

# Patients Administered Neoadjuvant Chemotherapy Could be Enrolled into an Enhanced Recovery after Surgery Program for Locally Advanced Gastric Cancer

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## Abstract

**Background:** Most studies on enhanced recovery after surgery (ERAS) for gastric cancer exclude patients who received neoadjuvant chemotherapy. Here, we aimed to evaluate whether patients who received neoadjuvant chemotherapy can be enrolled into the ERAS program for locally advanced gastric cancer.

**Methods:** From April 2015 to July 2017, 114 patients who received neoadjuvant chemotherapy for locally advanced gastric cancer were randomized into ERAS and standard care (SC) groups. Postoperative length of stay, complications, bowel function, and nutritional status were recorded.

**Results:** The postoperative length of stay of the ERAS group was shorter compared with that of the SC group ( $5.9 \pm 5.6$  vs.  $8.1 \pm 5.3$  days,  $P = 0.037$ ). The postoperative complication rate was 9.3% in the ERAS group and 11.5% in the SC group ( $P = 0.700$ ). The time to first flatus ( $2.7 \pm 2.0$  vs.  $4.5 \pm 4.6$  days,  $P = 0.010$ ) and time to a semi-liquid diet ( $3.2 \pm 2.1$  vs.  $6.3 \pm 4.9$  days,  $P < 0.001$ ) in the ERAS group were shorter compared with those in the SC group. On the 10<sup>th</sup> day after surgery, the values of weight, total protein, albumin, and prealbumin of the ERAS group were lower compared with those of the SC group.

**Conclusions:** Patients who received neoadjuvant chemotherapy could be enrolled into ERAS programs for locally advanced gastric cancer. The nutritional status of these patients was not adversely affected.

**Key words:** Advanced Gastric Cancer; Enhanced Recovery after Surgery; Gastrectomy; Length of Stay; Neoadjuvant Chemotherapy

## INTRODUCTION

The population of East Asia has a high prevalence of gastric cancer, which adversely affects health. According to the World Health Organization, approximately 46.8% of new cases of gastric cancer and 47.8% of gastric cancer-related deaths occur in China.<sup>[1]</sup> For example, in 2015, gastric cancer caused the second highest rates of morbidity and mortality among all malignancies in China.<sup>[2]</sup> Surgical resection remains the preferred choice for treating gastric cancer; however, the rate of occurrence of complications after gastrectomy ranges from 9.1% to 46.0%.<sup>[3-6]</sup> Thus, decreasing surgical trauma and stress, reducing the occurrence of complications, and accelerating rehabilitation are highly important for patients with gastric cancer who underwent gastrectomy.

Enhanced recovery after surgery (ERAS), which comprises a series of perioperative optimized measures according to

evidence-based medicine, aims to reduce surgical stress, accelerate postoperative rehabilitation, and shorten the length of stay.<sup>[7,8]</sup> ERAS programs are applied to gastrectomy in areas with a high prevalence of gastric cancer, such as China and Japan.<sup>[9-11]</sup> Studies on ERAS in these countries show that ERAS programs accelerate postoperative rehabilitation without increasing the rate of occurrence of postoperative complications. Although these results suggest that ERAS programs are safe and effective when applied to gastrectomy, we found that most studies investigating ERAS

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programs for gastric cancer excluded patients who were administered preoperative neoadjuvant chemotherapy.<sup>[12-14]</sup>

Advanced gastric cancer is difficult to resect, and long-term survival is very poor.<sup>[15]</sup> Unfortunately, more than 80% of Chinese patients are diagnosed at advanced stages.<sup>[6]</sup> Therefore, patients with advanced gastric cancer may be advised to consider treatment that combines chemotherapy, radiotherapy, and surgery.<sup>[16]</sup> Notably, neoadjuvant chemotherapy significantly increases the R0 resection rate<sup>[17]</sup> and does not influence perioperative outcomes.<sup>[18]</sup> Therefore, neoadjuvant chemotherapy is frequently used to downstage tumors and to increase the resection rate.<sup>[19,20]</sup>

To the best of our knowledge, few studies of ERAS focus on patients with locally advanced gastric cancer who are administered neoadjuvant chemotherapy. Therefore, we designed the present study to evaluate whether patients who received neoadjuvant chemotherapy can be enrolled into ERAS programs for locally advanced gastric cancer.

## METHODS

### Ethics approval

The Research Ethics Committee of Nanjing University approved this study. Written informed consent was obtained from all participants, and all procedures were performed in accordance with relevant guidelines and regulations.

### Study design

This study was a single-center, parallel, open-label randomized controlled trial. The primary endpoint was the postoperative length of stay. Secondary endpoints included postoperative complications, time to first flatus, time to semi-liquid diet, and nutritional status. The severity of complications was evaluated using the Clavien-Dindo classification,<sup>[21]</sup> which categorizes surgical complications from Grades I to V, according to the invasiveness of the required treatment.

### Patients

Eligibility criteria are listed in Table 1. Patients were diagnosed with locally advanced gastric cancer (T2-4N0-2M0) through enhanced computed tomography (CT) (Somatom Definition, Siemens Healthcare, Forchheim, Germany) of the abdomen. Preoperative diagnosis of T and N was evaluated using Habermann *et al.*'s method.<sup>[22]</sup> T2 tumors were defined as those with focal or diffuse thickening of the gastric wall with transmural involvement and a smooth outer border of the wall or only a few small linear strands of soft tissue extending into the fat plane, involving less than one-third of the tumor. T3 tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor or wide reticular strands surrounding the outer border of the tumor. T4 tumors were defined as those with obliteration of the fat plane between the gastric tumor and an adjacent organ or invasion of an adjacent organ. Involvement of regional lymph nodes was indicated by metastases >8 mm in their short-axis diameters. Enlarged perigastric nodes <3 cm

**Table 1: Eligibility criteria for enrolling patients**

Inclusion
Patients received neoadjuvant chemotherapy with locally advanced gastric cancer
Age >18 and <75 years
ASA Class: I–III
Participants can objectively describe the symptoms and actively cooperate
Written informed consent
Exclusions
Patients allergic to medications such as oxaliplatin, tegafur gimerac
Patients with ischemic heart disease, cerebrovascular disease and peripheral vascular disease, or cardiac function >II (NYHA)
Patients with complications (bleeding, perforation, and obstruction) caused by gastric cancer
Patients with severe liver and renal dysfunction (Child–Pugh ≥10; creatinine clearance <25 ml/min)
Patients who require simultaneous surgery for other diseases
Patients who received upper abdominal surgery
Pregnancy or breast-feeding

ASA: American Society of Anesthesiologists; NYHA: New York Heart Association.

from the primary lesion were graded as N1, and enlarged distant (>3 cm) paraesophageal nodes and the nodes along the main arteries supplying the stomach were assessed as representative of N2. Patients who met the eligibility criteria were randomly assigned to the ERAS or standard care (SC) group. Randomization was performed using opaque sealed envelopes.

### Interventions

All recruited patients were given an intravenous injection of 130 mg/m<sup>2</sup> oxaliplatin (Cisen Pharmaceutical Co., Ltd., China) on day 1, followed by oral administration of 50 mg of tegafur gimeracil (Shandong New Time Pharmaceutical Co., Ltd., China) twice daily on days 1–14, every 3 weeks. Robotic (Intuitive Surgical Inc., Sunnyvale, CA, USA) radical gastrectomy was performed one week after completion of the second course of chemotherapy. Surgeries were performed by Jiang ZW. Total or distal gastrectomy, together with D2 lymphadenectomy, was performed according to the tumor site.<sup>[23]</sup> A Roux-en-Y anastomosis was performed in patients who received total gastrectomy, and a Billroth II anastomosis was performed in patients who received distal gastrectomy. The perioperative periods of the ERAS and SC groups were managed in accordance with their respective programs (see below). The discharge criteria were as follows: (1) intravenous infusions ceased and semifluid intake recovered; (2) the patient could independently perform ambulatory activities; (3) the patient's pain was not controlled by pain medications or oral analgesics; and (4) the patient and his or her family agreed to discharge.

### Enhanced recovery after surgery programs

Patients in the ERAS group were managed in accordance with ERAS programs during the perioperative period.<sup>[24]</sup> The ERAS program included sufficient preoperative patient education, no bowel preparation, a normal diet until 6 h

before surgery, liquid intake until 2 h before surgery, preoperative carbohydrate loading before surgery (100 g glucose/1000 ml water taken orally at 10 p.m. on the evening before the surgery and 50 g glucose/500 ml water taken 2–3 h preoperatively), analgesia with nonsteroidal anti-inflammatory drugs, minimization of opioid pain management, avoidance of perioperative fluid overload, no routine use of nasogastric tubes, no abdominal drains unless required, early removal of bladder catheters, liquid diet on recovery from anesthesia, semi-liquid diet on return of bowel function (stool or repeated flatus), tolerated liquid diet, and forced ambulation on the day of surgery.

### Standard care programs

Patients in the SC group were managed in accordance with SC programs during the perioperative period.<sup>[9]</sup> SC programs are used daily in our center and are still routinely used in most hospitals in China. In the present study, patients received gastrointestinal preparation before surgery, and they fasted from midnight. Nasogastric tubes were placed preoperatively and usually remained until flatus occurred and no gastric retention presented after surgery. Intra-abdominal drains were placed during surgery, and in most cases, were maintained until the day before discharge. After surgery, the patients were not allowed oral intake until bowel flatus or obvious gastrointestinal movement occurred. The patients mobilized at will and usually remained in bed for approximately 2 days after surgery.

### Sample size

Sample size was calculated using PASS 11 (NCSS, LLC, Kaysville, Utah, USA). The projected standard deviation (SD) of postoperative length of stay was 2.3 days.<sup>[24]</sup> According to the superiority of design, this analysis was based on  $\alpha = 0.05$ , 90% power, and margin  $\delta = 1.5$  days, revealing that  $\geq 51$  patients were required per group. Considering an expected dropout rate of 10%, each group required  $\geq 57$  patients.

### Statistical analysis

The data are presented as the mean  $\pm$  standard deviation (SD) for continuous variables and as a number for categorical variables. The differences between groups were calculated using the Pearson test, the Mann–Whitney test, or an independent sample *t*-test as appropriate. *P* values were derived from two-tailed tests. Statistical significance was defined as 5%. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Patient recruitment

We recruited 114 patients who received neoadjuvant chemotherapy for locally advanced gastric cancer from April 2015 to July 2017. In the ERAS group, two patients' tumors could not be removed, and one patient harbored a peritoneal metastasis that was discovered during the surgery. In the SC group, four patients' tumors could not be resected, and one patient harbored a peritoneal metastasis

that was discovered during surgery. Therefore, we analyzed the data of 54 and 52 patients in the ERAS and SC groups, respectively [Figure 1].

### Patients' clinical and pathological characteristics

Table 2 shows that the mean ages of patients in the ERAS and SC groups were 60.8 years and 59.8 years ( $P = 0.552$ ), respectively. The ERAS and SC groups comprised 38 and 37 men ( $P = 0.929$ ), respectively. The mean body mass indexes of the ERAS and SC groups were 22.7 kg/m<sup>2</sup> and 22.9 kg/m<sup>2</sup> ( $P = 0.819$ ), respectively. There were no significant differences in comorbidities (33.3% vs. 30.8%,  $P = 0.777$ ), American Society of Anesthesiologists scores (I/II/III, 22/26/6 vs. 20/25/7,  $P = 0.926$ ), clinical T (T2/T3/T4, 12/18/24 vs. 13/19/20,  $P = 0.822$ ), and N (N0/N1/N2, 27/21/6 vs. 29/16/7,  $P = 0.675$ ) on enrollment. After radical gastrectomy, tissues were diagnosed with malignant. Postoperative pathological tumor type (differentiated/undifferentiated, 34/20 vs. 31/21,  $P = 0.724$ ), pathological T (T0/T1/T2/T3/T4a/T4b, 1/3/16/14/17/3 vs. 0/1/11/17/19/4,  $P = 0.172$ ), and N (N0/N1/N2/N3a/N3b, 20/19/8/4/3 vs. 19/17/7/6/3,  $P = 0.791$ ) were similar between groups.

### Surgical outcomes

Surgical outcomes are detailed in Table 3. Except for six patients with unresected tumors and two patients with peritoneal metastasis, other surgeries were completed successfully without injury, and these patients achieved R0 resections. In the ERAS group, 24 patients underwent distal gastrectomy, the others underwent total gastrectomy, and 21 patients underwent distal gastrectomy. Thirty-one patients in the SC groups underwent total gastrectomy ( $P = 0.672$ ). Billroth II anastomosis was performed for all patients who underwent distal gastrectomy, and Roux-en-Y anastomosis was performed for all patients who underwent total gastrectomy. The values of surgical time ( $226.1 \pm 29.2$  vs.

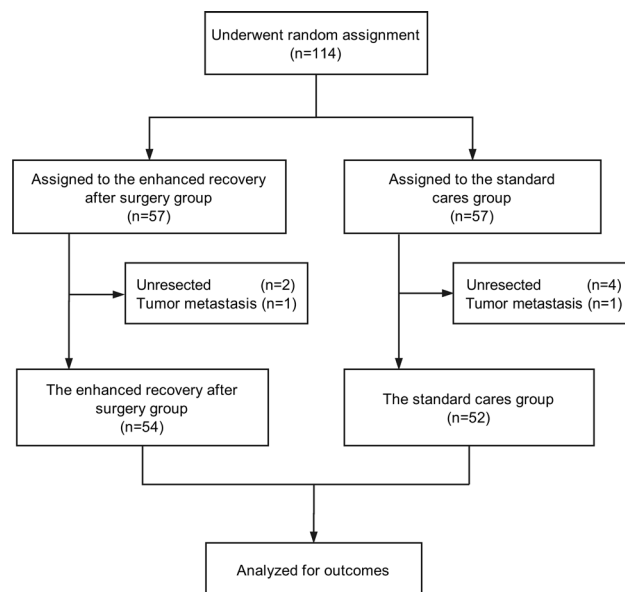


Figure 1: CONSORT diagram.

221.6 ± 35.6 min,  $P = 0.479$ ), blood loss (90.4 ± 19.6 vs. 93.1 ± 34.2 ml,  $P = 0.616$ ), and the number of dissected lymph nodes (27.2 ± 6.3 vs. 28.4 ± 7.4,  $P = 0.351$ ) were similar between groups.

### Postoperative short-term outcomes

Table 3 shows the postoperative outcomes. The postoperative length of stay in the ERAS group was shorter compared with that in the SC group (5.9 ± 5.6 vs. 8.1 ± 5.3 days,  $P = 0.037$ ). The time to first flatus (2.7 ± 2.0 vs. 4.5 ± 4.6 days,  $P = 0.010$ ) and time to semi-liquid diet (3.2 ± 2.1 vs. 6.3 ± 4.9 days,  $P < 0.001$ ) in the ERAS group were shorter compared with those in the SC group. In the ERAS group, one patient developed a fever, and one patient developed a surgical-site infection (Grade I); two patients who developed gastroparesis were treated with total parenteral nutrition (Grade II); and one patient who developed an anastomotic leak received a second

surgery (Grade III). In the SC group, two patients developed surgical site infections (Grade I); one patient who developed pneumonia and one patient who developed lymphatic leakage were managed with antibiotics and total parenteral nutrition, respectively (Grade II), while two patients received subsequent surgery because of anastomotic leaks (Grade III). The similar complication rates demonstrate that undergoing ERAS programs is safe for patients who received preoperative neoadjuvant chemotherapy (9.3% vs. 11.5%,  $P = 0.700$ ).

### Nutritional status

Weight, total protein, serum albumin, and prealbumin were used to evaluate patients' nutritional status [Figure 2]. Before surgery, we did not find differences between groups in weight (63.3 ± 8.3 vs. 63.5 ± 7.5 kg,  $P = 0.881$ ), total protein (67.6 ± 5.9 vs. 68.3 ± 6.6 g/L,  $P = 0.580$ ), serum albumin (41.5 ± 2.8 vs. 41.7 ± 3.9 g/L,  $P = 0.700$ ), and prealbumin (253.0 ± 54.3 vs. 246.4 ± 48.6 mg/L,  $P = 0.511$ ). After robotic radical gastrectomy, weight, total protein, serum albumin, and prealbumin decreased significantly compared with preoperative levels. On the 3<sup>rd</sup> day after surgery, changes in weight (−0.8 ± 0.6 vs. −1.0 ± 0.4 kg,  $P = 0.101$ ), total protein (−7.5 ± 3.3 vs. −6.5 ± 4.2 g/L,  $P = 0.206$ ), serum albumin (−4.8 ± 2.5 vs. −5.1 ± 4.0 g/L,  $P = 0.625$ ), and prealbumin (−61.0 ± 40.7 vs. −58.5 ± 40.1 mg/L,  $P = 0.747$ ) were similar between groups. However, weight (−2.0 ± 1.1 vs. −2.6 ± 0.9 kg,  $P = 0.001$ ), total protein (−12.0 ± 3.8 vs. −14.5 ± 4.6 g/L,  $P = 0.003$ ), serum albumin (−7.5 ± 3.6 vs. −9.5 ± 4.5 g/L,  $P = 0.012$ ), and prealbumin (−97.1 ± 44.4 vs. −116.6 ± 41.6 mg/L,  $P = 0.021$ ) 10 days after surgery in the ERAS group were lower compared with those of the SC group.

**Table 2: Patients' clinical and pathological characteristics (mean ± SD)**

Characteristics	ERAS group (n = 54)	SC group (n = 52)	P
Age (years)	60.8 ± 9.4	59.8 ± 7.9	0.552
Sex			
Men	38	37	0.929
Women	16	15	
BMI (kg/m <sup>2</sup> )	22.7 ± 3.0	22.9 ± 2.5	0.819
Comorbidity (n/%)	18 (33.3)	16 (30.8)	0.777
ASA class			
I	22	20	0.926
II	26	25	
III	6	7	
Clinical T when enrolled			
T2	12	13	0.822
T3	18	19	
T4	24	20	
Clinical N when enrolled			
N0	27	29	0.675
N1	21	16	
N2	6	7	
Pathologic tumor type			
Differentiated	34	31	0.724
Undifferentiated	20	21	
Pathologic T			
T0	1	0	0.172
T1	3	1	
T2	16	11	
T3	14	17	
T4a	17	19	
T4b	3	4	
Pathologic N			
N0	20	19	0.791
N1	19	17	
N2	8	7	
N3a	4	6	
N3b	3	3	

ERAS: Enhanced recovery after surgery; SC: Standard care; BMI: Body mass index; SD: Standard deviation; ASA: American Society of Anesthesiologists.

## DISCUSSION

In China, gastric cancer accounts for the second highest morbidity and mortality among all malignancies.<sup>[2]</sup> Surgical resection has long been considered the preferred treatment for gastric cancer.<sup>[25]</sup> However, complications affecting the stomach occur after gastrectomy.<sup>[3-5,13]</sup> Wilmore and Kehlet first reported the ERAS programs,<sup>[7]</sup> which apply a series of perioperative optimized measures with evidence-based medicine to reduce surgical trauma and stress, to accelerate postoperative rehabilitation, and to shorten the length of stay.<sup>[7,8]</sup> Subsequently, certain gastric cancer treatment centers have applied ERAS programs to gastrectomy<sup>[9-11]</sup> that confirms their safety and effectiveness. However, we found that patients who received neoadjuvant chemotherapy were excluded from most studies.<sup>[3,12-14]</sup> Therefore, we designed the present study, which was completed on July 2017. Here, we were aimed to determine whether patients who received neoadjuvant chemotherapy could be enrolled into ERAS programs for locally advanced gastric cancer.

In the present study, we show that compared with patients who received SC, ERAS shortened the postoperative length of stay without increasing complications. We found further that ERAS shortened the time to first flatus and time to semi-liquid diet,



indicating that these factors accounted for the early discharge of members of the ERAS group. Moreover, the nutritional status of the ERAS group was relatively improved on the postoperative day 10, demonstrating that ERAS protected nutritional status. Together, our findings show that patients who received neoadjuvant chemotherapy can be enrolled into ERAS programs for locally advanced gastric cancer and that these patients benefited from ERAS similarly to patients who were not administered neoadjuvant chemotherapy.

**Table 3: Perioperative outcomes (mean ± SD)**

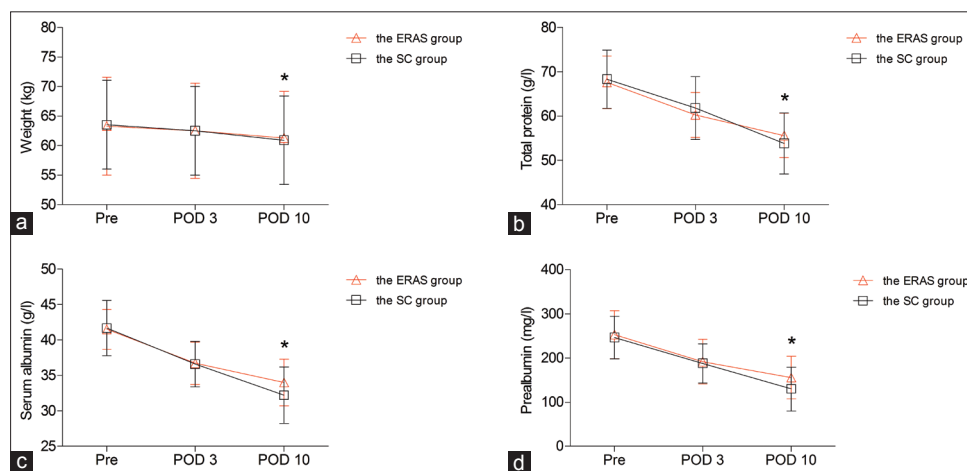
Items	ERAS group (n = 54)	SC group (n = 52)	P
Resection style			
Distal gastrectomy	24	21	0.672
Total gastrectomy	30	31	
Reconstruction style			
Billroth II	24	21	0.672
Roux-en-Y	30	31	
R0 resection			
Yes	54	52	1.000
No	0	0	
Operative time (min)	226.1 ± 29.2	221.6 ± 35.6	0.479
Blood loss (ml)	90.4 ± 19.6	93.1 ± 34.2	0.616
Number of lymph nodes dissected	27.2 ± 6.3	28.4 ± 7.4	0.351
Time to first flatus (day)	2.7 ± 2.0	4.5 ± 4.6	0.010
Time to semi-liquid diet (day)	3.2 ± 2.1	6.3 ± 4.9	<0.001
Postoperative length of stay (day)	5.9 ± 5.6	8.1 ± 5.3	0.037
Complications			
I	2	2	0.700
II	2	2	
III	1	2	

ERAS: Enhanced recovery after surgery; SC: Standard care; SD: Standard deviation.

Similar to this study, others show that ERAS programs accelerate the postoperative rehabilitation of patients with gastric cancer and shorten their lengths of stay without increasing the frequency of postoperative complications.<sup>[10,11,14]</sup> ERAS programs comprise a full set of intervention measures and technologies, although the superiority of each measure is unclear. Conventionally, early intake was believed to stimulate anastomoses and increase the intracavitary pressure in the gastrointestinal tract, leading to anastomotic leaks. However, evidence indicates that early food intake is safe and will not increase the rate of anastomotic leaks.<sup>[13,26]</sup> Early food intake avoids excessive intravenous infusion and accelerates the recovery of postoperative bowel function.<sup>[27,28]</sup> Therefore, early oral food intake is likely a crucial component of ERAS programs for gastrectomy and an important contributor to the decrease in the postoperative length of stay.<sup>[12,26,29]</sup>

Preoperative oral administration of carbohydrates, which is extensively recognized as an important component of ERAS programs, accelerates the early release of insulin and avoids postoperative insulin resistance and excessive protein degradation.<sup>[13,30,31]</sup> However, preoperative oral carbohydrates do not improve postoperative nutritional status or contribute to maintaining muscle strength.<sup>[12]</sup> Although little attention is paid to perioperative liquid management, we know that excessive intravenous infusion leads to interstitial edema in tissues and organs. A meta-analysis shows that intestinal interstitial edema affects the recovery of postoperative intestinal function.<sup>[27]</sup> Therefore, perioperative liquid management requires more attention.

In the present study, we avoided the use of opioids, because they induce side effects such as nausea, vomiting, urinary dysfunction, intestinal obstruction, and respiratory inhibition,<sup>[32,33]</sup> which are disadvantageous to rehabilitation after gastrectomy. Moreover, we reasoned that earlier flatus may be related to avoidance of perioperative fluid



**Figure 2:** Perioperative nutritional status of patients. (a) On POD 10, the change of weight in the ERAS group was smaller than that in the SC group. (b) On POD 10, the change of total protein in the ERAS group was smaller than that in the SC group. (c) On POD 10, the serum albumin in the ERAS group dropped lesser than that in the SC group. (d) On POD 10, the prealbumin in the ERAS group dropped lesser than that in the SC group. \*Change compared with SC group,  $P < 0.05$ . Pre: Preoperation; POD: Postoperative day; ERAS: Enhanced recovery after surgery; SC: Standard care.

overload, early oral intake, and minimization of opioid pain management in ERAS programs. Thus, patients who consume a semi-liquid diet earlier are discharged earlier. Further, an early semi-liquid diet, which may offer sufficient energy to patients after gastrectomy, and the preoperative oral administration of carbohydrates, which may avoid excessive protein degradation, led to the better nutritional status of the ERAS group.

Most studies on ERAS programs for gastrectomy excluded patients who received neoadjuvant chemotherapy.<sup>[3,12,14]</sup> Thus, it was assumed that patients who received neoadjuvant chemotherapy should not be enrolled into ERAS programs because of their relatively weak and vulnerable condition. However, it is unclear whether patients who received neoadjuvant chemotherapy can be enrolled into ERAS programs for locally advanced gastric cancer. The major effect of neoadjuvant chemotherapy is to improve the R0 resection rate through tumor down-staging to reduce the frequency of systemic metastases by eliminating undetectable micrometastases.<sup>[19,34]</sup> Evidence indicates that neoadjuvant chemotherapy increases curative resection, 5-year disease-free survival, and 5-year overall survival.<sup>[35]</sup>

In the present study, we found that ERAS shortened the postoperative length of stay, time to first flatus, and time to semi-liquid diet of patients who received neoadjuvant chemotherapy, without increasing complications. Together, these findings suggest that ERAS is safe and effective for patients who receive neoadjuvant chemotherapy. Therefore, we conclude that patients who receive neoadjuvant chemotherapy can benefit by enrollment into ERAS programs. However, the remission rate of neoadjuvant chemotherapy ranges from 33.3% to 70%,<sup>[36]</sup> requiring reexamination of the CT scan during neoadjuvant chemotherapy to evaluate the sensitivity of patients to this treatment and to avoid disease progression.

The disease stage may be associated with the implementation and effects of ERAS programs, and patients with early gastric cancer account for a large proportion of those who are successfully managed using ERAS programs.<sup>[3]</sup> The authors of this study conclude that the scope of lymph node dissection is less extensive for patients with early gastric cancer, which may explain why these patients exhibit a lower rate of complications. These findings are similar to those of another study.<sup>[13]</sup> Unfortunately, the rate of diagnosis of early gastric cancer is only 10% in China. Further, the 5-year survival of patients with advanced gastric cancer after surgery is 20–50%.<sup>[37]</sup> Therefore, the early diagnosis of gastric cancer is of particular importance for treatment and prognosis. Moreover, the stage of esophageal or esophagogastric junction adenocarcinoma after neoadjuvant chemotherapy determines prognosis rather than the clinical stage before the administration of neoadjuvant chemotherapy.<sup>[38]</sup> These findings indicate that neoadjuvant chemotherapy may be required for patients with advanced gastric cancer.

The postoperative length of stay and postoperative complications rate are major indicators of the effectiveness and safety of ERAS programs. Studies on ERAS programs for gastrectomy are primarily performed in China and Japan. The results of previous studies show that the median postoperative length of stay is 6–9 days,<sup>[3,10,13]</sup> which is similar to our present findings. However, we found that complications may greatly affect the trend of the postoperative length of stay. Although the safety of ERAS is still controversial in certain area, investigations performed with large sample sizes indicates that ERAS is safe and does not increase the rate of postoperative complications.<sup>[9,12,13]</sup> The results reported here further support this conclusion.

In the present study, five patients were diagnosed with pathological T0 and T1 after gastrectomy, though these patients were diagnosed with clinical T2 and T3 through preoperative enhanced CT scans. CT and endoscopic ultrasonography are used for preoperative staging of gastric cancer. However, both techniques have unique limitations for preoperative staging, particularly for T staging. For example, a method for preoperative staging using CT found that correct T and N staging are each >70%.<sup>[22]</sup> Thus, although bias was introduced, we used Habermann's method here.

There are several limitations in our study. First, the effects of ERAS programs on patients who received neoadjuvant chemotherapy were not observed. The comparison of patients who are administered neoadjuvant chemotherapy with those who are not may be more significant. Thus, a study will be designed to evaluate the effects of patients administered neoadjuvant chemotherapy. Second, the present study was a single-center clinical trial, and results from other centers are required. Further, the long-term survival rate was not determined. Therefore, patients in this study should be followed to evaluate whether neoadjuvant chemotherapy in ERAS programs benefits long-term survival.

In conclusion, patients who receive neoadjuvant chemotherapy can be enrolled into ERAS programs for locally advanced gastric cancer. There was little change in the nutritional status of these patients.

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### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D, *et al.* Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90. doi: 10.3322/caac.20107.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, *et al.* Cancer statistics in china, 2015. *CA Cancer J Clin* 2016;66:115-32. doi: 10.3322/caac.21338.
3. Sugisawa N, Tokunaga M, Makuuchi R, Miki Y, Tanizawa Y,

- Bando E, *et al.* A phase II study of an enhanced recovery after surgery protocol in gastric cancer surgery. *Gastric Cancer* 2016;19:961-7. doi: 10.1007/s10120-015-0528-6.
4. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, *et al.* Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: Preliminary results of the MRC randomised controlled surgical trial. The surgical cooperative group. *Lancet* 1996;347:995-9. doi: 10.1016/S0140-6736(96)90144-0.
  5. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, *et al.* Gastric cancer surgery: Morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy – Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;22:2767-73. doi: 10.1200/jco.2004.10.184.
  6. Hu Y, Huang C, Sun Y, Su X, Cao H, Hu J, *et al.* Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: A Randomized controlled trial. *J Clin Oncol* 2016;34:1350-7. doi: 10.1200/JCO.2015.63.7215.
  7. Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ* 2001;322:473-6. doi: 10.1136/bmj.322.7284.473.
  8. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008;248:189-98. doi: 10.1097/SLA.0b013e31817f2c1a.
  9. Liu XX, Pan HF, Jiang ZW, Zhang S, Wang ZM, Chen P, *et al.* “Fast-track” and “Minimally invasive” surgery for gastric cancer. *Chin Med J* 2016;129:2294-300. doi: 10.4103/0366-6999.190659.
  10. Wang D, Kong Y, Zhong B, Zhou X, Zhou Y. Fast-track surgery improves postoperative recovery in patients with gastric cancer: A randomized comparison with conventional postoperative care. *J Gastrointest Surg* 2010;14:620-7. doi: 10.1007/s11605-009-1139-5.
  11. Yamada T, Hayashi T, Cho H, Yoshikawa T, Taniguchi H, Fukushima R, *et al.* Usefulness of enhanced recovery after surgery protocol as compared with conventional perioperative care in gastric surgery. *Gastric Cancer* 2012;15:34-41. doi: 10.1007/s10120-011-0057-x.
  12. Makuuchi R, Sugisawa N, Kaji S, Hikage M, Tokunaga M, Tanizawa Y, *et al.* Enhanced recovery after surgery for gastric cancer and an assessment of preoperative carbohydrate loading. *Eur J Surg Oncol* 2017;43:210-7. doi: 10.1016/j.ejso.2016.07.140.
  13. Yamada T, Hayashi T, Aoyama T, Shirai J, Fujikawa H, Cho H, *et al.* Feasibility of enhanced recovery after surgery in gastric surgery: A retrospective study. *BMC Surg* 2014;14:41. doi: 10.1186/1471-2482-14-41.
  14. Jeong O, Ryu SY, Park YK. Postoperative functional recovery after gastrectomy in patients undergoing enhanced recovery after surgery: A Prospective assessment using standard discharge criteria. *Medicine (Baltimore)* 2016;95:e3140. doi: 10.1097/MD.00000000000003140.
  15. Ychou M, Boige Y, Pignon JP, Conroy T, Bouché O, Lebreton G, *et al.* Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-21. doi: 10.1200/jco.2010.33.0597.
  16. Takahashi T, Saikawa Y, Kitagawa Y. Gastric cancer: Current status of diagnosis and treatment. *Cancers (Basel)* 2013;5:48-63. doi: 10.3390/cancers5010048.
  17. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, *et al.* Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and Cardia: European organisation for research and treatment of cancer randomized trial 40954. *J Clin Oncol* 2010;28:5210-8. doi: 10.1200/jco.2009.26.6114.
  18. Li Z, Shan F, Wang Y, Li S, Jia Y, Zhang L, *et al.* Laparoscopic versus open distal gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy: Safety and short-term oncologic results. *Surg Endosc* 2016;30:4265-71. doi: 10.1007/s00464-015-4739-z.
  19. Wang X, Zhao L, Liu H, Zhong D, Liu W, Shan G, *et al.* A phase II study of a modified FOLFOX6 regimen as neoadjuvant chemotherapy for locally advanced gastric cancer. *Br J Cancer* 2016;114:1326-33. doi: 10.1038/bjc.2016.126.
  20. Qu J, Qu X. The predictors of response to neoadjuvant chemotherapy in patients with locally advanced gastric cancer. *Cancer Biomark* 2016;17:49-54. doi: 10.3233/CBM-160616.
  21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13. doi: 10.1097/01.sla.0000133083.54934.ae.
  22. Habermann CR, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, *et al.* Preoperative staging of gastric adenocarcinoma: Comparison of helical CT and endoscopic US. *Radiology* 2004;230:465-71. doi: 10.1148/radiol.2302020828.
  23. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver 4). *Gastric Cancer* 2017;20:1-9. doi: 10.1007/s10120-016-0622-4.
  24. Wang G, Jiang Z, Zhao J, Liu J, Zhang S, Zhao K, *et al.* Assessing the safety and efficacy of full robotic gastrectomy with intracorporeal robot-sewn anastomosis for gastric cancer: A randomized clinical trial. *J Surg Oncol* 2016;113:397-404. doi: 10.1002/jso.24146.
  25. Etoh T, Inomata M, Shiraishi N, Kitano S. Minimally invasive approaches for gastric cancer-Japanese experiences. *J Surg Oncol* 2013;107:282-8. doi: 10.1002/jso.23128.
  26. Lassen K, Kjaeve J, Fetveit T, Tranø G, Sigurdsson HK, Horn A, *et al.* Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: A randomized multicenter trial. *Ann Surg* 2008;247:721-9. doi: 10.1097/SLA.0b013e31815cca68.
  27. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: Getting the balance right. *Proc Nutr Soc* 2010;69:488-98. doi: 10.1017/s0029665110001734.
  28. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP, *et al.* Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. *Lancet* 2002;359:1812-8. doi: 10.1016/S0140-6736(02)08711-1.
  29. Terashima M. The earlier the better? *Gastric Cancer* 2014;17:197-9. doi: 10.1007/s10120-013-0287-1.
  30. Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J, *et al.* Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. *Br J Surg* 2007;94:1342-50. doi: 10.1002/bjs.5919.
  31. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc* 2002;61:329-36. doi: 10.1079/PNS2002168.
  32. Pyati S, Gan TJ. Perioperative pain management. *CNS Drugs* 2007;21:185-211. doi: 10.2165/00023210-200721030-00002.
  33. Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: Evidence from published data. *Br J Anaesth* 2004;93:212-23. doi: 10.1093/bja/aeh180.
  34. Mezhir JJ, Tang LH, Coit DG. Neoadjuvant therapy of locally advanced gastric cancer. *J Surg Oncol* 2010;101:305-14. doi: 10.1002/jso.21483.
  35. Marano L, Polom K, Patrili A, Roviello G, Falco G, Stracqualursi A, *et al.* Surgical management of advanced gastric cancer: An evolving issue. *Eur J Surg Oncol* 2016;42:18-27. doi: 10.1016/j.ejso.2015.10.016.
  36. Zhao JH, Gao P, Song YX, Sun JX, Chen XW, Ma B, *et al.* Which is better for gastric cancer patients, perioperative or adjuvant chemotherapy: A meta-analysis. *BMC Cancer* 2016;16:631. doi: 10.1186/s12885-016-2667-5.
  37. Lu J, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, *et al.* Consideration of tumor size improves the accuracy of TNM predictions in patients with gastric cancer after curative gastrectomy. *Surg Oncol* 2013;22:167-71. doi: 10.1016/j.suronc.2013.05.002.
  38. Davies AR, Gossage JA, Zylstra J, Mattsson F, Lagergren J, Maisey N, *et al.* Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. *J Clin Oncol* 2014;32:2983-90. doi: 10.1200/JCO.2014.55.9070.

# 接受新辅助化疗的局部进展期胃癌患者可被纳入加速康复外科程序

## 摘要

**背景:** 在大多数胃癌手术加速康复外科的研究中,接受新辅助化疗的患者都被排除。我们设计本试验的目的是用来评估接受新辅助化疗的局部进展期胃癌患者能否被纳入加速康复外科程序。

**方法:** 从2015年4月到2017年7月,共有114例局部进展期胃癌患者被纳入本研究并被随机分配至加速康复外科组和传统围手术期处理组。术后住院时间,并发症,肠功能恢复指标以及营养状况被记录。

**结果:** 加速康复外科组患者术后住院时间短于传统围手术期处理组 ( $5.9 \pm 5.6$  vs.  $8.1 \pm 5.3$  days,  $P = 0.037$ )。加速康复外科组中并发症发生率为9.3%,传统围手术期处理组中并发症发生率为11.5%,两组间并发症发生率无明显差异 ( $P = 0.700$ )。加速康复外科组术后通气时间 ( $2.7 \pm 2.0$  vs.  $4.5 \pm 4.6$  days,  $P = 0.010$ ) 和恢复半流饮食时间 ( $3.2 \pm 2.1$  vs.  $6.3 \pm 4.9$  days,  $P < 0.001$ ) 短于传统围手术期处理组。术后第10天,加速康复外科组患者体重,总蛋白,白蛋白及前白蛋白的降低程度小于传统围手术期处理组。

**结论:** 接受新辅助化疗的局部进展期胃癌患者能够被纳入加速康复外科程序,而且这些患者营养状况的改变更加平缓。