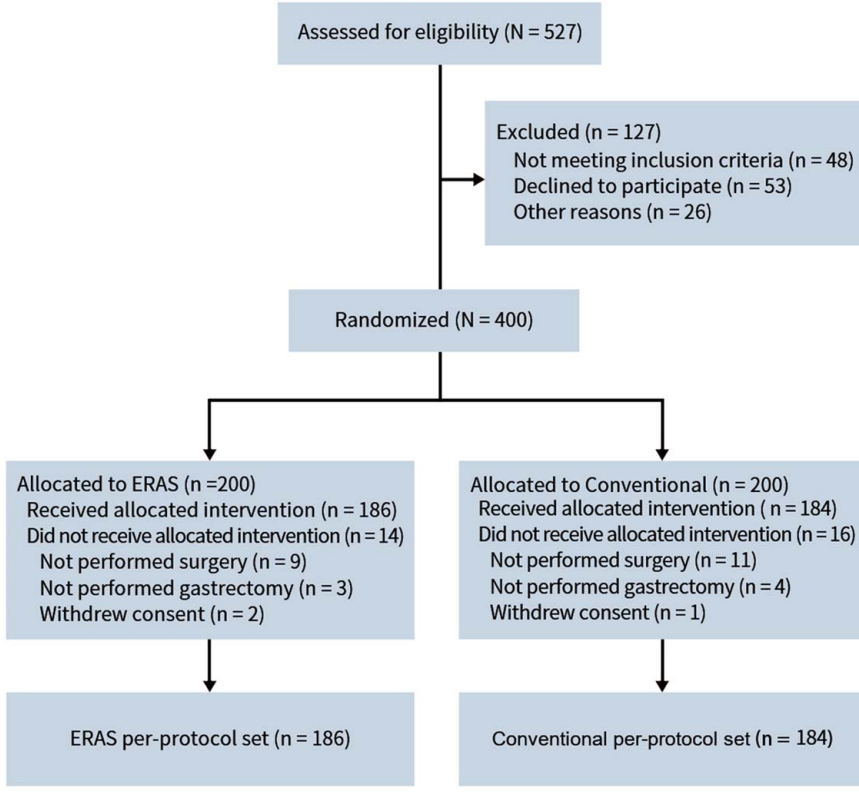

FIGURE 1. CONSORT flow diagram of patient enrollment and randomization. CONSORT indicates consolidated standards of reporting trials.

increasing complications or readmission rates.[17] Here, we present the oncologic outcomes of ERAS by comparing 3-year OS and disease-free survival (DFS) with conventional care-attended LDG.

METHODS

Study Design and Participants

This study compared the outcomes and safety of ERAS and conventional care in LDG at 13 hospitals and registered with the Chinese Clinical Trial Registry (ID: CHiCTR1900022438) and approved by each center's ethics committee. All cases enrolled in the research signed informed consent. Patients were enrolled in the GISSG1901 randomized clinical trial (RCT) with previously reported eligibility criteria and clinical endpoints[16,17] in patients with lower gastric adenocarcinoma suitable for curative resection by LDG as detailed in eTable 2 (Supplemental Digital Content eTable 2, http://links.lww.com/SLA/F355).

Randomization and Masking

For the randomization method, a central dynamic, stratified strategy is adopted. The randomization sequence is generated by using the Pocock–Simon minimization method in SAS, version 9.4 (SAS Institute Inc.) and stratified by participating sites (13 hospitals) and surgical procedures (laparoscopic or robotic). Participating centres will submit the previous information to the data centre at the Department of Gastrointestinal Surgery, Affiliated Hospital of Qingdao University, Qingdao, China, where central randomization will be performed. Information on treatment allocation is subsequently sent to each participating centre.

The study objects were divided into the ERAS or conventional group equally (Fig. 1). The data were separated from the cases who accepted eligibility evaluation and recruitment until cases were formally assigned to a corresponding group, the order was hidden from the surgeon and informed the anesthesiologists, nurses, and cases of the group assignments, so as to conduct the relevant perioperative care. In the research process, the radiologists, data managers, and pathologists were blind to the care program.

Surgical Quality Evaluation

To uphold the standard of surgical quality within the RCT, each surgeon executed more than 100 LG procedures, and the surgeon's team performed a minimum of 100 annual surgeries. Moreover, in adherence to the aforementioned criteria, surgeons submitted 6 LDG videos featuring unedited D2 procedures, which were subsequently evaluated by five impartial experts. Ultimately, a total of 13 surgeons from 13 distinct hospitals met the established eligibility criteria. Following the commencement of the RCT, unaltered videos and photographs pertaining to the surgical position were gathered and subjected to censorship. Subsequently, a panel of experts assessed the surgical techniques employed by the surgeons and, in cases where deemed essential, offered surgical assistance to the surgeons.

Perioperative Care and Follow-up

Before the surgical procedure, chest, total abdominal, pelvic computed tomography (CT), gastroscopy, or ultrasonic gastroscopy, were employed to ascertain the precise location and dimensions of the cancer. Patients with potential distant metastasis had a positron emission tomography-CT, and if verified by 2 experienced radiologists excluded from the study. In addition, upper abdominal CT angiography was conducted, thereby reducing bleeding and vascular damage arising from vascular anomalies and facilitating lymphadenectomy.[18] Blood samples and clinical assessment of nutritional status, hepatic and renal function, inflammatory markers, and immune response were performed. The cardiopulmonary function was assessed using cardiac ultrasound to ascertain their suitability for surgery.

During the surgical procedure, an examination of the abdominal organs was conducted, followed by the implementation of standard LDG with D2 lymphadenectomy, adhering to the treatment guidelines for gastric cancer established by the Japanese.[4] The choice of reconstruction technique was left to the discretion, who could opt for either

TABLE 1. Patient Demographics and Baseline Characteristics

Variables	ERAS (n = 186)	Conventional (n = 184)	*P*
Age, yr ± SD	58.3 ± 10.5	58.6 ± 10.9	0.305†
Sex, n (%)			0.685‡
Male	129 (69.4)	124 (67.4)	—
Female	57 (30.6)	60(32.6)	—
BMI, kg/m^2 ± SD	23.6 ± 3.2	23.7 ± 3.3	0.351†
ASA score, n (%)			0.804‡
I	98 (50.0)	93 (50.5)	—
II	74 (39.8)	79 (42.9)	—
III	14 (7.5)	12 (6.5)	—
NRS 2002, n (%)			0.757‡
< 3	89 (47.8)	91 (49.5)	—
≥ 3, n (%)	97 (52.2)	93 (50.5)	—
ECOG, n (%)			0.609‡
0	121 (65.1)	115 (62.5)	—
1	65 (34.9)	69 (37.5)	—
Comorbidity, n (%)			0.686‡
None	112 (60.2)	107 (58.2)	—
One or more	74 (39.8)	77 (41.8)	—
Histologic type, n (%)			0.651‡
Well	14 (7.5)	14 (7.6)	—
Moderate	56 (30.1)	60 (32.6)	—
Poor	116 (62.4)	110 (59.8)	—
pT stage			0.445§
T1	24 (12.9)	15 (8.2)	—
T2	41 (22.0)	35 (19.0)	—
T3	44 (23.7)	43 (23.4)	—
T4a	71 (38.2)	84 (45.7)	—
T4b	6 (3.2)	7 (3.8)	—
pN stage			0.582‡
N0	37 (19.9)	29 (15.8)	—
N1	41 (22.0)	35 (19.0)	—
N2	46 (24.7)	44 (23.9)	—
N3a	42 (22.6)	48 (26.1)	—
N3b	20 (10.8)	28 (15.2)	—
pTNM stage			0.564*‡
I	41 (22.0)	34 (18.5)	—
II	77 (41.4)	74 (40.2)	—
III	68 (36.6)	76 (41.3)	—
Previous abdominal operation, n (%)	28 (15.1)	22 (12.0)	0.384‡

*Pathologic stage according to the American Joint Committee on Cancer, eighth edition.
†Mann-Whitney test.
‡χ^2 test.
§Fisher exact test.
ASA indicates American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; NRS, nutrition risk screening.

extracorporeal or intracorporeal methods, drawing upon their own expertise and experience. Intraoperative complications and duration of surgery were recorded as reported previously.[16]

Cases with stage II cancer or above had 6 to 8 cycles of adjuvant chemotherapy (Tegafur, Gimeracil, and Oteracil Potassium Capsules (S-1) and Oxaliplatin or Xeloda and Oxaliplatin) and were accepted for lifelong follow-up.[18] The care program for each group included clinical medical history, physical examination, hematological examination, Helicobacter pylori testing, nutritional assessment, and imaging studies such as chest, abdomen, and pelvic CT scans, as well as gastroscopy examination as reported previously.[19]

Objectives and End Points

The aim of this research was to compare the oncological effects of ERAS versus conventional care in LDG for gastric cancer. The primary endpoints were 3-year OS and DFS.

Sample Size and Statistical Analysis

This study applied a noninferiority test in the experiment process, and to determine the sample size. According to the historical data, it was concluded that the 3-year OS rate under ERAS from 2011 to 2014 was nearly 65%.[20] The case selection required 10 months, and the median follow-up time was 3 years; thus, it was calculated that the noninferiority cutoff value was 1.33. Assuming the significance level of $\alpha = 0.05$ and $1\text{-}\beta = 80\%$, the required case number in every group is at least 178. A target enrollment of 400 cases was chosen to allow a dropout rate of 10%.

Categorical variables are reported as numbers and ratios and the difference in the 2 groups was compared based on the Pearson test or F exact test and continuous variables were expressed as means ± SD. Non-normally distributed continuous data were expressed through medians, and the difference in various groups was compared through t test. Significance level was 0.05. The prognosis of cases was determined based on the Kaplan-Meier method. Subgroup analyses using log-rank tests were conducted for DFS and OS stratified by pathologic stage (ie, stage I, II, or

TABLE 2. Surgical, Recovery, and Adjuvant Chemotherapy Outcomes

Variables	ERAS (n = 186)	Conventional (n = 184)	*P*
Operation time (min ± SD)	204.12 ± 45.81	208.41 ± 44.56	0.242*
Estimated blood loss (mL ± SD)	88.54 ± 37.15	92.82 ± 40.17	0.207*
Extent of resection, n (%)			0.470†
Total gastrectomy	10 (5.4)	7 (3.8)	—
Distal gastrectomy	176 (94.6)	177 (96.2)	—
Operation method			0.262†
Total laparoscopic gastrectomy	24 (12.9)	17 (9.2)	—
Laparoscopic-assisted gastrectomy	162 (87.1)	167 (90.8)	—
Combined operation	8 (4.3)	7 (3.8)	0.808†
LN dissection			0.442†
< D2	9 (4.8)	6 (3.3)	—
D2	177 (95.2)	178 (96.7)	—
Reconstruction, n (%)			0.570†
Billroth-I	7 (3.8)	11 (6.0)	—
Billroth-II	54 (29.0)	49 (26.6)	—
Roux-en-Y	125 (67.2)	124 (67.4)	—
Intraoperative transfusion, n (%)	8 (4.3)	11 (6.0)	0.465†
Length of incision (cm ± SD)	7.18 ± 1.45	7.27 ± 1.51	0.482*
Retrieved LN number (mean ± SD)	32.76 ± 13.08	32.81 ± 13.54	0.617*
Retrieved LNs < 15	7 (3.8)	5 (2.7)	0.570†
Positive margin	2 (1.1)	1 (0.5)	0.569‡
Time to first flatus (d ± SD)	2.52 ± 0.83	3.37 ± 1.28	< 0.001*
Time to first liquid intake (d ± SD)	1.13 ± 0.51	3.09 ± 1.14	< 0.001*
Time to ambulation (d ± SD)	1.38 ± 0.58	2.85 ± 1.42	< 0.001*
Remove the drainage tube (d ± SD)	2.36 ± 1.91	4.17 ± 1.28	< 0.001*
Allowed day of discharge (d ± SD)	5.83 ± 1.42	6.96 ± 1.63	< 0.001*
Postoperative hospital stay (d ± SD)	7.27 ± 1.83	8.85 ± 2.18	< 0.001*
30-day readmission, n (%)	9 (4.8)	8 (4.3)	0.821*
Adjuvant chemotherapy	116 (62.4)	111 (60.3)	0.687†
Time to adjuvant chemotherapy (d), median (IQR), days	29 (26–32)	32 (29–40)	0.035
Chemotherapy regimen, n (%)			0.537†
SOX/XELOX	69 (37.1)	65 (35.3)	—
S-1	32 (17.2)	36 (19.6)	—
Other	15 (8.1)	10 (5.4)	—
Completion adjuvant chemotherapy	98 (52.7)	89 (48.5)	0.406†
Medical cost (dollars ± SD)	6328 ± 925	6826 ± 1174	< 0.001*

*Mann-Whitney test.
†χ^2 test.
‡Fisher exact test.
IQR indicates interquartile range.
SOX indicates Tegafur, Gimeracil, and Oteracil Potassium Capsules (S-1) and Oxaliplatin; XELOX, Xeloda and Oxaliplatin.

III). All the statistical analyses were conducted on SPSS 26.0 (SPSS) and R Studio version 4.3.2 (R Studio, Inc.).

RESULTS

Patients

From April 4, 2019 to March 18, 2020, 527 patients with locally advanced lower gastric adenocarcinoma were recruited. After excluding 127 cases, 400 patients were randomly assigned to the ERAS group (n = 200 per group). In the ERAS group, 2 patients withdrew informed consent, 9 did not undergo surgery, and 3 did not undergo radical distal gastrectomy. In the conventional group, 1 patient withdrew informed consent, 11 did not undergo surgery, and 4 did not undergo radical distal gastrectomy with D2 lymph node dissection. After excluding 30 cases, the outcome of 186 ERAS group cases and 184 conventional group cases were analyzed. Thus, the full analysis set included 186 cases in the ERAS group and 184 cases in the conventional group (Fig. 1). The 2 groups were well-balanced in baseline features, so the requirement of comparison is met (Table 1).

Operative, Recovery Outcomes and Surgical Complications

Patient surgical and recovery outcomes and adjuvant chemotherapy outcomes, including operation time, degree of resection, operation method, combined operation, lymph node dissection, length of incision, and retrieved lymph node number, were similar in different groups (Table 2). According to the comparison result, patients in the ERAS group received earlier adjuvant therapy (29 vs 32 d, $P = 0.035$). Although the proportion of patients receiving adjuvant chemotherapy was not statistically different between the two groups (62.4% in ERAS vs 60.3% in the conventional group, $P > 0.05$), it was higher in the ERAS than in the conventional group [80% (116/145) vs 74% (111/150)] for stage II and stage III gastric cancer patients. In addition, no obvious differences were found in the chemotherapy regimen type or the completion rate of adjuvant chemotherapy (Table 2).

As shown in Table 3, comparisons of the incidence of intraoperative complications, postoperative complications, and late complications revealed no significant differences (4.8% vs 5.4%, $P = 0.795$; 11.8% vs 15.8%, $P = 0.273$; 4.3% vs 8.7%, $P = 0.086$, respectively). Compared with the conventional group, the ERAS group suffered fewer overall complications (21.0% vs 30.4%, $P = 0.037$). Clavien-Dindo grade III or higher complications were more frequent in the conventional group (9.8%) compared with the ERAS group (6.5%) and with no significant difference ($P = 0.113$).

TABLE 3. Postoperative Complications Data

Variables	ERAS (n = 186)	Conventional (n = 184)	*P*
Intraoperative complications, n (%)	9 (4.8)	10 (5.4)	0.795*
Postoperative early complications, n (%)	22 (11.8)	29 (15.8)	0.273*
Wound infection	2 (1.1)	2 (1.1)	1.000†
Pulmonary	6 (3.2)	10 (5.4)	0.296*
Gastroparesis	2 (1.1)	4 (2.2)	0.403†
Anastomotic leakage	2 (1.1)	3 (1.6)	0.684†
Lymphatic leakage	0	1(0.5)	0.497‡
Pancreatic fistula	1 (0.5)	2 (1.1)	0.622†
Intra-abdominal bleeding	1 (0.5)	1 (0.5)	1.000‡
Intraluminal bleeding	3 (1.6)	2 (1.1)	0.661†
Intra-abdominal abscess	1 (0.5)	1 (0.5)	1.000‡
Deep vein thrombosis	0	0	1.000‡
Ileus	2 (1.1)	1 (0.5)	0.569†
Cerebrovascular	1 (0.5)	0	0.319‡
Cardiac	0	1 (0.5)	0.497‡
Cholecystitis	0	0	1.000‡
Hepatic	0	1 (0.0)	0.497‡
Renal	1 (0.5)	0	1.000‡
Postoperative late complications, n (%)	8 (4.3)	16 (8.7)	0.086*
Intestinal obstruction	4 (2.2)	6 (3.3)	0.542‡
Reflux symptoms	0	1 (0.5)	0.497‡
Stenosis	0	1 (0.5)	0.497‡
Ascites	0	1 (0.5)	0.497‡
Postgastrectomy symptoms	1 (0.5)	2 (1.1)	0.622‡
Malnutrition	2 (1.1)	3 (1.6)	0.684†
Others	1 (0.5)	2 (1.1)	0.622‡
Overall complications	39 (21.0)	56 (30.4)	0.037*
Clavien-Dindo classification, n (%)			0.113*
I or II	27 (14.5)	38 (20.7)	—
≥ III	12 (6.5)	18 (9.8)	—

*χ^2 test.
†Correction χ^2 test.
‡Fisher exact test.
LN indicates lymph node.

Overall and Disease-free Survival

The follow-up endpoint was March 31, 2023. The median (interquartile range) follow-up for all patients was 42.17 (range: 3.12–48.50) months. The 3-year OS rates were 86.56% in the ERAS group and 77.72% in the conventional group [log-rank $P = 0.025$, hazard ratio (95%CI): 0.57 (0.35–0.94); Fig. 2A]. Overall, 38 patients (20.43%) experienced recurrence or death in the ERAS group, whereas 56 patients (30.43%) experienced recurrence or death in the conventional group. The 3-year DFS of ERAS and conventional group were 79.57% and 69.57%, respectively (log-rank $P = 0.027$; Fig. 2B). Among patients with multiple site recurrence, peritoneal recurrence was most common in both groups [ERAS group, 8 patients (4.4%); conventional group, 11 patients (6.3%)]. Otherwise, the recurrence patterns for both groups were similar.

Kaplan-Meier survival analysis revealed that 3-year OS and DFS were obviously different in 2 groups. However, 3-year OS and DFS were similar in groups in the subgroup analysis of stage I disease patients (97.56% of ERAS vs 97.06% of conventional group for OS, log-rank $P = 0.901$; 95.12% vs 94.12% for DFS, log-rank $P = 0.859$; Supplemental Digital Content eFig. 1A and 1B, http://links.lww.com/SLA/F355). Three-year OS and DFS were similar between groups of stage II disease patients (87.01% in the ERAS vs 82.43% in the conventional for OS, log-rank $P = 0.421$; 79.22% vs 74.32% for DFS, log-rank $P = 0.459$; Fig. 3A and B). Based on the subgroup analysis of stage III disease, the ERAS group exhibited longer 3-year OS and DFS than the conventional group (79.41% vs 64.47% for OS, log-rank $P = 0.046$; 70.59% vs 53.95% for DFS, log-rank $P = 0.046$; Fig. 4A and B).

DISCUSSION

The primary objective of the GISSG1901 RCT study being the first and largest multicenter trial, was to assess the safety and oncological outcomes of ERAS in such patients. As demonstrated previously, the short-term results

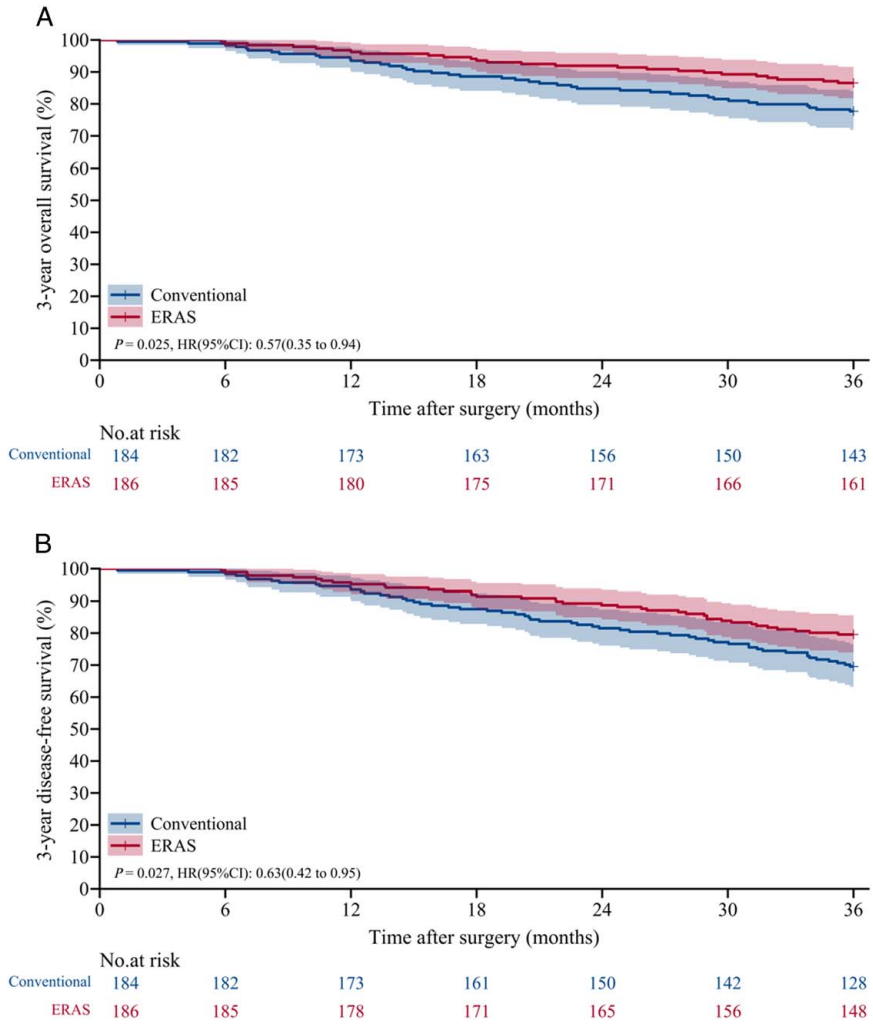

FIGURE 2. OS (A) and DFS (B) for ERAS versus conventional at 3 years after surgery in all patients.

demonstrated that ERAS provided faster recovery, and reduced medical expenses, all while maintaining complications comparable to those in the conventional group.[17] In addition, ERAS enabled more efficient delivery of adjuvant therapy.[17] This research results demonstrated that cases in the ERAS group exhibited superior OS and DFS compared with the conventional group. Notably, when adjusting for the pathologic stage, 3-year OS and DFS rates in cases with stage III gastric cancer were higher after ERAS LDG.

In addition, patients in the ERAS group received prompt initiation of adjuvant chemotherapy and a reduction in health care costs. These favorable results can be attributed to the adoption of the ERAS protocol, which enhances postoperative recovery through a range of interventions, including patient education, prerehabilitation, preoperative nutritional evaluation and intervention, goal-directed fluid management, anesthesia techniques, multimodal analgesia, early nutritional support, early mobilization, and the removal of catheters early.[21–23]

This study investigated the perioperative ERAS protocol, which consists of 23 distinct components for patients.[13] The implementation of the ERAS protocol poses considerable challenges, primarily stemming from a lack of knowledge, acceptance, willingness to change, and clinical leadership.[24,25] However, a positive outcome was achieved through the concerted efforts of surgical teams, including enhanced ERAS training and education as well as improved clinical leadership. As a result, the compliance rate for all patients surpassed 80%, particularly in relation to the critical components of the protocol. In this study, patients in both groups underwent LG, ruling out the influence of surgical methods on the results. Nowadays, some RCTs in Japan, Korea have verified the safety of LG for advanced gastric cancer and can meet the clinical application of requirement.[6–8]

ERAS has been extensively utilized in LG for gastric cancer treatment, with increasing evidence suggesting its safety and effectiveness.[26] The current study found that the overall morbidity of the ERAS group was markedly lower compared with the conventional group, consistent with previous clinical results.[27] It is widely acknowledged that ERAS can enhance clinical outcomes for cases undergoing LG compared with conventional protocols. Nevertheless, our RCT is the first to validate its ability to improve the oncological outcomes of these cases, particularly those with advanced-stage gastric cancer. Previous real-world studies on gastric cancer surgery and colorectal cancer surgery have similarly revealed the aforementioned findings,[15,28,29] but our study is the largest RCT in a well-defined detailed set-up.

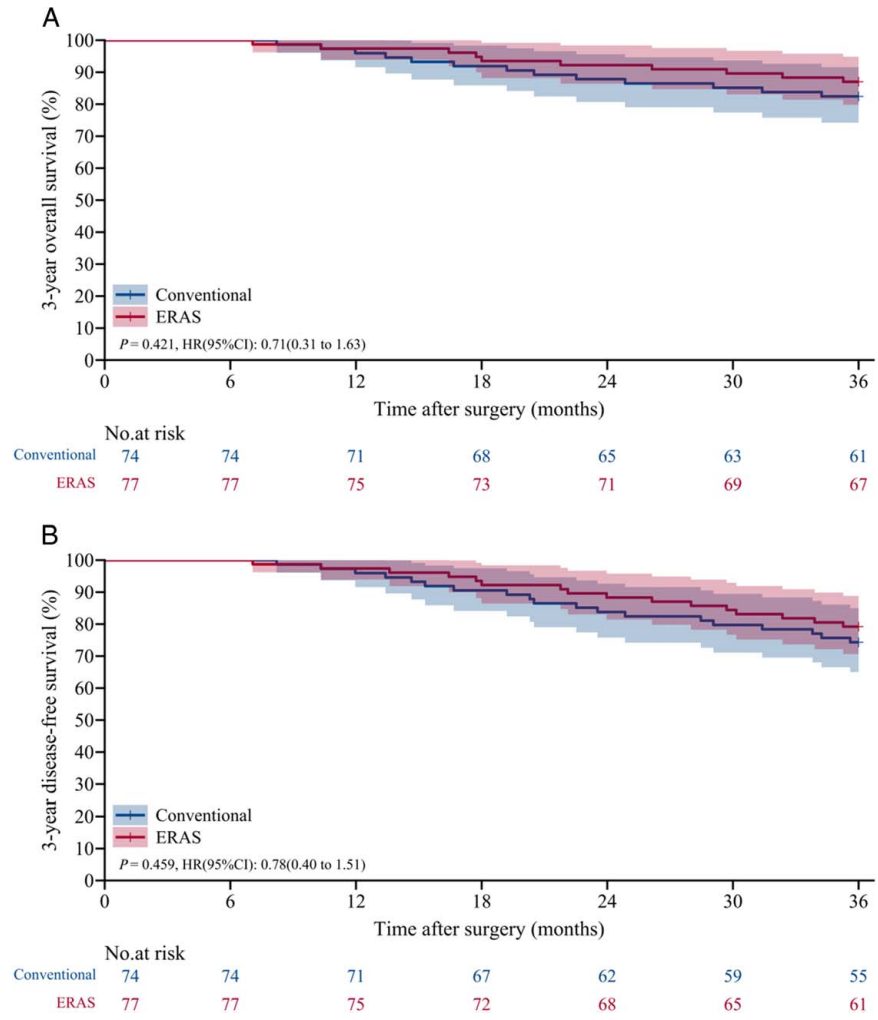

FIGURE 3. OS (A) and DFS (B) for ERAS versus conventional at 3 years after surgery in patients with stage II.

Various mechanisms could account for the findings in our study. First, the incidence of overall complications in the ERAS group was significantly lower. It is important to note that postoperative complications may have a negative effect on prognosis after radical gastrectomy.[30,31] Second, increasing evidence suggests that postoperative rejection, delay, and discontinuation of adjuvant chemotherapy are correlated with poor survival outcomes in advanced gastric cancer.[32–34] The ERAS group demonstrated expedited postoperative physical recovery, improved nutritional status, and timely administration of adjuvant chemotherapy. In addition, a greater proportion of cases in the ERAS group received adjuvant chemotherapy and completed adjuvant chemotherapy. Previous research has indicated that intraoperative blood loss adversely affects the prognosis of individuals with advanced gastric cancer.[35] Surgical stress refers to a complex response of the body to surgical trauma, involving multiple systems such as neuroendocrine, metabolic, and immune systems. The core of ERAS is to alleviate the surgical stress of the body during the perioperative period, block the transmission of stress signals by incoming nerves, and reduce psychological and physical damage to patients. Previous studies have found that ERAS can help alleviate surgical stress, protect immune function, and reduce inflammatory responses, thereby improving postoperative recovery and oncological outcomes for gastric cancer patients.[26,36] The whole process management during the perioperative period, including appropriate anesthesia methods and drugs, multimodal analgesia, nutritional support, fluid management, early activity, and early removal of drainage tubes, can effectively reduce surgical stress and inflammatory reactions.[26,37,38] Perhaps, prehabilitation also plays a positive role in the prognosis of these patients, and past research discovered that prehabilitation is associated with improved 5-year DFS in colorectal cancer.[39] Our study findings suggest that the ERAS group exhibited lower rates of blood loss, although there is no obvious difference and thereby have a minor influence on oncological safety.[40] Last, high compliance, good nutritional status, moderate exercise, lifestyle changes (smoking cessation, alcohol limitation, reasonable diet), and timely follow-up are all favorable factors for improving the survival of gastric cancer patients. Although the data in our article do not reflect these rational aspects, we observed that patients in the ERAS group performed better.[41–44] In the present study, ERAS was associated with an improved 3-year OS and DFS in all patients and patients with stage III disease. A similar result was not observed because of the low rates of recurrences in stage I and II gastric

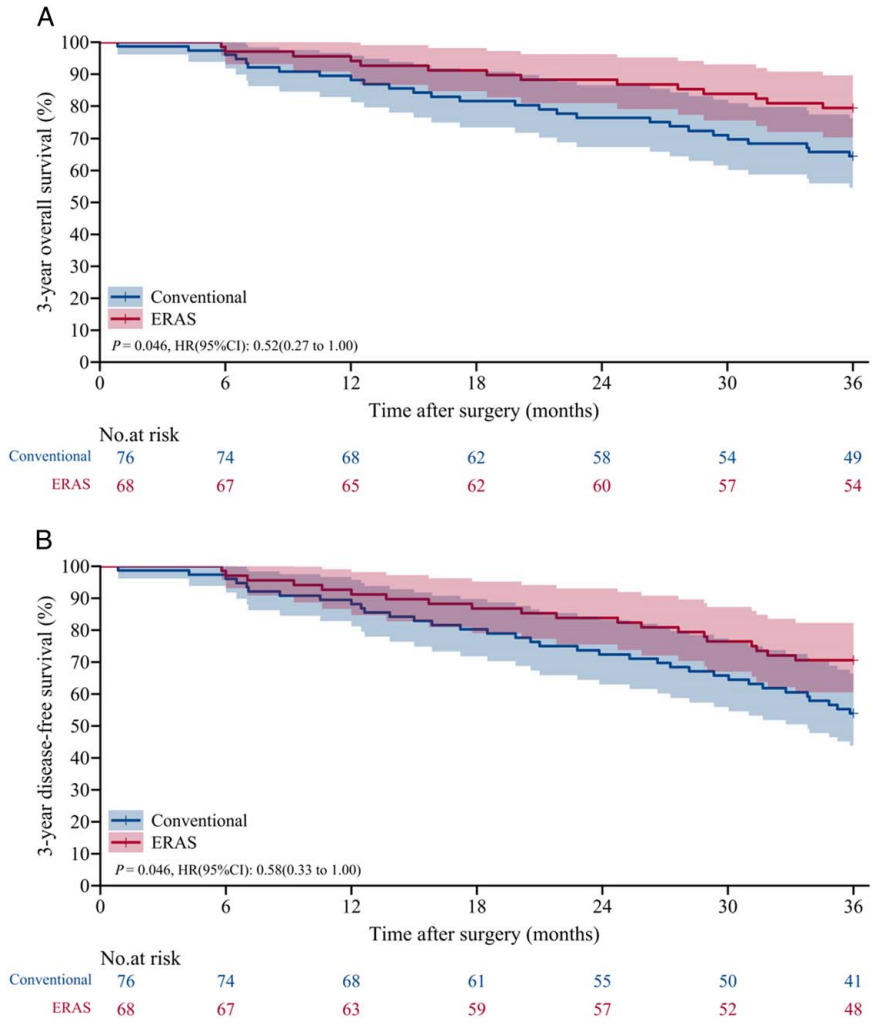

FIGURE 4. OS (A) and DFS (B) for ERAS versus conventional at 3 years after surgery in patients with stage III.

cancer patients. In our multivariate analysis, ERAS was identified as an independent predictor of better OS and DFS in all patients after adjusting for possible confounders. In recent years, it has become increasingly clear that the magnitude of the response to surgical injury is patient-specific and involves a plethora of inflammatory and immunologic responses which have been shown to be related to post-operative recovery and oncological results.[41]

This RCT has several limitations. Primarily, the study design is an open randomized controlled trial, potentially introducing bias into the results due to the subjective consciousness of surgeons. In addition, a detailed analysis of the survival benefits conferred by strict adherence to components of the ERAS protocol, such as nutritional optimization, psychological counseling, goal-directed periodic fluid therapy, preoperative oral intake of carbohydrates, early postoperative nutritional support, and optimization of anesthesia methods, is unavailable.[45,46] Nevertheless, our research suggests that the ERAS program improves oncological outcomes for patients. Nevertheless, due to missing data and varying postoperative testing times, we did not dynamically compare changes in inflammatory indicators between the groups, despite their potential impact on clinical outcomes.[47] In addition, further research is needed to understand the mechanisms, such as surgical stress, immune response, and the tumor microenvironment, that impact patient prognosis. Furthermore, despite the exclusion of elderly and neoadjuvant therapy gastric cancer patients in the original study, individuals with diminished baseline functional capacities appeared to derive the most substantial advantages from the ERAS program, potentially exerting a more pronounced influence on prognosis.[48] Lastly, at present, the survival rate of gastric cancer patients has been greatly improved. Our sample size calculation was based on the survival data from 10 years ago. This may have an impact on the study results. Consequently, continuous optimization of ERAS protocols and heterogeneity in patients' whole-course management should be fully considered, we hope that present research findings can be extrapolated further to other populations or surgical diseases worldwide through rigorously designed RCT studies.[49]

CONCLUSIONS

The findings of this RCT trial demonstrate that strict adherence to the ERAS protocol in patients undergoing LDG can lead to a decrease in overall complication rates, shorter hospital stays, reduced medical costs, and improved 3-year OS and DFS rates, particularly in those with stage III gastric cancer.

ACKNOWLEDGMENTS

The authors thank all the statistical experts statisticians, pathologists, imaging specialists, radiologists, oncologists, anesthesiologists, nurses, clinical dietitians, and rehabilitative physicians who support this study.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
2. Qiu H, Cao S, Xu R. Cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020. *Cancer Commun (Lond)*. 2021;41:1037–1048.
3. Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer. *Lancet (Lond)*. 2020;396:635–648.
4. Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). *Gastric Cancer*. 2023;26:1–25.
5. Kitano S, Iso Y, Moriyama M, et al. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc*. 1994;4:146–148.
6. Etoh T, Ohyama T, Sakuramoto S, et al. Five-year survival outcomes of laparoscopy-assisted vs open distal gastrectomy for advanced gastric cancer: the JLSSG0901 randomized clinical trial. *JAMA Surg*. 2023;158:445–454.
7. Hyung WJ, Yang HK, Park YK, et al. Long-term outcomes of laparoscopic distal gastrectomy for locally advanced gastric cancer: the KLASS-02-RCT randomized clinical trial. *J Clin Oncol*. 2020;38:3304–3313.
8. Yu J, Huang C, Sun Y, et al. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. *Jama*. 2019;321:1983–1992.
9. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth*. 1997;78:606–617.
10. Huang ZD, Gu HY, Zhu J, et al. The application of enhanced recovery after surgery for upper gastrointestinal surgery: meta-analysis. *BMC Surg*. 2020;20:3.
11. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg*. 2008;248:189–198.
12. Wang D, Kong Y, Zhong B, et al. Fast-track surgery improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care. *J Gastrointest Surg*. 2010;14:620–627.
13. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS) Society recommendations. *Br J Surg*. 2014;101:1209–1229.
14. Rubinkiewicz M, Pisarska M, Zarzycki P, et al. High compliance to ERAS protocol does not improve overall survival in patients treated for resectable advanced gastric cancer. *Wideochir Inne Tech Maloinwazyjne*. 2020;15:553–559.
15. Tian YL, Cao SG, Liu XD, et al. Short- and long-term outcomes associated with enhanced recovery after surgery protocol vs conventional management in patients undergoing laparoscopic gastrectomy. *World J Gastroenterol*. 2020;26:5646–5660.
16. Tian Y, Cao S, Li L, et al. Effects of perioperative enhanced recovery after surgery pathway management versus traditional management on the clinical outcomes of laparoscopic-assisted radical resection of distal gastric cancer: study protocol for a randomized controlled trial. *Trials*. 2020;21:369.
17. Tian Y, Cao S, Liu X, et al. Randomized controlled trial comparing the short-term outcomes of enhanced recovery after surgery and conventional care in laparoscopic distal gastrectomy (GISSG1901). *Ann Surg*. 2022;275:e15–e21.
18. Meng C, Cao S, Tian Y, et al. Short- and long-term outcomes of laparoscopic or robotic radical gastrectomy based on preoperative perigastric artery CTA surgical decision-making: a high-volume center retrospective study with propensity score matching. *Surg Endosc*. 2023;37:6930–6942.
19. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20:167–192.
20. Yang FZ, Wang H, Wang DS, et al. The effect of perioperative ERAS pathway management on short-and long-term outcomes of gastric cancer patients. *Zhonghua Yi Xue Za Zhi (Taipei)*. 2020;100:922–927.
21. Kehlet H. Enhanced postoperative recovery: good from afar, but far from good? *Anaesthesia*. 2020;75(suppl 1):e54–e61.
22. Petrowsky H, Demartines N, Rousson V, et al. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. *Ann Surg*. 2004;240:1074–1084; discussion 1084-1075.
23. Zhu Z, Wang C, Xu C, et al. Influence of patient-controlled epidural analgesia versus patient-controlled intravenous analgesia on postoperative pain control and recovery after gastrectomy for gastric cancer: a prospective randomized trial. *Gastric Cancer*. 2013;16:193–200.
24. Jeong O, Kim HG. Implementation of enhanced recovery after surgery (ERAS) program in perioperative management of gastric cancer surgery: a nationwide survey in Korea. *J Gastric Cancer*. 2019;19:72–82.
25. Kehlet H. ERAS Implementation-time to move forward. *Ann Surg*. 2018;267:998–999.
26. Wee IJY, Syn NL, Shabbir A, et al. Enhanced recovery versus conventional care in gastric cancer surgery: a meta-analysis of randomized and non-randomized controlled trials. *Gastric Cancer*. 2019;22:423–434.
27. Yuan W, Huang G, Dai P, et al. Application of enhanced recovery after surgery in perioperative patients undergoing laparoscopic surgery for gastric cancer: a meta-analysis. *Medicine*. 2023;102:e32962.
28. Gustafsson UO, Oppelstrup H, Thorell A, et al. Adherence to the ERAS protocol is associated with 5-year survival after colorectal cancer surgery: a retrospective cohort study. *World J Surg*. 2016;40:1741–1747.
29. Pisarska M, Torbicz G, Gajewska N, et al. Compliance with the ERAS protocol and 3-year survival after laparoscopic surgery for non-metastatic colorectal cancer. *World J Surg*. 2019;43:2552–2560.
30. Pucher PH, Aggarwal R, Qurashi M, et al. Meta-analysis of the effect of postoperative in-hospital morbidity on long-term patient survival. *Br J Surg*. 2014;101:1499–1508.
31. Wang S, Xu L, Wang Q, et al. Postoperative complications and prognosis after radical gastrectomy for gastric cancer: a systematic review and meta-analysis of observational studies. *World J Surg Oncol*. 2019;17:52.
32. Chen QY, Liu ZY, Zhong Q, et al. Clinical impact of delayed initiation of adjuvant chemotherapy among patients with stage II/III gastric cancer: can we do better? *Front Oncol*. 2020;10:1149.
33. Jiang Y, Li T, Liang X, et al. Association of adjuvant chemotherapy with survival in patients with stage II or III gastric cancer. *JAMA Surg*. 2017;152:e171087.
34. Lu H, Zhao B, Zhang J, et al. Does delayed initiation of adjuvant chemotherapy following the curative resection affect the survival outcome of gastric cancer patients: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2020;46:1103–1110.
35. Ripollés-Melchor J, Abad-Motos A, Zorrilla-Vaca A. Enhanced Recovery After Surgery (ERAS) in Surgical Oncology. *Curr Oncol Rep*. 2022;24:1177–1187.
36. Murakami Y, Saito H, Shimizu S, et al. Increased regulatory B cells are involved in immune evasion in patients with gastric cancer. *Sci Rep*. 2019;9:13083.
37. Wang Y, Qu M, Qiu Z, et al. Surgical Stress and Cancer Progression: New Findings and Future Perspectives. *Curr Oncol Rep*. 2022;24:1501–1511.

38. Kelliher LJS, Scott M. Modifying the Stress Response - Perioperative Considerations and Controversies. *Anesthesiol Clin*. 2022;40:23–33.
39. Trépanier M, Minnella EM, Paradis T, et al. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. *Ann Surg*. 2019;270:493–501.
40. Ito Y, Kanda M, Ito S, et al. Intraoperative Blood Loss is Associated with Shortened Postoperative Survival of Patients with Stage II/III Gastric Cancer: Analysis of a Multi-institutional Dataset. *World J Surg*. 2019;43:870–877.
41. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. *Ann Surg*. 2015;261:1153–1159.
42. Aarts MA, Rotstein OD, Pearsall EA, et al. Postoperative ERAS Interventions Have the Greatest Impact on Optimal Recovery: Experience With Implementation of ERAS Across Multiple Hospitals. *Ann Surg*. 2018;267:992–997.
43. Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012;104:815–840.
44. Horowitz M, Neeman E, Sharon E, et al. Exploiting the critical perioperative period to improve long-term cancer outcomes. *Nat Rev Clin Oncol*. 2015;12:213–226.
45. Rollins KE, Lobo DN. Intraoperative Goal-directed Fluid Therapy in Elective Major Abdominal Surgery: A Meta-analysis of Randomized Controlled Trials. *Ann Surg*. 2016;263:465–476.
46. Yan X, Zhou FX, Lan T, et al. Optimal postoperative nutrition support for patients with gastrointestinal malignancy: A systematic review and meta-analysis. *Clin Nutr*. 2017;36:710–721.
47. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev*. 2013;39:534–540.
48. Sun Y, Tian Y, Cao S, et al. Multimodal prehabilitation to improve the clinical outcomes of frail elderly patients with gastric cancer: a study protocol for a multicentre randomised controlled trial (GISSG(+)2201). *BMJ Open*. 2023;13:e071714.
49. Kehlet H, Lobo DN. Exploring the need for reconsideration of trial design in perioperative outcomes research: a narrative review. *EClinicalMedicine*. 2024;70:102510.

