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Randomized Controlled Trial Comparing the Short-term Outcomes of Enhanced Recovery After Surgery and Conventional Care in Laparoscopic Distal Gastrectomy (GISSG1901)

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Objective: This study aimed to compare the effects of ERAS and conventional programs on short-term outcomes after LDG.

Summary of Background Data: Currently, the ERAS program is broadly applied in surgical areas. Although several benefits of LDG with the ERAS program have been covered, high-level evidence is still limited, specifically in advanced gastric cancer.

Methods: The present study was designed as a randomized, multicenter, unblinded trial. The enrollment criteria included histologically confirmed cT2-4aN0-3M0 gastric adenocarcinoma. Postoperative complications, mortality, readmission, medical costs, recovery, and laboratory outcomes were compared between the ERAS and conventional groups.

Results: Between April 2019 and May 2020, 400 consecutive patients who met the enrollment criteria were enrolled. They were randomly allocated to either the ERAS group (n = 200) or the conventional group (n = 200). After excluding patients who did not undergo surgery or gastrectomy, 370 patients were analyzed. The patient demographic characteristics were not different between the 2 groups. The conventional group had a significantly longer allowed day of discharge and postoperative hospital stay (6.96 vs 5.83 days, $P < 0.001$; 8.85 vs 7.27 days, $P < 0.001$); a longer time to first flatus, liquid intake and ambulation (3.37 vs 2.52 days, $P < 0.001$; 3.09 vs 1.13 days, $P < 0.001$; 2.85 vs 1.38 days, $P < 0.001$, respectively); and higher medical costs (6826 vs 6328 $, $P = 0.027$) than the ERAS group. Additionally, patients in the ERAS group were more likely to initiate adjuvant chemotherapy earlier (29 vs 32 days, $P = 0.035$). There was no significant difference in postoperative complications or in the mortality or readmission rates. Regarding laboratory outcomes, the procalcitonin and C-reactive protein levels on postoperative day 3 were significantly lower and the hemoglobin levels on postoperative day 5 were significantly higher in the ERAS group than in the conventional group.

Conclusion: The ERAS program provides a faster recovery, a shorter postoperative hospitalization length, and lower medical costs after LDG without increasing complication and readmission rates. Moreover, enhanced recovery in the ERAS group enables early initiation of adjuvant chemotherapy.

Keywords: advanced gastric cancer, conventional care, enhanced recovery after surgery, laparoscopic distal gastrectomy, short-term outcomes

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Globally, gastric cancer (GC) is the fifth most common cancer, and its cancer-related mortality ranks third.[1] Among GC cases, advanced gastric cancer (AGC) accounts for the majority in China.[2] The diagnosis, treatment, and survival data of GC have improved dramatically over recent decades due to the introduction of new surgical techniques, chemotherapeutics, and targeted drugs.[3,4] A randomized controlled trial (RCT) of laparoscopic distal gastrectomy (LDG) versus open distal gastrectomy (KLASS-02) showed that compared with open distal gastrectomy patients, LDG patients had a faster recovery, fewer complications, and less pain.[5] Although LDG has been generally accepted, GC surgery remains a high-risk procedure that is significantly associated with surgical stress responses, complications, and mortality.[6,7]

Enhanced recovery after surgery (ERAS) has been accepted as a standard surgical perioperative management program, and it has also developed rapidly in the field of GC.[8] ERAS refers to the adoption of a series of optimization measures to reduce stress and complications and speed up the recovery of patients during the perioperative period through multidisciplinary cooperation. Several gastrectomy studies from single medical centers using the ERAS program for GC have been reported in China, Korea, and Japan.[9–12] A review of RCTs and observational studies comparing ERAS versus conventional care after gastrectomy showed that ERAS reduced postoperative hospital stay, medical costs and surgical stress, and

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optimized recovery without increasing postoperative morbidity.[13] The formulation of ERAS guidelines after gastrectomy standardized is used in perioperative care in 2014.[14] Currently, the ERAS program is accepted by the majority of patients with GC in East Asian countries.[9–13]

Emerging evidence indicates that the ERAS program can affect prognosis after colorectal surgery and elective orthopedic surgery.[15–17] In addition, a retrospective study showed that the ERAS program improved the 5-year overall survival (OS) of patients with GC, especially those with AGC.[18] The mechanism behind this phenomenon may be related not only to the reduction of complications and surgical stress responses but also to changes in the immune response leading to higher rates of recurrence and metastasis.[19–22] However, there are still a lack of RCTs studying whether ERAS can increase the survival of patients with AGC undergoing LDG.

Based on this background, the Shandong Gastrointestinal Surgery Study Group designed a multicenter, randomized, unblinded controlled trial to compare the short-term outcomes and long-term prognoses of ERAS and conventional care in LDG for patients with AGC. This paper is an early result concentrating on short-term outcomes, such as complications, mortality, postoperative recovery, and inflammatory indexes.

TABLE 1. Eligibility Criteria for Enrolling Patients

Inclusion
(1) patient's age between 18 and 80 years;
(2) histologically confirmed gastric adenocarcinoma;
(3) tumor of cT2∼4aN0∼3M0;
(4) tumor can be resected by distal gastrectomy in curative intention;
(5) ECOG performance status of 0 or 1;
(6) ASA score of class I to III;
(7) patient agreed to participate in this trial through informed consent.
Exclusion
(1) other malignant tumors within 5 years;
(2) history of previous gastric resection;
(3) distant metastasis found during the operation;
(4) severe or uncontrolled medical diseases and infections found at the same time;
(5) use of opioid analgesics or hormones within 7 d before the operation;
(6) severe or uncontrollable mental illness;
(7) history of gastric cancer treatment by endoscopic resection, chemotherapy, and/or radiotherapy;
(8) participation and treatment with anti-cancer drugs in other clinical trials.

ASA indicates American Society of Anesthesiology; ECOG PS, Eastern Cooperative Oncology Group performance status.

METHODS

Design, Patients, and Randomization

This study was designed as a multicenter, randomized, unblinded control trial comparing the short-term outcomes and oncologic safety of ERAS and conventional care in LDG (Chinese Clinical Trial Registry, CHiCTR1900022438), and the program used in this RCT was reported previously.[23] The primary endpoints were 3-year OS and disease-free survival. The secondary endpoints were complications, mortality, postoperative recovery, and medical costs. The exploratory results were changes in perioperative inflammatory and immune responses (leukocytes, neutrophil percentage, C-reactive protein (CRP), procalcitonin, tumor necrosis factor (TNF)-α, and interleukin (IL)-6). The trial program was approved by the Affiliated Hospital of Qingdao University Ethics Committee, and all participants signed informed consent.

Eligible participants were between 18 and 80 years of age and had pathologically proven gastric adenocarcinoma with a clinical stage of T2-4aN0-3M0. The detailed inclusion and exclusion criteria are shown in the published trial program (Table 1).

Eligible patients were randomized to the ERAS or conventional care group at a 1:1 ratio before the operation (Fig. 1). The data collectors were separate from those who conducted the eligibility evaluation and recruitment of patients, and they performed the randomization with a list of randomly ordered treatment identifiers generated by a permuted block design using SAS, version 9.4 (SAS Institute Inc., North Carolina, USA). Until patients had been formally assigned to their group, the order of assignment was hidden from the surgeon who registered the patient. After randomization, the surgeons immediately informed the anesthesiologists, nurses, and patients of the group assignments to carry out the different types of perioperative care. Although it was not possible to blind the doctors and patients, the radiologists, data manager, and pathologists were not aware of the program received by the patients.

Surgical Quality Evaluation

To ensure surgical quality in the RCT, we conducted a rigorous evaluation of the surgeon's surgical expertise. In brief, each surgeon independently performed more than 100 laparoscopic gastrectomy procedures. At least 100 surgeries are performed by the surgeon's team each year. In addition to meeting the above conditions, surgeons submitted 6 LDGs with D2 lymphadenectomy unedited videos, and each video was recognized by 5 blinded evaluation experts; eventually, 13 surgeons from 13 hospitals were eligible. After starting the RCT, unedited videos and intraoperative photos of the surgical areas in LDG were collected and censored. The expert committee evaluated the surgical procedures of surgeons and, if necessary, provided surgical support to surgeons.

Surgical Procedure and Perioperative Care

First, we explored the abdominal organs and then performed standard LDG with D2 lymphadenectomy and total omentectomy. In both groups, the extents of gastrectomy and D2 lymphadenectomy were based on the Japanese GC treatment guidelines.[24] The type of reconstruction was determined by the tumor location and surgeon's preference (Billroth I/II or Roux-en-Y gastrojejunostomy). According to their own experience, surgeons could choose extracorporeal or intracorporeal methods and stapling instruments or hand sewing methods for anastomosis, but extracorporeal anastomosis using a minilaparotomy was recommended. If complications (bleeding, invasion of adjacent organs, or organ injury) occurred before laparoscopic D2 lymph node dissection was completed or if the length of the incision exceeded 10 cm, the surgery was defined convert to open.

Before surgery, gastroscopy, ultrasonic gastroscopy, chest, total abdominal, and pelvic computed tomography (CT) was performed to verify the location and size of the cancer. In addition, positron emission tomography-CT is recommended for patients with suspected distant metastasis, and patients with distant metastasis were excluded according to the assessments of 2 seasoned radiologists. We did not routinely perform diagnostic laparoscopy with washings to stage and rule out occult metastatic disease before operation in this study. However, for all patients, we asked for taking abdominal flushing water during the operation for exfoliative cytological examination. Upper abdominal CT angiography was performed to accurately determine the distribution of perigastric blood vessels, avoid intraoperative bleeding and vascular injury caused by vascular variation, and guide lymphadenectomy.[25] The cardiopulmonary function of patients was strictly evaluated through

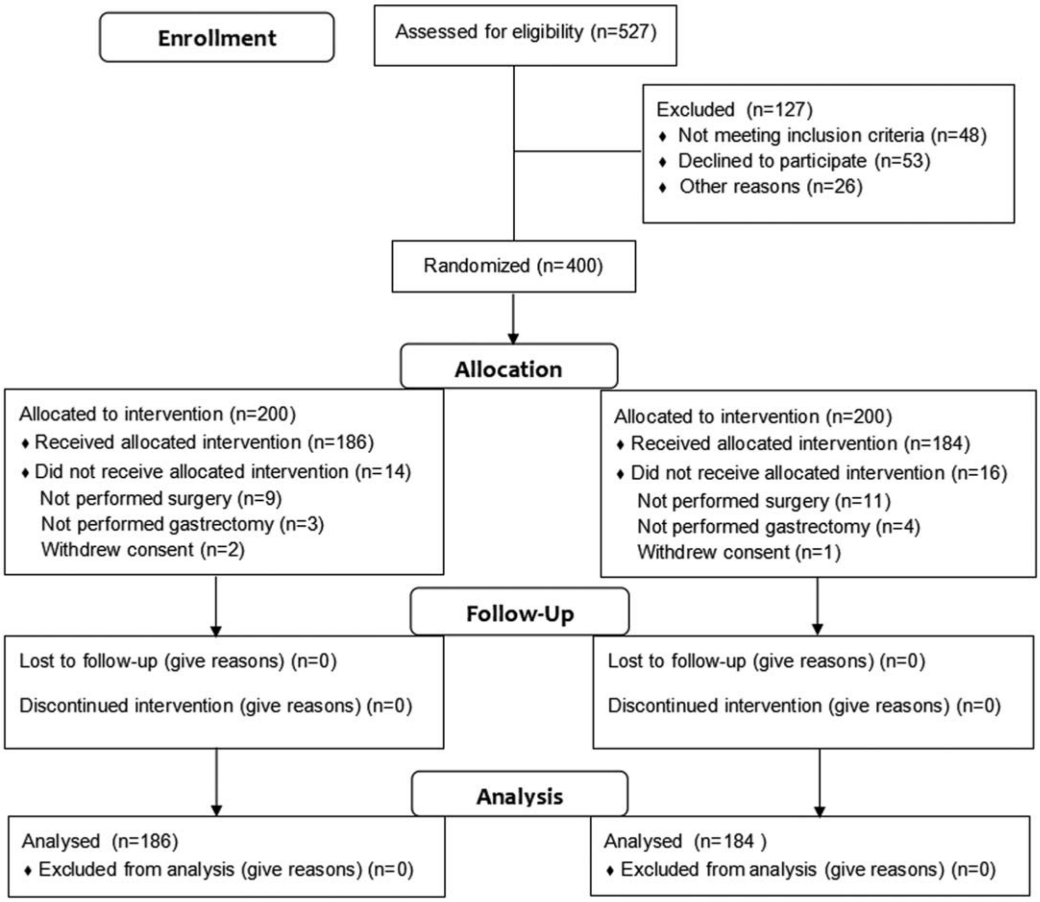

FIGURE 1. CONSORT flow diagram of patient enrollment and randomization.

cardiac ultrasound and pulmonary function tests to ensure that the patients could tolerate laparoscopic surgery.

During the operation, we followed GC treatment guidelines; performed LDG and D2 lymphadenectomy; selected the appropriate reconstruction method; and recorded the intraoperative complications, blood loss, and operation time.

After the operation, all adverse events were closely observed and treated. The measures taken and the drugs used in response to the adverse events were recorded and described on the case report form. The detailed postoperative management program was previously described (Table 2).[23] Laboratory examinations were performed preoperatively and 1, 3, and 5 days postoperatively. The measurements included blood routine, kidney function, liver function, electrolyte, CRP, IL-6, procalcitonin, and TNF-α tests. For patients with pathological stage II cancer or above, S-1 capsule combined with oxaliplatin was recommended for 6–8 cycles of adjuvant chemotherapy.

Definition of Surgical Complications and Mortality

The operation-related complications that occurred within the first 30 postoperative days (PODs) were defined as early complications. Complications included intraoperative and postoperative complications. Briefly, postoperative complications included wound and pulmonary infections, gastroparesis, anastomotic leakage, lymphatic leakage, pancreatic fistulas, intra-abdominal bleeding, intraluminal bleeding, intra-abdominal abscesses, deep vein thrombosis, ileus, cholecystitis and cerebrovascular, cardiac, hepatic, and renal complications. The severity of postoperative complications was assessed in accordance with the Clavien-Dindo classification.[26]

Admission for surgery-related complications within 30 days after discharge was defined as readmission. Any death during hospitalization or related to surgery-related complications within 30 PODs was defined as mortality.

Sample Size and Statistical Analysis

This study adopted the design of a noninferiority test, and the calculation of sample size was based on the following assumptions and historical data. The study found that the 3-year OS rate of patients who underwent radical gastrectomy under the ERAS program from 2011 to 2014 was approximately 65%.[18] Given that patient selection required 10 months, the median follow-up time will be 3 years; therefore, the noninferiority threshold was set to 1.33, according to a 1:1 random ratio. Assuming a significance level of $\alpha = 0.05$ (bilateral) and test efficiency of $1\text{-}\beta = 80\%$, revealing that at least 178 patients would be necessary per group. A target enrollment of 400 patients was chosen to allow for a dropout rate of approximately 10%.

Categorical variables are described as numbers and percentages and were compared between groups using Pearson chi-square test or Fisher exact test. Continuous variables are described as the mean $\pm$ standard deviation. Nonnormally distributed continuous data were compared with medians and interquartile ranges, and Student's *t*-test was used for normally distributed continuous variables. Significance was defined as $P < 0.05$. All statistical tests were

TABLE 2. Perioperative Pathway Management for Gastric Cancer

Program clauses	ERAS Group	Conventional Group
Preoperative		
Health education, exercise advice*	Yes	Yes
Organ function evaluation*	Yes	Yes
Prerehabilitation treatment*	Yes	No
MDT, clinical decision making*	Yes	Yes
Nutritional assessment, intervention*	Yes	Yes
Intestinal preparation	Enteral nutrition	No
	No mechanical bowel preparation	Mechanical intestinal preparation
Fasting and abstinence from drinking*	Fasting 6 h before operation	Fasting and drinking for 6 h before operation
	2-h oral glucose infusion 200 mL	
Intraoperative		
Intraoperative safety check (checklist)*	Yes	Yes
Target-oriented liquid management*	Yes	No
Local anesthesia in the deep incision	Local anesthesia (0.5% ropivacaine)	No
Prevention of antibiotic use	Yes	Yes
Surgical incision*	Small midline (<8 cm) incision	Small midline (<8 cm) incision
Precision surgery*	Laparoscopic surgery	Laparoscopic surgery
Anesthesia mode*	General anesthesia combined with epidural anesthesia (T7–T9)†	General anesthesia
Intraoperative heat preservation‡	Yes	Yes
Postoperative		
Urinary catheter	Remove within 24 h	Routine indwelling for 1–3 d
Abdominal drainage tube	Do not place or remove early after operation as far as possible	Remove it before discharge§
Gastric tube	No	Retention for 1–3 d‖
Early bedside activity*	Start soberly and plan your activities	2–3 d after operation
Postoperative analgesia*	Multimodal analgesia¶	Opioids#
Target-oriented liquid management*	Yes	No
Prevention of deep venous thrombosis	Basic, physical, and drug prevention	Basic and drug prevention
Early EN after operation*	Sequential EN treatment after awakening	Gradually start EN after exhaust

*Core provisions of perioperative ERAS pathway management.
†Dose/drug: ropivacaine 500 mg + lidocaine 400 mg and liquid velocity: 2 mL/h.
‡Heat preservation measures: preheating fluid replenishment, thermal blanket, heater.
§Extubation indication: the drainage fluid is light red or clear, 24 h less than 20 mL, and no pancreatic and lymphatic fistula.
‖The criteria of removal of nasogastric tube: recovery of intestinal peristalsis, anal exhaust, and oral clear fluid.
¶Multimodal analgesia: POD1–2 patient controlled epidural analgesia (lidocaine + ropivacaine), POD3–5 regular oral paracetamol 0.65 g q8 h 50 mg when the VAS ≥4 flurbiprofen 50 mg is injected intravenously.
#Opioids: POD1–2 tramadol 50 mg q8 h, when the VAS ≥4 tramadol 50 mg is injected intravenously (dose ≤400 mg/d).
NSAID indicates nonsteroidal anti-inflammatory drugs; EN, enteral nutrition; ERAS, enhanced recovery after surgery.

2-sided and performed using SPSS software version 24.0 (SPSS, Chicago, IL).

RESULTS

Safety Analysis of Early Complications

After a total of 212 patients were enrolled in the RCT, the expert committee conducted the safety evaluation in January 2020. The rate of surgery-related complications was 16.4% in the ERAS group and 21.8% in the conventional group ($P = 0.162$); therefore, the expert committee decided to continue this RCT until the full enrollment of patients was achieved (n = 400).

Demographics Characteristics

Figure 1 shows the CONSORT flow diagram of patient enrollment and randomization. From April 2019 to March 2020, 400 patients were enrolled and randomly assigned to each group. After excluding 14 patients in the ERAS group and 16 patients in the conventional group, 186 patients in the ERAS group, and 184 patients in the conventional group were analyzed for outcomes.

The patient demographics and baseline characteristics, including age, sex, body mass index, American Society of Anesthesiology scores, nutrition risk screening 2002, Eastern Cooperative Oncology Group performance status, comorbidities, histologic type, clinical T and N stages, and previous abdominal operations, are shown in Table 3. The characteristics of laparoscopic gastrectomy were well balanced between the ERAS and conventional groups. The completion rates of the protocol for each items were all greater than 95%, apart from anesthesia mode was 92.0% (171/186) for the ERAS group. Happily, the completion rates for the conventional group were near 100%.

Surgical, Pathologic, and Postoperative Recovery Outcomes

As shown in Table 4, the time to first flatus and time to first liquid intake were significantly shorter in the ERAS group than in the conventional group (2.52 vs 3.37 days, $P < 0.001$; 1.13 vs 3.09, $P < 0.001$); moreover, the time to ambulation was significantly shorter in the ERAS group than in the conventional group (1.38 vs 2.85 days, $P < 0.001$). The allowed day of discharge and postoperative hospital stay were significantly shorter in the ERAS group than in the conventional group (5.83 vs 6.96 days, $P < 0.001$; 7.27 vs 8.85, $P < 0.001$). Readmission rates of ERAS and conventional group were revealed as 4.8% (n = 9) and 4.3% (n = 8) ($P = 0.821$). Causes of

TABLE 3. Patient Demographics and Baseline Characteristics

Variables	ERAS (n = 186)	Conventional (n = 184)	P-value
Age, yr ± SD	58.3 ± 10.5	58.6 ± 10.9	0.305
Sex			0.685
Male, n (%)	129 (69.4)	124 (67.4)	
Female, n (%)	57 (30.6)	60 (32.6)	
BMI, kg/m^2 ± SD	23.6 ± 3.2	23.7 ± 3.3	0.351
ASA score			0.804
I, n (%)	98 (50.0)	93 (50.5)	
II, n (%)	74 (39.8)	79 (42.9)	
III, n (%)	14 (7.5)	12 (6.5)	
NRS 2002			0.757
<3, n (%)	89 (47.8)	91 (49.5)	
>=3, n (%)	97 (52.2)	93 (50.5)	
ECOG			0.609
0, n (%)	121 (65.1)	115 (62.5)	
1, n (%)	65 (34.9)	69 (37.5)	
Comorbidity			0.686
None, n (%)	112 (60.2)	107 (58.2)	
One or more, n (%)	74 (39.8)	77 (41.8)	
Histologic type			0.651
Well, n (%)	14 (7.5)	14 (7.6)	
Moderate, n (%)	56 (30.1)	60 (32.6)	
Poor, n (%)	116 (62.4)	110 (59.8)	
cT stage*			0.761
cT2, n (%)	61 (32.8)	54 (29.3)	
cT3, n (%)	40 (21.5)	43 (23.4)	
cT4a, n (%)	85 (45.7)	87 (47.3)	
cN stage*			0.759
cN0, n (%)	35 (18.8)	27 (14.7)	
cN1, n (%)	38 (20.4)	38 (20.7)	
cN2, n (%)	39 (21.0)	41 (25.5)	
cN3, n (%)	74 (39.8)	78 (41.8)	
Previous abdominal operation, n (%)	28 (15.1)	22 (12.0)	0.384

*Pathologic stage according to the American Joint Committee on Cancer, seventh edition.

ASA indicates American Society of Anesthesiologists; BMI, body mass index; ECOG: Eastern Cooperative Oncology Group; ERAS, enhanced recovery after surgery; NRS, nutrition risk screening, SD, standard deviation.

readmission were 2 gastroparesis, 1 pulmonary infection, 1 pancreatic fistula, 1 intraluminal bleeding, 2 ileus, 1 kidney dysfunction, 1 cerebrovascular in the ERAS group, and 4 gastroparesis, 1 pulmonary infection, 1 hematochezia, 1 ileus, 1 poor heart function in the conventional group.

The operation time, estimated blood loss, extent of resection, lymph node (LN) dissection, reconstruction, intraoperative transfusion, length of incision, retrieved LN number, retrieved LNs <15, positive margin, pathological tumor (pT), pathological node (pN), and pTNM stage were not significantly different between the groups. There was no significant difference in the exfoliated cancer cells positive rate between the 2 groups (8.1% vs 9.8%, $P = 0.562$). In the ERAS group, 8 patients underwent combined surgery due to cancer invasion to adjacent organs (n = 6) and surgical technical problems (n = 2). Additionally, patients in the ERAS group were more likely to initiate adjuvant chemotherapy earlier (29 [26–32] vs 32 [29–40] days, $P = 0.035$). Mean medical cost was 6328 $ in the ERAS group and 6826 $ in the conventional group ($P = 0.027$).

Surgical Complications and Mortality

Regarding surgical morbidity, the overall complications were not significantly different between the groups (16.7% vs 21.2% in ERAS and conventional group, $P = 0.266$, Table 5). Intraoperative complications were also not different between the groups (4.8% vs 5.4%, $P = 0.796$); notably, 22 patients in the ERAS group and 29 patients in the conventional group had postoperative complications, with no statistically significant difference between the 2 groups (11.8% vs 15.8%, $P = 0.273$). According to the Clavien-Dindo classification of surgical complications, the distribution of severity was similar between the 2 groups. The mortality rate was 0 in the ERAS group and 0.5% in the conventional group ($P = 0.314$). The reasons for mortality were duodenal leakage with abdominal infection.

TABLE 4. Surgical, Pathologic, and Recovery Outcomes for ERAS and Conventional Group

Variables	ERAS (n = 186)	Conventional (n = 184)	P-value
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			0.470
Total gastrectomy, n (%)	10 (5.4)	7 (3.8)	
Distal gastrectomy, n (%)	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			0.570
Billroth-I, n (%)	7 (3.8)	11 (6.0)	
Billroth-II, n (%)	54 (29.0)	49 (26.6)	
Roux-en-Y, n (%)	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, n (%)	7 (3.8)	5 (2.7)	0.570
Positive margin, n (%)	2 (1.1)	1 (0.5)	0.569
Exfoliated cancer cells positive, n (%)	15 (8.1)	18 (9.8)	0.562
pT stage			0.445
T1, n (%)	24 (12.9)	15 (8.2)	
T2, n (%)	41 (22.0)	35 (19.0)	
T3, n (%)	44 (23.7)	43 (23.4)	
T4a, n (%)	71 (38.2)	84 (45.7)	
T4b, n (%)	6 (3.2)	7 (3.8)	
pN stage			0.582
N0, n (%)	37 (19.9)	29 (15.8)	
N1, n (%)	41 (22.0)	35 (19.0)	
N2, n (%)	46 (24.7)	44 (23.9)	
N3a, n (%)	42 (22.6)	48 (26.1)	
N3b, n (%)	20 (10.8)	28 (15.2)	
pTNM stage			0.564
I, n (%)	41 (22.0)	34 (18.5)	
II, n (%)	77 (41.4)	74 (40.2)	
III, n (%)	68 (36.6)	76 (41.3)	
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-d readmission, n (%)	9 (4.8)	8 (4.3)	0.821
Surgical procedure-adjuvant chemotherapy interval, median (IQR), d	29 (26–32)	32 (29–40)	0.035
Medical cost (dollars ± SD)	6328 ± 925	6826 ± 1174	0.027

ERAS indicates enhanced recovery after surgery; IQR, interquartile range, SD, standard deviation.

Laboratory Outcomes

Supplemental Table 1, http://links.lww.com/SLA/D73 shows the changes in laboratory outcomes from blood samples before and after the operation. Regarding laboratory outcomes, the hemoglobin level on POD5 was significantly higher in the ERAS group (11.67 vs 11.30 g/dL $P = 0.036$). However, the CRP and procalcitonin levels on the third POD were significantly lower in the ERAS group (78.35 vs 90.61 mg/L $P < 0.001$; 0.58 vs 0.63 ug/L $P = 0.025$, respectively). White blood cell and amylase levels were similar between the groups.

TABLE 5. Postoperative Complications and Mortality

Variables	ERAS Group (n = 186)	Conventional Group (n = 184)	*P*-value
Intraoperative complication, n (%)	9 (4.8)	10 (5.4)	0.796
Postoperative complication, n (%)	22 (11.8)	29 (15.8)	0.273
Wound infection, n (%)	2 (1.1)	2 (1.1)	1.000
Pulmonary, n (%)	6 (3.2)	10 (5.4)	0.296
Gastroparesis, n (%)	2 (1.1)	4 (2.2)	0.403
Anastomotic leakage, n (%)	2 (1.1)	3 (1.6)	0.644
Lymphatic leakage, n (%)	0 (0.0)	1 (0.5)	0.314
Pancreatic fistula, n (%)	1 (0.5)	2 (1.1)	0.556
Intra-abdominal bleeding, n (%)	1 (0.5)	1 (0.5)	1.000
Intraluminal bleeding, n (%)	3 (1.6)	2 (1.1)	0.661
Intra-abdominal abscess, n (%)	1 (0.5)	1 (0.5)	1.000
Deep vein thrombosis, n (%)	0 (0.0)	0 (0.0)	—
Ileus, n (%)	2 (1.1)	1 (0.5)	0.569
Cerebrovascular, n (%)	1 (0.5)	0 (0.0)	0.319
Cardiac, n (%)	0 (0.0)	1 (0.5)	0.314
Cholecystitis, n (%)	0 (0.0)	0 (0.0)	—
Hepatic, n (%)	0 (0.0)	1 (0.0)	—
Renal, n (%)	1 (0.5)	0 (0.0)	0.319
Overall morbidity, n (%)	31 (16.7)	39 (21.2)	0.266
Mortality, n (%)	0 (0.0)	1 (0.5)	0.314
Clavien-Dindo classification			
I, n (%)	6 (3.2)	5 (2.7)	0.773
II, n (%)	17 (9.1)	21 (11.4)	0.471
III, n (%)	6 (3.2)	7 (4.9)	0.763
IV, n (%)	2 (1.1)	3 (1.6)	0.644
V, n (%)	0 (0.0)	1 (0.5)	0.314

ERAS indicates enhanced recovery after surgery.

DISCUSSION

This is the first and largest multicenter RCT study to evaluate the impact of the ERAS program on patient outcomes after laparoscopic gastrectomy. The short-term outcomes of this RCT show that ERAS can be safely performed by experienced surgical centers in patients who have received LDG and has the benefits of enhancing recovery and reducing medical costs, but it does not increase the rate of postoperative complications or readmission compared with the conventional care.

In our study, minimally invasive surgery, as part of the ERAS program, was performed in almost the same way in both groups, excluding possible variations in the procedure itself. At present, some prospective trials in Japan, Korea, and China have evaluated the safety and oncological feasibility of LAG for early or AGC, and the results have provided high-level evidence of the safety and feasibility of LAG in AGC.[3–5] Notably, according to the American Society of Clinical Oncology guidelines, patients in both groups were given adequate analgesia and early thrombus prevention although the treatment methods were not exactly the same.[23] The ERAS group were treated with basic prevention combined with antithrombotic pressure pump and low molecular weight heparin prevention. However, the conventional group did not use antithrombotic pressure pump.

In this study, the patient demographic characteristics of the 2 groups were similar, and the same surgical procedure was used, which led to no difference in the surgical or pathological results. However, the ERAS group had a faster postoperative recovery and a shorter hospital stay, and these results were closely related to the ERAS program. ERAS is a multimode perioperative management program designed to achieve rapid postoperative rehabilitation, including health education, prerehabilitation, preoperative nutritional assessment and intervention, target-oriented liquid management, anesthesia mode, multimodal analgesia, early nutrition, early activity, and the removal of abdominal drainage tubes and catheters as soon as possible.[27]

The time to first flatus is often used as a simple index to evaluate the recovery of intestinal function.[13] In this study, the time to first flatus was significantly shortened in ERAS group, which implies that ERAS management leads to faster recovery of bowel function. Preoperative carbohydrates may be an important item in the ERAS items, although debatable.[27] The guidelines of the American Association of Anesthesiologists allow to intake clear fluid 2 hours preoperatively[28] which does not increase the volume of the stomach, and aspiration.[29] Surgical stress and preoperative fasting are thought to lead to insulin resistance, which may lead to hyperglycemia and may increase postoperative complications.[30] The traditional views have been that early postoperative feeding increase the risk of postoperative anastomotic leakage and pneumonia, which was not supported by our study. Epidural patient-controlled analgesia can effectively control pain[31] and enhance patients' tolerance to mobilization and diet.[32] Thus, a meta-analysis of thoracic epidural patient-controlled analgesia for laparoscopic gastrectomy (LG) showed significantly faster bowel mobilization and less pain.[33]

The results of this RCT were similar to those previous reports that an ERAS program significantly shortened the allowed day of discharge and postoperative hospital stay.[8–13] This may be attributed to the rapid recovery of intestinal function and physical strength. In our study, the postoperative hospital stay was not evaluated alone because the postoperative hospital stay was greatly affected by external factors, so the allowed day of discharge may be more accurate.

Although the complication rate in the ERAS group decreased by 4.5%, the overall complication rates in the 2 groups showed no significant difference; however, we believe this result is of great significance. Our LDG was standardized by experienced surgeons and was strictly evaluated before the trial, so we believe that the implementation of the same surgical operation, and adherence to the ERAS program can reduce the incidence of complications.

In the laboratory examinations, CRP and procalcitonin were significantly lower on POD 3 in ERAS than in conventional group, supporting that ERAS reduces various surgical stress responses. Unfortunately, some of the participating centers did not measure IL-6 and TNF-α, hindering more detailed statistical analyses.

Many previous RCTs and retrospective studies with small sample sizes have suggested that the ERAS program can improve the short-term outcomes of patients with GC.[34,35] However, this study is the first to verify these benefits in a large multicenter RCT designed for AGC patients. In particular, enhanced recovery and lower complication after LG for the patients with AGC might allow earlier adjuvant chemotherapy. In this context, our retrospective study showed that an ERAS program may increase the survival of patients with GC.[8,18]

This RCT has several limitations. First of all, total blinding is a challenging goal to reach because the distinction in perioperative care is readily observable. Also, the surgeon's subjective consciousness may lead to bias in the results, for example, doctors subconsciously allow patients in the ERAS group to be discharged as soon as possible, thus affecting the postoperative hospital stay. Secondly, we did not include patients with neoadjuvant chemotherapy or high-risk patients with comorbidities. It is unknown whether the ERAS program can be applied to these patients. Thirdly, this RCT still had abdominal drains placed in the ERAS group, which may cause surgery-related complications and lengthen hospitalization time.[36] Finally, we did not reveal the survival data of Shandong Gastrointestinal Surgery Study Group 1901 which might confirm the final impact of LDG for AGC.

Despite the global success of ERAS program, many challenges lie ahead[27] with numerous ERAS factors to be further explored. In conclusion, an ERAS program provided faster recovery and less postoperative hospital stay and medical costs after LDG without increasing complication and readmission rates. Moreover, the ERAS program might offer advantages over conventional care in terms of an earlier start of adjuvant chemotherapy.

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