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ORIGINAL ARTICLE

Protocol for enhanced recovery after surgery improves short-term outcomes for patients with gastric cancer: a randomized clinical trial

Ryo Tanaka[1] · Sang-Woong Lee[1] · Masaru Kawai[1] · Keitaro Tashiro[1] · Satoshi Kawashima[1] · Syuji Kagota[1] · Kotaro Honda[1] · Kazuhisa Uchiyama[1]

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Abstract

Background The feasibility of the use of the enhanced recovery after surgery (ERAS) protocol in patients with gastric cancer remains unclear.

Methods This study was a single-center, prospective randomized trial involving patients with gastric cancer undergoing curative gastrectomy. The primary end point was the length of postoperative hospital stay. Secondary end points were the postoperative complication rate, admission costs, weight loss, and amount of physical activity.

Results From July 2013 to June 2015, we randomized 148 patients into an ERAS protocol group ($n = 73$) and a conventional protocol group ($n = 69$); six patients withdrew from the study. The hospital stay was significantly shorter in the ERAS protocol group than in the conventional protocol group (9 days vs 10 days; $P = 0.037$). The ERAS protocol group had a significantly lower rate of postoperative complications of grade III or higher (4.1% vs 15.4%; $P = 0.042$) and reduced costs of hospitalization (JPY 1,462,766 vs JPY 1,493,930; $P = 0.045$). The ratio of body weight to preoperative weight at 1 week and 1 month after the operation was higher in the ERAS protocol group (0.962 vs 0.957, $P = 0.020$, and 0.951 vs 0.937, $P = 0.021$, respectively). The ERAS protocol group recorded more physical activity in the first week after surgery.

Conclusions The ERAS protocol is safe and efficient, and seems to improve the postoperative course of patients with gastric cancer.

Keywords Gastric cancer · Perioperative care · Enhanced recovery after surgery

Introduction

Gastric cancer is the fifth commonest cancer and the third leading cause of cancer-related deaths worldwide [1]. Although a minimally invasive surgical approach has received general acceptance [2–4], gastric cancer surgery remains a high-risk procedure that is associated with clinically significant postoperative stress, postgastrectomy syndrome, and other complications. The morbidity and mortality rates after radical gastrectomy have been reported as 9.1–28.1% and 0–1.3% respectively [2, 5–8].

Enhanced recovery after surgery (ERAS) is a multidisciplinary protocol of care delivered to patients with the aim of maintaining normal physiology and thereby facilitating postoperative recovery [9]. Based the original work of Kehlet and Wilmore [10, 11], the ERAS protocol is now used routinely, especially in the field of surgery for colorectal cancer. The combination of various perioperative approaches has led to significant reductions in surgical morbidity and mortality rates, the duration of hospital stay, and the cost of hospitalization, and has greatly improved postoperative recovery [12–14].

Although some reports have described the use of the ERAS protocol for patients undergoing surgery for gastric cancer, clear and convincing evidence for the usefulness of this protocol for such patients has not been established [15–22]. Consensus guidelines for enhanced recovery after

✉ Sang-Woong Lee
sur079@osaka-med.ac.jp

[1] Department of General and Gastroenterological Surgery, Osaka Medical College, 2-7 Daigaku-Machi, Takatsuki, Osaka 569-8686, Japan

gastrectomy have been published [23]. However, surgical outcomes and recovery of the patients' physical condition have not been evaluated fully.

In this prospective randomized controlled trial, we aimed to clarify the clinical relevance of the ERAS protocol by evaluating the perioperative course in patients undergoing gastric cancer surgery.

Patients and methods

Study design, eligibility, and exclusion criteria

This was a prospective, single-center, randomized, controlled, parallel-group study to evaluate the safety and efficacy of the ERAS protocol for patients undergoing gastric cancer surgery. All patients were informed about the aims and details of the study and signed an informed consent form. Patients who met the eligibility criteria were randomized into two groups—a conventional protocol group and an ERAS protocol group—on the day of admission and were stratified according to the type of gastrectomy. Randomization was performed with a computer-generated permuted-block sequence by a research physician at Osaka Medical College Hospital. The physicians and nurses administering the interventions and collecting the data had no role in the randomization process. Patients and surgeons were not blinded to the allocation, but the analyst and individuals who performed the laboratory and physical examinations were blinded.

The study protocol received approval from the Institutional Review Board of Osaka Medical College under the principles of the seventh revision of the Declaration of Helsinki. The following inclusion criteria were used: histologically confirmed adenocarcinoma of the stomach for which curative gastrectomy was planned without simultaneous resection of other organs except for the gallbladder, no involvement of the duodenum or esophagus, age 20–85 years, sufficient oral intake, an American Society of Anesthesiologists (ASA) score of less than 4, and no prior chemotherapy or radiotherapy for any malignancy. Because the aim of this study was to evaluate the efficacy of the ERAS protocol, patients were excluded if they had factors that might impede a fast recovery, such as pregnancy, inflammatory bowel disease, chronic renal disease, severe cardiopulmonary dysfunction, or complicated diabetes. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000011572; https://upload.umin.ac.jp/ctr).

The operating procedure and lymph node dissection were planned on the basis of the 2010 Japanese gastric cancer treatment guidelines [24]. Indications for laparoscopic gastrectomy at our institute include the following: (1) all tumors are confined to the muscularis propria and are not amenable to endoscopic mucosal resection, with lymph node involvement limited to N1; (2) the patient requires salvage surgery after incomplete endoscopic resection; (3) the patient is 80 years or older with advanced gastric cancer; or (4) the patient is enrolled in a randomized controlled trial to evaluate laparoscopic versus open surgery for advanced gastric cancer (UMIN000003420: JLSSG0901). Patients with gastric cancer with indications other than those listed above underwent open surgery with curative intent. The clinical stage and residual tumor status were confirmed according to the Union for International Cancer Control classification system [25]. All patients had open or laparoscopic gastrectomy performed by the same team of five surgeons.

Common perioperative protocol

On the day of surgery, premedication for anesthesia was not administered. An antibiotic drug (cefazolin) was infused just before the skin incision was made and every 3 h during the operation. All patients received sterile lactated Ringer's solution at a rate of 10–12 ml/kg per hour throughout the intraoperative period. The nasogastric tube was removed in the operating room after surgery. A continuous thoracic epidural infusion of analgesics was given for 3 days after open surgery. Removal of urinary catheters was planned for postoperative day (POD) 1. Drainage catheters were removed on POD 2 in patients who had clear drainage fluid, an amylase concentration of less than 1000 U/l, and a drainage discharge of less than 100 ml/day. Patients aged 65 years or older received intervention by a physiotherapist to promote mobilization. Routine pharmacological thromboprophylaxis was not administered unless preoperative venous ultrasonography had shown deep venous thrombosis.

Conventional protocol

Patients in the conventional protocol group were allowed to have a solid diet up to and including dinner on the day before surgery and were allowed to drink clear fluid until 21:00, after which they fasted until surgery. Bowel preparation (24 mg of sennoside AB) was administered on the day before surgery. During surgery, a drain was used for all types of gastrectomy. After surgery, additional analgesics were administered when the patient reported pain. On POD 1, the patients started walking and were allowed to drink only water but less than 100 ml. The patients started to ingest a liquid diet on POD 3, after which the diet continued through five daily steps eventually to eating regular food on POD 8. A total of 2000 ml of 4.3% glucose solution and vitamins every 24 h was

Table 1 Perioperative protocols for the conventional protocol group and enhanced recovery after surgery (*ERAS*) protocol group

Perioperative intervention	Conventional protocol group	ERAS protocol group
Bowel preparation	Oral laxative (24 mg sennoside AB on the night before surgery	None
Diet before surgery	Intake of normal diet on the day before surgery	Intake of normal diet on the day before surgery
	No intake of food and drink after dinner on the day before surgery	Intake of 250 ml oral carbohydrate solution (Arginaid® water) on the night before surgery and 2 h before anesthesia
Antibiotics	Before skin incision and every 3 h during surgery	Before skin incision and every 3 h during surgery
	One administration after surgery	One administration after surgery
Abdominal drainage	Routine use of 1 drainage tube	Use of 1 drainage tube in patients undergoing total gastrectomy or proximal gastrectomy
		No drain in other procedures
Oral intake	Start to drink water on POD 1	Start to drink water and intake of 500 ml oral carbohydrate solution (Arginaid® water) on POD 1
	Start a liquid diet on POD 3 and 5 steps leading to regular food intake on POD 8	Start a liquid diet on POD 2 and 4 steps leading to regular food intake on POD 6
Pain management	Epidural analgesia for 3 days after open surgery	Epidural analgesia for 3 days after open surgery
	No routine additional analgesics	Acetaminophen twice daily orally until POD 5
Intravenous nutrition after surgery	Parenteral nutrition until POD 5	End of parenteral nutrition on POD 4
Mobilization after surgery	Encouraged to walk by themselves after POD 1	Encouraged to walk by themselves after POD 1

POD postoperative day

administered continuously until POD 2, and peripheral parenteral nutrition was continued until POD 5. The dose of 4.3% glucose solution was tapered off to 1500, 1000, and 1000 ml on PODs 3, 4, and 5 respectively (Table 1). The conventional protocol included 15 items recommended in the consensus guidelines for enhanced recovery after gastrectomy.

ERAS protocol

Patients in the ERAS protocol group were allowed to ingest a solid diet up to and including the day before surgery, and drank 250 ml of a carbohydrate-rich drink (18.0 g per 100 ml carbohydrate, Arginaid® water; Nestlé Health Science, Kobe, Japan) after dinner on the day before surgery. On the day of surgery, another 250 ml was consumed up to 2 h before anesthesia. During surgery, a drain was used for patients undergoing proximal gastrectomy or total gastrectomy, whereas no drain was inserted for other procedures. After surgery, additional analgesics were administered when the patient reported pain. On POD 1, patients started walking and were allowed to drink clear fluid, including 500 ml of the carbohydrate-rich drink (see above). To decrease postoperative pain, 400 mg acetaminophen was administered orally twice daily until POD 5. The patients started to ingest a liquid diet on POD 2, after which the diet continued through four daily steps eventually to eating regular food on POD 6. Patients were encouraged to walk by themselves. A total of 2000 ml of 4.3% glucose solution and vitamins was administered on POD 1, and peripheral parenteral nutrition was continued until POD 4. The dose of this solution was tapered off to 1500, 1000, and 1000 ml on PODs 2, 3, and 4 respectively (Table 1). The ERAS protocol included 22 of 25 items recommended in the consensus guidelines for enhanced recovery after gastrectomy; transversus abdominis plane block, antithrombotic prophylaxis, and fluid balance were excluded.

Discharge criteria

The discharge criteria included a normal body temperature, passage of normal bowel movements, good pain management with oral analgesics, no need for intravenous fluids, independent mobility, and a physical condition suitable for going home. Other discharge criteria included a serum C-reactive protein concentration less than 5 mg/dl and not increasing, a white blood cell count less than 9000/mm^3 and not increasing, and serum transaminase and creatinine concentrations not increasing above the baseline. Each

patient received nutritional guidance to explain postgastrectomy syndrome [26, 27] before hospital discharge.

Body composition and physical activity

Body weight and composition were measured on the day before surgery and 1 week and 1 month after surgery. Segmental body composition was analyzed with a multifrequency bioelectrical impedance analyzer (InBody 430; InBody, Tokyo, Japan), which is a noninvasive, portable, quick, and inexpensive method for measuring body composition [28]. Physical activity was assessed with a triaxial accelerometer (Active Style Pro HJA-350IT; Omron Healthcare, Kyoto, Japan) during hospitalization. Patients were instructed to wear the accelerometer on their waist throughout the day, except when showering or bathing. The numbers of steps per day and the amount of exercise were calculated with use of data from the accelerometer. All acceleration data were recorded as the mean values of 1-min epochs. The metabolic equivalent (MET) is an index of physical activity intensity. Physical activity with intensity of walking at a normal pace is equal to 3 METs. Exercise was calculated as METs multiplied by the hours spent in physical activity [29].

End points

The primary end point was the duration of postoperative hospital stay. The allowed day of discharge was defined as the day when patients met the criteria given in "Discharge criteria." The ward administrator determined the discharge date after consultation with the patient. The secondary end points were the incidence of postoperative complications, the readmission rate within 30 days after discharge, death, the admission cost, the postoperative body weight loss, body composition changes, and the amount of physical activity. Admission cost covered all costs incurred during the hospital stay, and was divided into charges for consultation, prescriptions, injections, nursing care, the operating theater, the laboratory, radiology, the ward and meals, and other services. Postoperative complications were classified according to the revised version of the Clavien–Dindo classification system [30]. Body composition changes and the amount of activity were evaluated as indicators of the recovery of physical condition.

Sample size and statistical analysis

It was initially estimated that most patients who underwent gastrectomy with curative intent would need to stay in the hospital for about 13 days after surgery. On the basis of the hypothesis that the ERAS protocol would reduce the postoperative length of hospital stay from 13 to 11 days, a sample size of at least 64 patients per arm was calculated to have a power of 0.80 and a significance level of 0.05. A total sample size of 140 patients was targeted, assuming an unexpected dropout rate of 10%. The χ^2 test or Fisher's exact test was used to analyze dichotomous data, and the Wilcoxon rank-sum test was used for continuous data. All statistical tests were two-sided, and $P < 0.05$ was considered to be significant. Statistical analysis was performed with JMP® 11 (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

From July 2013 to June 2015, 148 patients who fulfilled the inclusion criteria were enrolled and randomly assigned to the conventional protocol group ($n = 75$) or the ERAS protocol group ($n = 73$). Six patients were excluded: three underwent total gastrectomy with splenectomy for scirrhous gastric cancer, two exhibited peritoneal dissemination disease, and para-aortic lymph node metastasis was found during the operation in one patient (Fig. 1).

The clinical characteristics and baseline data were well balanced between the two groups. The statistical analysis of age, sex, body weight, body mass index, Eastern Cooperative Oncology Group performance status, and American Society of Anesthesiologists score for physical status suggested similar characteristics in the two groups. The distributions of oncological and surgical factors, except for the need for abdominal drainage, did not differ significantly between the groups (Table 2).

Clinical and physiological recovery outcomes

The rates of completion of the protocol for oral feeding were 87.7% for the ERAS protocol group and 81.2% for the conventional protocol group. Preoperative carbohydrate loading was achieved in all patients, and the mean intake of oral carbohydrate solution on POD 1 was 413 ml (82.6%) in the ERAS protocol group. The first day of flatus, the first day of defecation, and the allowed day of discharge did not differ significantly between the groups (Table 3). However, the duration of postoperative hospital stay, the primary outcome of this trial, was significantly shorter in the ERAS protocol group than in the conventional protocol group ($P = 0.037$). The number of additional doses of analgesics required was significantly lower in the ERAS protocol group than in the conventional protocol group ($P = 0.008$). The total cost of hospitalization was significantly less for the ERAS protocol group than for the conventional protocol group ($P = 0.045$). The ratio of postoperative to preoperative body weight was significantly greater at

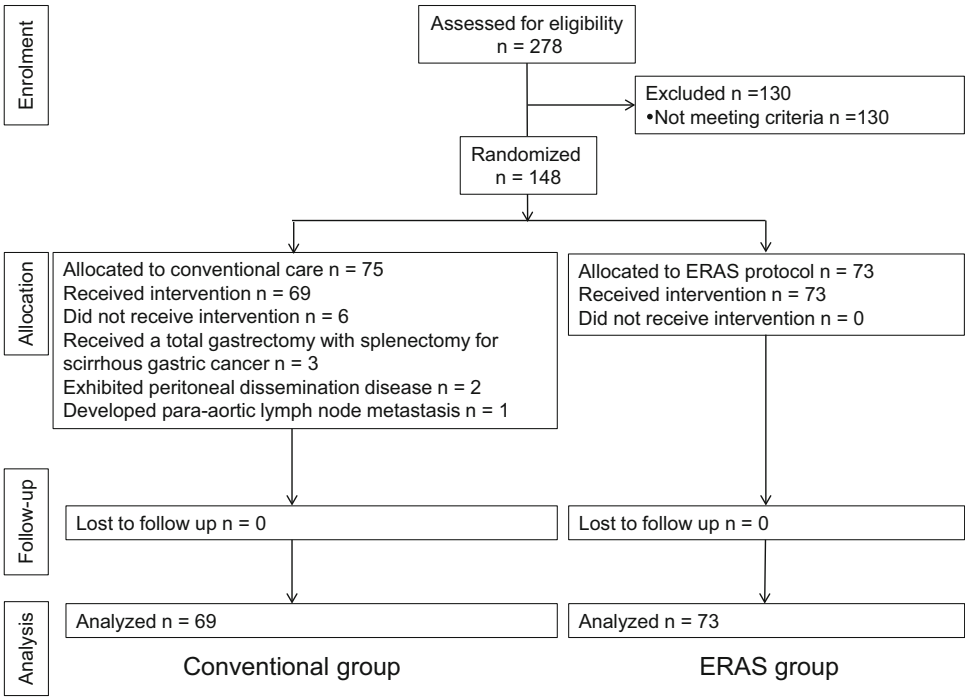

Fig. 1 Flow diagram of the randomized control trial designed to compare the safety and efficacy of the conventional protocol and the enhanced recovery after surgery (*ERAS*) protocol

1 week and 1 month postoperatively in the ERAS protocol group than in the conventional protocol group (Table 3, Fig. 2a). The ratio of postoperative to preoperative lean body mass did not differ between groups in the first postoperative month (Fig. 2b). Patients in the ERAS protocol group performed significantly more steps as measured by triaxial accelerometry on PODs 4 and 5 and more exercise on POD 5 compared with patients in the conventional protocol group (Fig. 3).

Laboratory findings

The median serum concentration of total protein on POD 7 was 6.2 g/dl (interquartile range 5.9–6.6 g/dl) in the ERAS protocol group and 6.1 g/dl (interquartile range 5.6–6.5 g/dl) in the conventional protocol group ($P = 0.049$). The median serum transthyretin concentration on POD 7 was 16.3 mg/dl (interquartile range 13.6–18.4 mg/dl) in the ERAS protocol group and 13.5 mg/dl (interquartile range 11.1–15.9 mg/dl) in the conventional protocol group ($P = 0.014$). The two groups did not differ significantly with regard to indicators of nutrition or inflammation, including albumin concentration, white blood cell and lymphocyte count, and C-reactive protein concentration.

Complications and readmissions

The rate of Clavien–Dindo grade II or higher postoperative complications did not differ significantly between the groups. However, the rate of Clavien–Dindo grade III or higher postoperative complications was significantly lower in the ERAS protocol group than in the conventional protocol group (Table 4). All patients who experienced postoperative complications were cured by surgery or conservative treatment. Reoperation was required for three patients in the conventional protocol group because of intra-abdominal bleeding in two patients and leakage of the duodenal stump caused by a pancreatic fistula in one patient.

One patient in each group required readmission. One patient in the conventional protocol group was readmitted on day 32 after laparoscopic distal gastrectomy because of an anastomotic stricture and was treated successfully by endoscopic balloon dilation. One patient in the ERAS protocol group was readmitted on day 25 after laparoscopic proximal gastrectomy because of an intra-abdominal abscess and was treated with antibiotics.

Discussion

This is the largest prospective study to evaluate the safety and efficacy of the ERAS protocol in patients with gastric cancer. Compared with the conventional protocol group, the ERAS protocol group had a shorter hospital stay, a significantly lower rate of postoperative complications of grade III or higher, and reduced hospitalization cost. The ERAS protocol group also lost less body weight in the first

Table 2 Patient characteristics

	Conventional protocol group ($n = 69$)	ERAS protocol group ($n = 73$)
Age (years)[a]	67 (44–85)	68 (29–85)
Sex		
Male	49	49
Female	20	24
Body mass index (kg/m^2)[a]	22.1 (15.8–28.3)	22.2 (13.2–28.3)
ECOG PS		
0	48	51
1	20	20
2	1	2
ASA PS		
1	25	19
2	41	46
3	3	8
Tumor size (mm)[a]	28 (14.5–49)	38 (22–54.7)
Pathological stage		
I	47	55
II	7	8
III	15	10
IV	0	0
Residual tumor		
R0	68	71
R1	1	2
Approach		
Open	9	10
Laparoscopic	60	63
Type of gastrectomy		
Distal	49	54
Total	6	6
Pylorus preserving	8	7
Proximal	4	5
Segmental	2	1
Lymph node dissection		
D1+	45	48
D2	24	25
Reconstruction		
B1	25	32
RY	30	28
GG	9	8
DT	5	4
EG	0	1
Operating time (min)[a]	245 (145–442)	259 (160–498)
Blood loss (ml)[a]	10 (5–430)	10 (5–350)
Drainage	69 (100%)	12 (16.4%)

ASA PS American Society of Anesthesiologists physical status, *B1* Billroth I reconstruction, *DT* double tract, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ERAS* enhanced recovery after surgery, *GG* gastrogastrostomy, *EG* esophagogastrostomy, *RY* Roux-en-Y reconstruction

[a] The median is given, with the range in *parentheses*

Table 3 Postoperative outcomes

	Conventional protocol group ($n = 69$)	ERAS protocol group ($n = 73$)	*P*
First day of flatus[a]	2 (1–3)	2 (1–2)	0.564
First day of defecation[a]	4 (3–5)	3 (2–5)	0.730
Number of additional doses of analgesics[a]	5 (2–7)	3 (2–6)	0.008
Allowed day of discharge[a]	7 (5–9.5)	5 (5–7)	0.059
Postoperative hospital stay (days)[a]	10 (9–11.5)	9 (8–10)	0.037
Admission cost (JPY)[a]	1,493,930 (1,449,172–1,621,128)	1,462,766 (1,421,364–1,586,539)	0.045
Readmission	1 (1.4%)	1 (1.4%)	1.000
Deaths	0	0	
Ratio of postoperative to preoperative body weight at 1 week after surgery[a]	0.957 (0.947–0.967)	0.962 (0.955–0.976)	0.020
Ratio of postoperative to preoperative body weight at 1 month after surgery[a]	0.937 (0.919–0.959)	0.951 (0.928–0.971)	0.021

ERAS enhanced recovery after surgery

[a] The median is given, with the interquartile range in *parentheses*

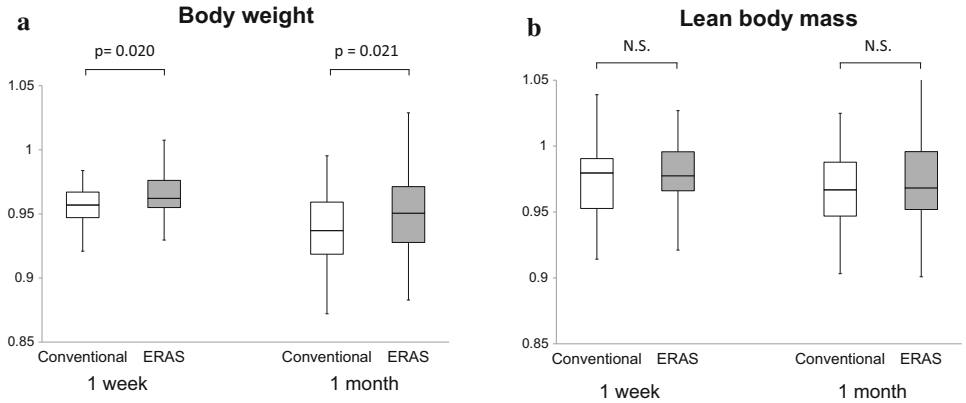

Fig. 2 **a** Comparison of the postoperative to preoperative body weight ratios at 1 week and 1 month postoperatively in the conventional protocol group and the enhanced recovery after surgery (*ERAS*) protocol group. **b** Comparison of the postoperative to preoperative lean body mass ratios at 1 week and 1 month postoperatively in the conventional protocol group and the ERAS protocol group. The *central line* represents the median, the *edges of the box* are the 25th and 75th percentiles and the *whiskers* extend to ±1.5 of the interquartile range. *N.S.* not significant

month after surgery and performed more physical activity in the first week.

The primary end point of the study was the duration of hospitalization, which was shorter after gastric cancer surgery in the ERAS protocol group than in the conventional protocol group. We anticipate that a shorter hospitalization facilitates the recovery of physical condition and leads to an earlier return to usual life. We found that body weight loss in the first postoperative month was significantly less in the ERAS protocol group than in the conventional protocol group. The financial benefits to health providers associated with a shorter hospital stay are indisputable. In our trial, introduction of the ERAS protocol in patients with gastric cancer resulted in lower total hospital admission costs. This suggests that the ERAS protocol might limit the increase in medical costs in the future. Although the postoperative hospital stay in our study seemed to be longer than in other reports [16–19], the age range of our patients was wide, and a variety of surgical procedures were used to treat their gastric cancer. The length of hospitalization may also differ according to the culture and health insurance system of each country.

To identify the factors affecting postoperative recovery and length of hospitalization, univariate and multivariate analyses were used to analyze the risk factors for delayed discharge. Delayed discharge was defined as a prolonged length of stay beyond the third quartile in this series (11 days or more). The univariate analysis identified as

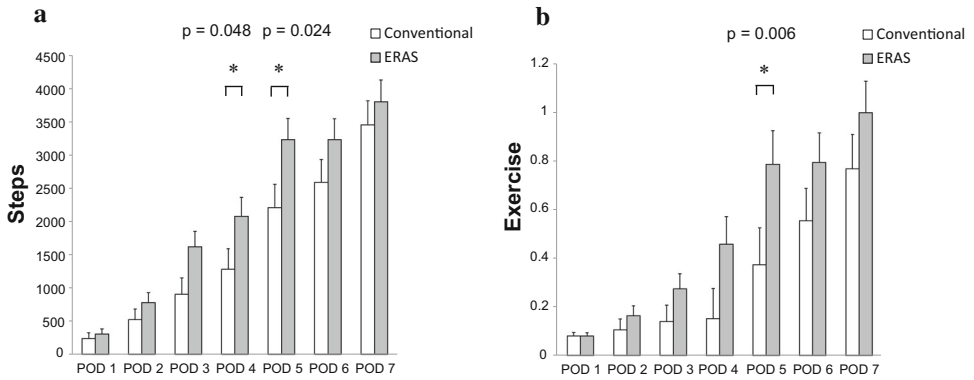

Fig. 3 **a** Comparison of the number of steps measured by triaxial accelerometry during the first postoperative week in the conventional protocol group and the enhanced recovery after surgery (*ERAS*) protocol group. **b** Comparison of the amount of exercise measured by the same means during the first postoperative week in the conventional protocol group and the ERAS protocol group. Each value represents the mean ± standard error of the mean. *POD* postoperative day

Table 4 Postoperative complications

	Conventional protocol group ($n = 69$)	ERAS protocol group ($n = 73$)	*P*
C–D classification grade ≥ II	22 (31.9%)[a]	14 (19.2%)	0.087
Anastomotic leakage	2 (2.9%)	2 (2.7%)	1.000
Pancreatic fistula	3 (4.3%)	2 (2.7%)	0.674
Intra-abdominal abscess	6 (8.7%)	2 (2.7%)	0.157
Intra-abdominal bleeding	2 (2.9%)	0	0.143
Gastrointestinal bleeding	1 (1.4%)	0	0.302
Anastomotic stricture	1 (1.4%)	1 (1.4%)	0.968
Abdominal wall bleeding	1 (1.4%)	2 (2.7%)	1.000
Wound infection	1 (1.4%)	0	0.486
Ileus	1 (1.4%)	0	0.486
Delayed gastric emptying	2 (2.9%)	1 (1.4%)	0.612
Pneumonia	1 (1.4%)	1 (1.4%)	1.000
Pleural effusion	0	1 (1.4%)	1.000
Liver dysfunction	0	1 (1.4%)	1.000
Urinary retention	1 (1.4%)	0	0.486
Delirium	2 (2.9%)	1 (1.4%)	0.612
C–D classification grade ≥ III	10 (14.5%)	3 (4.1%)	0.042
Anastomotic leakage	1 (1.4%)	2 (2.7%)	1.000
Pancreatic fistula	3 (4.3%)	0	0.112
Intra-abdominal abscess	2 (2.9%)	1 (1.4%)	0.612
Intra-abdominal bleeding	2 (2.9%)	0	0.234
Gastrointestinal bleeding	1 (1.4%)	0	0.486
Anastomotic stricture	1 (1.4%)	0	0.486

C–D Clavien–Dindo, *ERAS* enhanced recovery after surgery

[a] There were 24 complications in 22 patients

significant factors being a member of the conventional protocol group, total gastrectomy, being pathological N factor positive, an operating time of 5 h or more, and blood loss of 50 ml or more. Being a member of the conventional protocol group, total gastrectomy, an operating time 5 h or more, and blood loss of 50 ml or more remained significant in the multivariate analysis. Total gastrectomy is likely to be more complicated than distal gastrectomy because it is difficult to dissect lymph nodes along the splenic artery and perform an esophagojejunostomy. It is found that a prolonged operating time and major operative blood loss are associated with poorer outcomes, which may contribute to

delayed recovery even in the presence of an established enhanced recovery program [31].

Carbohydrate loading is an important item in the ERAS protocol. Surgical stress and preoperative fasting are thought to cause insulin resistance, which can lead to hyperglycemia and possibly increase postoperative complications, whereas preoperative carbohydrate loading is intended to reduce the risk of developing postoperative insulin resistance [32]. However, the effects of preoperative carbohydrate loading remain controversial, especially in diabetic patients. There are concerns about the possibility that early postoperative feeding may induce postoperative anastomotic leakage and pneumonia, especially after gastric surgery. In our study, the ERAS protocol group and the conventional protocol group did not differ significantly regarding the incidence of anastomotic leakage of grade II or higher (2.7% and 2.9% respectively) or the incidence of pneumonia (1.4% and 1.4% respectively). Our results suggest that early oral feeding is feasible and does not increase the risk of postoperative anastomotic leakage or pneumonia.

In our series, no abdominal drainage was used for 83.6% of the patients who underwent gastric resections other than proximal gastrectomy or total gastrectomy in the ERAS protocol group, whereas an abdominal drain was used routinely for all patients in the conventional protocol group. Omission of an abdominal drain might have reduced the rate of postoperative infectious complications such as pancreatic fistula and intra-abdominal abscess. Increasing evidence suggests that surgical drainage does not reduce the prevalence of complications but increases intra-abdominal fluid collection, infections, and risk of a fistula [33, 34]. However, we refrained from omitting the use of drains for patients undergoing proximal gastrectomy or total gastrectomy because of concern about severe surgical site infection in the region of an esophagojejunal anastomosis, which is associated with a high incidence of leaks [4]. The use of a drain after proximal gastrectomy or total gastrectomy will continue to be an issue for debate in future developments of the ERAS protocol.

The body weight loss at 1 week postoperatively was significantly lower in the ERAS protocol group than in the conventional protocol group. Early postoperative oral feeding may have helped to maintain nutritional status in the ERAS protocol group and to prevent or attenuate the weight loss. The short-term nutritional status of patients after surgery is affected by surgical stress, preoperative nutritional status, and postoperative caloric intake. In this study, the serum concentrations of transthyretin, which has a half-life in plasma of about 2 days, and total protein on POD 7 were significantly higher in the ERAS protocol group than in the conventional protocol group. Yamada et al. [20] reported that the ratio of postoperative to preoperative body weight at 1 week postoperatively was higher in an ERAS protocol group than in a control group (0.95 vs 0.94; $P = 0.01$). In the present prospective study, the ratio of postoperative to preoperative body weight was significantly higher at both 1 week postoperatively and 1 month postoperatively in the ERAS protocol group than in the conventional protocol group. Some investigators have reported that body weight loss at 1 month after surgery is a significant risk factor for continuation of adjuvant chemotherapy with S-1 [35]. Therefore, attenuation of body weight loss by use of the ERAS protocol might lead to improved adherence to adjuvant chemotherapy, which might help to prolong overall survival for patients with gastric cancer.

We also used triaxial accelerometry to measure postoperative physical activity, which is the first such objective method used to assess the efficacy of the ERAS protocol. Although patients in both groups received similar encouragement to walk after surgery, the ERAS protocol group registered more steps and exercise, especially during the first five PODs. The higher levels of physical activity might be related to components of the ERAS protocol, such as the use of oral prophylactic analgesics, the omission of an abdominal drain in most patients, and an early end to peripheral parenteral nutrition. Control of postoperative pain and omission or early removal of unnecessary catheters seem to have facilitated early mobilization, which may have led to an earlier recovery of physical activity.

There are several limitations to the present trial. First, it was performed at a single institution in Japan, and it is unknown whether our findings are applicable to global populations where more advanced cancers are treated. Japanese patients with gastric cancer are older and leaner than European and American patients, and have an earlier onset of cancer [36, 37]. Second, we did not include patients with advanced gastric cancer, such as those requiring combined resection of the adjacent organs or needing neoadjuvant chemotherapy or induction chemoradiotherapy. The efficacy of the ERAS protocol for such patients remains unclear. Similarly, it is unknown whether the ERAS protocol can also be applied to high-risk patients with comorbidities. Finally, the length of hospital stay, which is considered to be a general indicator, might not be the best indicator of recovery after surgery. The goal of ERAS should be debated. Several researchers have considered the loss of body weight or lean body mass to be more reflective of patients' health status, quality of life, and physical activity [35, 38, 39].

In conclusion, the ERAS protocol shortened the postoperative hospital stay after gastric cancer surgery, reduced the rate of complications, decreased admission costs, and accelerated the recovery of good physical condition. These findings indicate that the ERAS protocol can help to

improve the postoperative course of patients with gastric cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki (1964 and later versions).

Informed consent Informed consent for inclusion in the study was obtained from all patients who participated.

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