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Effect of Laparoscopic Proximal Gastrectomy With Double-Tract Reconstruction vs Total Gastrectomy on Hemoglobin Level and Vitamin B_{12} Supplementation in Upper-Third Early Gastric Cancer

A Randomized Clinical Trial

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Abstract

IMPORTANCE Patients undergoing proximal gastrectomy (PG) with double-tract reconstruction (DTR) have been reported to have an incidence of reflux esophagitis that is as low as that observed after total gastrectomy (TG). It is unclear whether PG has an advantage over TG for the treatment of patients with upper early gastric cancer (GC).

OBJECTIVE To evaluate the effect of laparoscopic PG with DTR (LPG-DTR) vs laparoscopic TG (LTG) on levels of hemoglobin and vitamin B_{12} supplementation required among patients with clinically early GC in the upper third of the stomach (upper-third early GC).

DESIGN, SETTING, AND PARTICIPANTS This multicenter open-label superiority randomized clinical trial was conducted at 10 institutions in Korea. A total of 138 patients with upper-third cT1N0M0 GC were enrolled between October 27, 2016, and September 9, 2018. Follow-up ended on December 3, 2020.

INTERVENTIONS Patients were randomized to undergo either LPG-DTR or LTG.

MAIN OUTCOMES AND MEASURES The primary co-end points were change in hemoglobin level and cumulative amount of vitamin B_{12} supplementation at 2 years after LPG-DTR or LTG. The secondary end points included morbidity, postoperative reflux esophagitis, quality of life, overall survival, and disease-free survival. Quality of life outcomes were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) 30-item core questionnaire (C30) and the EORTC QLQ stomach cancer–specific questionnaire at 3 months, 12 months, and 24 months.

RESULTS Among 138 patients (mean [SD] age, 60.0 [10.9] years; 87 men [63.0%]; all of Asian race and Korean ethnicity), 68 (mean [SD] age, 56.7 [10.4] years; 39 men [57.4%]) were randomized to receive LPG-DTR and 69 (mean [SD] age, 61.3 [11.3] years; 48 men [69.6%]) were randomized to receive LTG. The mean (SD) changes in hemoglobin levels from baseline to month 24 were −5.6% (7.4%) in the LPG-DTR group and −6.9% (8.3%) in the LTG group, for an estimated difference of −1.3% (95% CI, −4.0% to 1.4%; $P = .35$). The mean (SD) cumulative amount of vitamin B_{12} supplementation was 0.4 (1.3) mg in the LPG-DTR group and 2.5 (3.0) mg in the LTG group, for an estimated difference of 2.1 mg (95% CI, 1.3-2.9 mg; $P < .001$). The late complication rates in the LPG-DTR and LTG groups were 17.6% and 10.1%, respectively ($P = .31$). The incidence of reflux

(continued)

Key Points

Question Is laparoscopic proximal gastrectomy with double-tract reconstruction (LPG-DTR) superior to laparoscopic total gastrectomy (LTG) for the treatment of patients with clinically early gastric cancer (GC) in the upper third of the stomach (upper-third early GC)?

Findings In this randomized clinical trial of 138 patients with upper-third early GC, surgical treatment with LPG-DTR compared with LTG resulted in a significantly decreased mean amount of vitamin B_{12} supplementation (0.4 mg in the proximal gastrectomy group and 2.5 mg in the total gastrectomy group) but no significant difference in hemoglobin change (−5.6% in the proximal gastrectomy group and −6.9% in the total gastrectomy group). No increase in complication rates and no difference in overall and disease-free survival rates were found in those who received LPG-DTR vs LTG.

Meaning These findings suggest that LPG-DTR may be superior to LTG with regard to vitamin B_{12} supplementation and as safe as LTG for the treatment of patients with upper-third early GC.

+ Visual Abstract

+ Supplemental content

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Abstract (continued)

esophagitis was not different between the LPG-DTR and LTG groups (2.9% vs 2.9%; *P* = .99). Compared with the LTG group, the LPG-DTR group had better physical functioning scores (85.2 [15.6] vs 79.9 [19.3]; *P* = .03) and social functioning scores (89.5 [17.9] vs 82.4 [19.4]; *P* = .03) on the EORTC QLQ-C30. Two-year overall survival (98.5% vs 100%; *P* = .33) and disease-free survival (98.5% vs 97.1%; *P* = .54) did not significantly differ between the LPG-DTR vs LTG groups.

CONCLUSIONS AND RELEVANCE In this study, patients with upper-third early GC who received LPG-DTR required less vitamin B_{12} supplementation than those who received LTG, with no increase in complication rates and no difference in overall and disease-free survival rates. There was no difference in change in hemoglobin level between groups. In addition, the LPG-DTR group had better physical and social functioning than the LTG group. These findings suggest that LPG-DTR may be as safe as LTG and may be a function-preserving procedure for the treatment of patients with upper-third early GC.

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Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide and the fourth leading cause of death.[1] As the proportion of patients with upper GC increases, there is growing interest in the treatment of upper or gastroesophageal junction GC.[2]

Currently, total gastrectomy (TG) is the most commonly performed surgical procedure for upper GC, and it is accepted as the standard treatment. In the case of upper early GC and advanced Siewert type II gastroesophageal junction cancer, there is little metastasis to the lower lymph nodes (LNs); therefore, substantial evidence suggests that proximal gastrectomy (PG) is possible.[3,4] However, TG is still being performed more frequently, even in these cases, because reflux esophagitis and resulting stricture can occur when direct esophagogastrostomy is performed after PG. Thus, the postoperative course is not good.[5-7]

In the last 10 years, PG with double-tract reconstruction (DTR) was introduced and was reported to result in an incidence of reflux esophagitis that was approximately the same as that of TG.[8,9] Patients who undergo TG have poorer quality of life (QOL) after the procedure due to reduced food intake, changes in the gastrointestinal hormonal environment, and changes in nutritional status because of malabsorption. Although PG has several theoretical advantages over TG, its superiority has not yet been proven in randomized clinical trials (RCTs).[10-12] This study aimed to evaluate the effect of laparoscopic PG with DTR (LPG-DTR) vs laparoscopic TG (LTG) in a multicenter RCT involving patients with clinically early GC in the upper third of the stomach (upper-third early GC).

Methods

Study Design

This study was an investigator-initiated multicenter prospective phase 3 RCT conducted by 19 surgeons (all study coauthors) from 10 institutions in Korea. For quality control, we designed and implemented a strict evaluation process for surgeons who wanted to participate in the trial. A total of 138 patients with upper-third cT1N0M0 GC were enrolled between October 27, 2016, and September 9, 2018. Follow-up ended on December 3, 2020. The trial protocol was approved by the institutional review boards of each participating institution (the trial protocol and statistical analysis plan are available in Supplement 1). All participants provided written informed consent after they

were given sufficient explanation of the trial's purpose and protocol. Patient registration and management were performed using a web-based electronic case report form provided by the Seoul National University Bundang Hospital Medical Research Collaborating Center. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs.

Study Population

The eligibility criteria were (1) diagnosis of GC by tissue biopsy; (2) age 20 to 80 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 (indicating fully active and able to continue all predisease activities without restriction) or 1 (indicating restricted in physically strenuous activities but ambulatory and able to perform work of a light or sedentary nature); (4) American Society of Anesthesiology physical status classification of I (indicating normal and healthy), II (indicating mild systemic disease), or III (indicating severe systemic disease); (5) voluntary participation by signing the written informed consent form approved by the institutional review board before study participation; (6) ability to undergo LPG, with preoperative test results showing the following oncological characteristics: tumor located in the proximal third of the stomach, tumor size of 5 cm or less, clinical T1 stage, and all LNs not exceeding 8 mm (especially LN stations 4d, 5, 6, and 10); and (7) ability to undergo curative-intent surgical resection. Exclusion criteria were (1) preoperative diagnosis of anemia (hemoglobin [Hb] levels of <13 g/dL for men and <12 g/dL for women [to convert grams per deciliter to grams per liter, multiply by 10]), (2) LTG as the only appropriate treatment because of the presence of other GC lesions in the distal stomach, (3) receipt of chemotherapy or radiotherapy for the treatment of GC before either surgical procedure, (4) combined resection required due to other diseases (except cholecystectomy), (5) history of cancer or concurrent cancer in other organs, (6) previous or current receipt of treatment for systemic inflammatory disease or history of gastrectomy, and (7) vulnerable status (eg, lacking decision-making capacity, pregnant, or planning to become pregnant).

Randomization

Randomization to receive LPG-DTR or LTG was performed during the procedure. If no other organ abnormality was found, advanced stage disease was not detected in the preoperative study, or peritoneal seeding was not found using laparoscopic exploration, the surgeon contacted the data center to request randomization. Patients were randomized on a 1:1 ratio using confidential block size and web-based assignment at the Seoul National University Bundang Hospital Medical Research Collaborating Center.

Interventions

A diagram showing LTG with Roux-en-Y anastomosis and LPG-DTR is available in eFigure 1 in Supplement 2.[13] All patients in the LPG-DTR group had 3 anastomoses (esophagogastrostomy, gastrojejunostomy, and jejunojejunostomy). Based on guidelines from the Korean Gastric Cancer Association and the Japanese Gastric Cancer Association, the scope of LN dissection was D1+ (LN stations 1-7, 8a, 9, and 11p for LTG and LN stations 1, 2, 3a, 4sa, 4sb, 7, 8a, 9, and 11p for LPG).[3,14]

Outcomes

The primary end point of this study was the comparison of changes in Hb levels and amount of vitamin B_{12} supplementation between the LPG-DTR and LTG groups at 2 years postoperatively. The secondary end point was the comparison of reflux esophagitis, morbidity, mortality, QOL, overall survival, and disease-free survival between the 2 groups. Patients were followed up every 3 months for the first year and every 6 months for the second year. Weight measurement and blood tests were performed at every visit, endoscopy was performed at 12 months and 24 months after the procedures to evaluate reflux esophagitis by using endoscopic Los Angeles classification (grades A-D, with grades A-B indicating mild and grades C-D indicating severe), and scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)

30-item core questionnaire (C30), version 3, and the EORTC QLQ 22-item stomach cancer–specific questionnaire (STO22) were assessed at 3 months, 12 months, and 24 months after both procedures. For the EORTC QLQ-C30, separate analyses were performed for the global health status scale, the 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). For the EORTC QLQ-STO22, separate analyses were performed for the 5 GC-related scales (dysphagia, eating restriction, pain, reflux, and anxiety) and 4 single items (dry mouth, body image, taste, and hair loss). For patients receiving LPG-DTR, a gastric emptying scan was performed at 3 months, 12 months, and 24 months after the procedure to determine effective food passage without delayed gastric emptying in the remnant stomach.

Early morbidity was defined as complications related to either surgical procedure that occurred within 30 days after the procedure. Late complications were defined as those occurring within 2 years after the procedure. Patients' conditions were managed according to the guidelines of the critical pathway set by each institution.[13] If a patient's vitamin B_{12} level decreased to less than 200 pg/mL (to convert picograms per milliliter to picograms per liter, multiply by 1000) during the follow-up period, an intramuscular injection of vitamin B_{12} (actinamide, 1 mg/2 mL) was administered, and its frequency and dose were recorded.

Statistical Analysis

Based on a retrospective study performed at Seoul National University Bundang Hospital,[9] the mean (SD) Hb reduction rates at 2 years postoperatively were assumed to be 8.6% (8.5%) in the LTG group and 3.4% (11.1%) in the LPG-DTR group. The mean (SD) amounts of vitamin B_{12} supplementation at 2 years after the procedures were 3.1 (2.2) mg in the LTG group and 0.1 (0.4) mg in the LPG-DTR group. Because there were 2 primary end points, the type 1 errors (α) for Hb reduction rate and vitamin B_{12} supplementation were set at 4% and 1%, respectively. With 80% power, the numbers of patients required to analyze the Hb reduction rate and the amount of vitamin B_{12} supplementation were 62 and 10, respectively. The total number of patients included in the study was 138 (69 patients per group), considering a study withdrawal rate of 10%.

Two different populations were defined for analysis: the intention-to-treat (ITT) group, which included all patients except those who did not undergo either surgical procedure or voluntarily withdrew their consent for either procedure, and the per-protocol group, which included patients who completed the study without major protocol deviations. The primary analyses were ITT.

A Fisher exact or χ^2 test was used to investigate differences in the proportions of patients between the groups and evaluate differences in late postoperative complications and differences in reflux esophagitis (identified using endoscopic Los Angeles classification) between the groups. A 2-sided *t* test was used to evaluate continuous variables and assess whether LPG-DTR was superior to LTG in terms of changes in Hb levels and total amount of vitamin B_{12} supplementation required at 2 years after the procedures. Because the data collected were repeated measures over time, the analysis was performed using multilevel mixed-effects linear regression models to examine whether there were differences in QOL between the LPG-DTR and LTG groups. Because of the potential increase in type I errors due to multiple comparisons, QOL analyses were conducted as prespecified exploratory analyses.

The time from randomization to recurrence or death was estimated using the Kaplan-Meier method. For patients with recurrence, the time from randomization to recurrence or death was assessed; for censored patients, the time from randomization to censored point was assessed. For patients who died, the time from randomization to death was assessed. Patients without events were administratively censored at 2 years of follow-up. A log-rank test was performed to compare the disease-free survival rates between the 2 groups.

All statistical analyses were performed with a statistical significance level of 2-sided $P = .05$ unless otherwise noted. Statistical analyses were conducted using IBM SPSS Statistics software, version 23.0 (IBM Corporation).

Results

Patient Characteristics

Among 138 patients (mean [SD] age, 60.0 [10.9] years; 87 men [63.0%]; all of Asian race and Korean ethnicity) enrolled between October 2016 and September 2018, 69 were randomized to each group (**Figure 1**). One patient in the LPG-DTR group withdrew consent; therefore, 68 patients in the LPG-DTR group (mean [SD] age, 56.7 [10.4] years; 39 men [57.4%]) and 69 patients in the LTG group (mean [SD] age, 61.3 [11.3] years; 48 men [69.6%]) were included in the ITT analysis. Patients' demographic and clinical characteristics were well balanced between groups and are shown in **Table 1**. There was no significant difference in preoperative clinical stages between the LPG-DTR vs LTG groups (cT1aN0M0: 29 patients [42.6%] vs 38 patients [55.1%]; cT1bN0M0: 39 patients [57.4%] vs 31 patients [44.9%]; $P = .15$). The per-protocol analysis was conducted after excluding 9 patients, resulting in 63 patients in the LPG-DTR group and 65 patients in the LTG group.

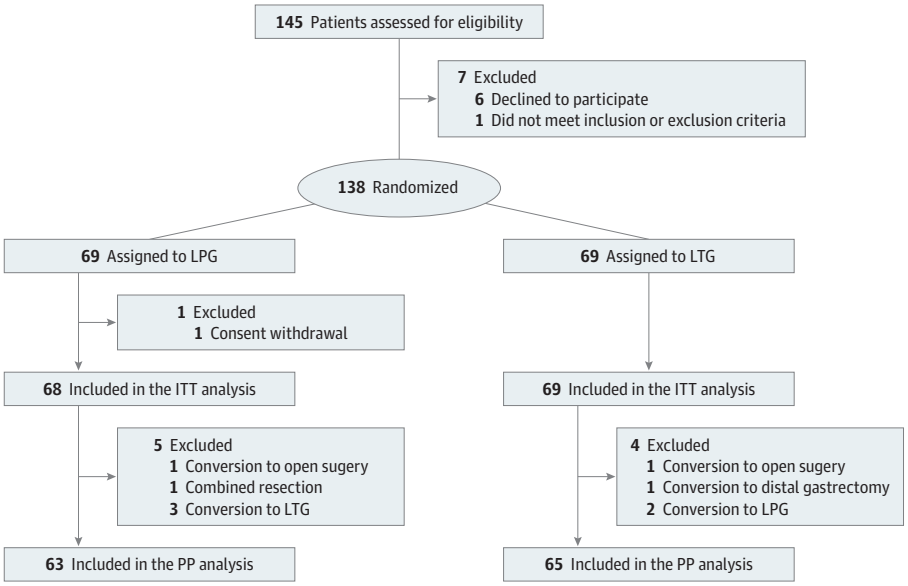
Surgical Outcomes

The short-term results have been reported in a previous article.[13] In the LPG-DTR vs LTG groups, surgical outcomes, including operative time (mean [SD], 219.5 [66.4] minutes vs 201.9 [51.2] minutes; $P = .09$), estimated blood loss (mean [SD], 76.0 [76.9] mL vs 66.1 [63.6] mL; $P = .41$), and length of hospital stay (mean [SD], 7.4 [3.1] days vs 7.7 [4.1] days; $P = .57$), did not differ significantly. There were no operative deaths in either of the groups. In the ITT analysis, overall early morbidity was not significantly different between the LPG-DTR vs LTG groups (23.5% vs 17.4%; $P = .37$).[13] The late complication rates were 17.6% in the LPG-DTR group and 10.1% in the LTG group ($P = .31$). The incidence of reflux esophagitis was not significantly different between the LPG-DTR vs LTG groups (2.9% vs 2.9%; $P = .99$), nor was the incidence of anastomosis stricture (2.9% vs 0%; $P = .25$) (**Table 2**). The mean (SD) body weight values measured at 24 months after the procedures were 57.3 (8.9) kg in the LPG-DTR group and 57.9 (11.3) kg in the LTG group ($P = .74$).

Hemoglobin Change

At 2 years after the procedures, the mean (SD) rates of Hb reduction were −5.6% (7.4%) in the LPG-DTR group and −6.9% (8.3%) in the LTG group, for an estimated difference of −1.3% (95% CI,

Figure 1. Flowchart of Patient Enrollment, Randomization, and Follow-up



ITT indicates intention to treat; LPG, laparoscopic proximal gastrectomy; LTG, laparoscopic total gastrectomy; and PP, per-protocol.

−4.0% to 1.4%; *P* = .35). The incidence of anemia was 20.6% (14 of 68 patients) in the LPG-DTR group and 30.4% (21 of 69 patients) in the LTG group (*P* = .22) (**Table 3**).

Amount of Vitamin B_{12} Supplementation

A total of 134 vitamin B_{12} supplements were administered during the study period, 20 of which (14.9%) were administered orally. The oral supplement dose was converted to an intramuscular dose based on the results of a previous study,[15] which found that a cumulative dose of intramuscular vitamin B_{12}, 5 mg, for 6 months was equivalent to a daily dose of oral vitamin B_{12}, 1 mg, for 6 months. The mean (SD) cumulative amount of vitamin B_{12} supplementation was 0.4 (1.3) mg for the LPG-DTR group and 2.5 (3.0) mg for the LTG group, for an estimated difference of 2.1 mg (95% CI, 1.3-2.9 mg; *P* < .001). In the LPG-DTR group, 14.7% of patients (10 of 68) received vitamin B_{12} supplementation, and 85.3% (58 of 68) did not. In comparison, 58.0% of patients (40 of 69) in the LTG group received vitamin B_{12} supplementation, and 42.0% (29 of 69) did not (*P* < .001) (Table 3).

Gastric Emptying

Among patients who received LPG-DTR, 27 underwent gastric emptying tests at 3 months, 12 months, and 24 months after the procedure. Gastric emptying scans showed that the mean (SD) half-lives of gastric emptying were 322.3 (452.2) minutes at 3 months after the procedure, 204.0 (250.9) minutes at 12 months after the procedure, and 295.3 (349.7) minutes at 24 months after the procedure. The mean (SD) percentages of food passage into the remnant stomach vs the jejunum were 49.8% (22.8%) vs 50.3% (22.8%) at 3 months, 55.7% (22.6%) vs 44.4% (22.5%) at 12 months, and 58.3% (23.4%) vs 41.7% (23.4%) at 24 months.

QOL Outcome

With regard to the QOL outcome as measured by the EORTC QLQ-C30, the LPG-DTR group exhibited better scores than the LTG group in terms of physical functioning (85.2 [15.6] vs 79.9 [19.3]; *P* = .03) and social functioning (89.5 [17.9] vs 82.4 [19.4]; *P* = .03). There were no statistically significant differences between the 2 groups in terms of global health status, role functioning, emotional functioning, and cognitive functioning scales. Regarding symptom scales, the 2 groups showed no

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Characteristic	Patients, No. (%)			
	Intention-to-treat analysis		Per-protocol analysis	
	LPG-DTR (n = 68)	LTG (n = 69)	LPG-DTR (n = 63)	LTG (n = 65)
Sex				
Male	39 (57.4)	48 (69.6)	35 (55.6)	47 (72.3)
Female	29 (42.6)	21 (30.4)	28 (44.4)	18 (27.7)
Age, mean (SD), y	56.7 (10.4)	61.3 (11.3)	58.6 (10.3)	61.3 (11.5)
Preoperative BMI, mean (SD)	24.5 (2.8)	24.3 (3.0)	24.5 (2.9)	24.5 (2.9)
ASA physical status classification[a]				
I	30 (44.1)	31 (44.9)	27 (42.9)	28 (43.1)
II	32 (47.1)	33 (47.8)	30 (47.6)	33 (50.8)
III	6 (8.8)	5 (7.2)	6 (9.5)	4 (6.2)
ECOG status[b]				
0	62 (91.2)	60 (87.0)	58 (92.1)	56 (86.2)
1	6 (8.8)	9 (13.0)	5 (7.9)	9 (13.8)
Previous abdominal operation	0	2 (2.9)	0	1 (1.5)
Preoperative endoscopic treatment	8 (11.8)	6 (8.7)	8 (12.7)	6 (9.2)
Preoperative TNM cancer stage				
cT1aN0M0	29 (42.6)	38 (55.1)	27 (42.9)	36 (55.4)
cT1bN0M0	39 (57.4)	31 (44.9)	36 (57.1)	29 (44.6)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECOG, Eastern Cooperative Oncology Group; LPG-DTR, laparoscopic proximal gastrectomy with double-tract reconstruction; LTG, laparoscopic total gastrectomy; TNM, tumor, node, metastasis.

[a] ASA physical status ranges from I to VI, with I indicating normal and healthy, II indicating mild systemic disease, III indicating severe systemic disease, IV indicating severe systemic disease that is a constant threat to life, V indicating moribund and not expected to survive without the operation, and VI indicating brain death.

[b] ECOG status ranges from 0 to 5, with 0 indicating fully active and able to continue all predisease activities without restriction, 1 indicating restricted in physically strenuous activities but ambulatory and able to perform work of a light or sedentary nature, 2 indicating ambulatory and capable of all self-care but unable to perform any work activities, 3 indicating capable of limited self-care only, 4 indicating completely disabled, and 5 indicating dead.

differences in fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The pattern of change in dyspnea scale scores over time was different in the 2 groups, with the LPG-DTR group having lower dyspnea scale scores than the LTG group (9.8 [16.7] vs 13.7 [19.9]; *P* = .05). On the EORTC QLQ-STO22, there was a significant difference between the 2 groups in terms of dysphagia (11.3 [13.4] vs 12.6 [14.8]; *P* = .01), but no significant differences were found in body image, pain, reflux symptoms, eating restrictions, anxiety, dry mouth, taste, and hair loss (eFigure 2 in Supplement 2).

Overall and Disease-Free Survival

The median (range) follow-up time was 24.6 (2.9-35.3) months. In 1 patient with pT1bN0 disease, the cancer relapsed in the liver at 11.5 months after LPG-DTR. In another patient with pT2N0 disease who underwent LTG, the cancer recurred in the liver after 12.7 months. Peritoneal seeding occurred 6.2 months later in the other patients with pT2N0 disease who underwent LTG (2 recurrences [2.9%] vs 1 recurrence [1.5%] in the LPG-DTR group; *P* = .99). One death (1.5%) occurred in the LPG-DTR group, and 0 deaths occurred in the LTG group (*P* = .50). There was no significant difference in overall survival (**Figure 2**A) or disease-free survival (Figure 2B) between the 2 groups. The 2-year overall survival rates were 98.5% in the LPG-DTR group and 100% in the LTG group (*P* = .33). The 2-year disease-free survival rates were 98.5% in the LPG-DTR group and 97.1% in the LTG group (*P* = .54).

Table 2. Surgical Outcomes

	Patients, No. (%)					
	Intention-to-treat analysis			Per-protocol analysis		
Outcome	LPG-DTR (n = 68)	LTG (n = 69)	*P* value	LPG-DTR (n = 63)	LTG (n = 65)	*P* value
Operative time, mean (SD), min	219.5 (66.4)	201.9 (51.2)	.09	217.1 (67.5)	200.8 (51.9)	.12
Estimated blood loss, mean (SD), mL	76.0 (76.9)	66.1 (63.6)	.41	75.5 (74.6)	65.5 (62.7)	.42
Retrieved lymph nodes, mean (SD), No.	42.3 (21.6)	56.4 (26.0)	.002	40.8 (18.3)	55.1 (24.9)	<.001
Tumor size, mean (SD), cm	2.6 (1.2)	2.6 (1.5)	.92	2.5 (1.1)	2.5 (1.4)	.91
TNM cancer stage						
Ia	59 (86.8)	53 (76.8)	.40	55 (87.3)	49 (75.4)	.33
Ib	6 (8.8)	9 (13.0)		5 (7.9)	9 (13.8)	
IIa	2 (2.9)	6 (8.7)		2 (3.2)	6 (9.2)	
IIb	1 (1.5)	1 (1.4)		1 (1.6)	1 (1.5)	
Hospital stay, mean (SD), d	7.4 (3.1)	7.7 (4.1)	.57	7.4 (3.2)	7.3 (2.9)	.92
Early operative morbidity	16 (23.5)	12 (17.4)	.37	15 (23.8)	10 (15.4)	.23
Reoperation (early)	1 (1.5)[a]	2 (2.9)[b]	.57	1 (1.6)	1 (1.5)	.98
Operative mortality	0	0	.99	0	0	.99
Late complications	12 (17.6)	7 (10.1)	.31	9 (14.3)	7 (10.8)	.74
Dumping syndrome	3 (4.4)	2 (2.9)	.68	3 (4.8)	2 (3.1)	.68
Adhesive ileus	2 (2.9)	2 (2.9)	.99	2 (3.2)	2 (3.1)	.99
Reflux esophagitis	2 (2.9)	2 (2.9)	.99	1 (1.6)	2 (3.1)	.99
Anastomosis stricture	2 (2.9)	0	.25	2 (3.2)	0	.24
Internal hernia	1 (1.5)	0	.50	0	0	.99
Other	3 (4.4)	1 (1.4)	.37	2 (3.2)	1 (1.5)	.62
Reoperation (late)	2 (2.9)[c]	1 (1.4)[d]	.62	0	1 (1.5)	.99
Recurrence	1 (1.5)[e]	2 (2.9)[f]	.99	1 (1.6)	2 (3.1)	.99
Death	1 (1.5)	0	.50	1 (1.6)	0	.99

Abbreviations: LPG-DTR, laparoscopic proximal gastrectomy with double-tract reconstruction; LTG, laparoscopic total gastrectomy; TNM, tumor, node, metastasis.

[a] Adhesiolysis due to ileus.

[b] Includes 1 wound closure due to surgical site dehiscence after distal gastrectomy (excluded in per-protocol analysis) and 1 neojejunojejunostomy.

[c] Includes 1 internal hernia and 1 hiatal hernia.

[d] Omental biopsy.

[e] Recurrence in the liver.

[f] Includes 1 recurrence in the liver and 1 peritoneal seeding.

Discussion

This RCT found that patients with upper-third early GC who underwent LPG-DTR required less vitamin B_{12} supplementation at 2 years after the procedure than those who underwent LTG, with no significant difference in complication and survival rates. Reflux esophagitis is the reason that TG is performed in most patients with upper GC and even upper early GC. Numerous attempts have been made to prevent this complication, such as the use of a gastric tube, hanging method, fundoplication, or pyloroplasty, but results have been inconsistent. Against this background, a retrospective study[9] reported that the newly introduced DTR procedure had results that were similar to TG in terms of reflux esophagitis. Therefore, the current study's finding that LPG-DTR did not have a higher

Table 3. Primary End Points

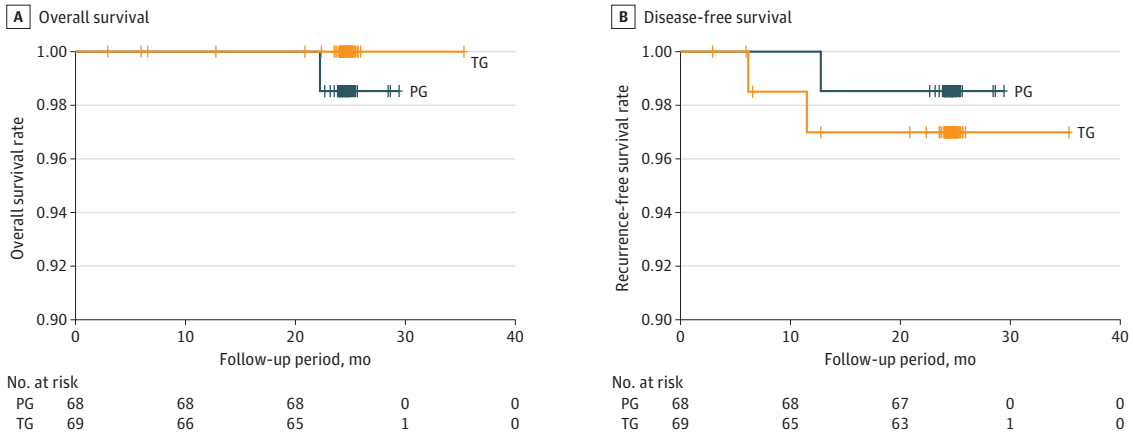
	Intention-to-treat analysis			Per-protocol group analysis		
End point	LPG-DTR (n = 68)	LTG (n = 69)	*P* value	LPG-DTR (n = 63)	LTG (n = 65)	*P* value
Hemoglobin change, g/dL[a]	−0.8 (1.1)	−1.0 (1.2)	.31	−0.8 (1.0)	−1.1 (1.1)	.07
Hemoglobin change, %	−5.6 (7.4)	−6.9 (8.3)	.35	−5.2 (6.8)	−7.5 (7.8)	.08
Anemia incidence, No. (%)	14 (20.6)	21 (30.4)	.22	12 (19.0)	21 (32.3)	.10
Cumulative amount of vitamin B_{12} supplementation, mg						
Mean (SD)	0.4 (1.3)	2.5 (3.0)	<.001	0.3 (1.1)	2.6 (3.0)	<.001
Median (IQR)	0 (0 to 0)	2 (0 to 4)	<.001	0 (0 to 0)	2 (0 to 4)	<.001
Time from surgical procedure, mean (SD), mo						
<3	0 (0.2)	0.1 (0.3)	.15	0 (0.1)	0.1 (0.3)	.10
3 to <6	0 (0.1)	0.1 (0.4)	.005	0 (0)	0.1 (0.3)	.002
6 to <9	0 (0.3)	0.3 (0.7)	<.001	0 (0.3)	0.3 (0.7)	<.001
9 to <12	0 (0.2)	0.4 (0.6)	<.001	0 (0.2)	0.4 (0.6)	<.001
12 to <18	0.1 (0.4)	0.7 (1.2)	<.001	0.1 (0.3)	0.7 (1.2)	<.001
18 to 24	0.2 (0.6)	0.9 (1.2)	<.001	0.2 (0.5)	0.9 (1.2)	<.001
Receipt of vitamin B_{12} supplementation, No. (%)						
No	58 (85.3)	29 (42.0)	<.001	55 (87.3)	27 (41.5)	<.001
Yes	10 (14.7)	40 (58.0)		8 (12.7)	38 (58.5)	

Abbreviations: LPG-DTR, laparoscopic proximal gastrectomy with double-tract reconstruction; LTG, laparoscopic total gastrectomy.

SI conversion factor: To convert hemoglobin from grams per deciliter to grams per liter, multiply by 10.

[a] Calculated as 24-month postoperative hemoglobin level minus preoperative hemoglobin level.

Figure 2. Overall and Disease-Free Survival of Patients Who Received Laparoscopic Proximal Gastrectomy With Double-Tract Reconstruction vs Laparoscopic Total Gastrectomy



PG indicates proximal gastrectomy; and TG, total gastrectomy.

postoperative complication rate than LTG and that LPG-DTR had advantages over LTG in terms of B_{12} supplementation suggest that it will be possible to perform LPG as a function-preserving procedure for many patients with upper GC.

In a previous study on which this RCT was based,[9] a significant difference in Hb change was found between the LTG-DTR and LTG groups. However, in the present study, the LPG-DTR group had less Hb change and anemia than the LTG group, but the differences between groups were not statistically significant. The current study excluded patients with preoperative anemia, which may explain the lack of difference in Hb change between the 2 groups. Perhaps LPG-DTR improves Hb levels only in those who are likely to develop anemia. There is a possibility that there was no difference between the 2 groups because Hb levels were within the normal limit at 24 months after iron supplementation when anemia was present. However, iron absorption in those who undergo LPG-DTR is less than in those who undergo direct esophagogastrostomy, which allows 100% of the passage of food through the remnant stomach and duodenum, because only an estimated 60% of food passes through the remnant stomach and duodenum. These factors may explain why the LPG-DTR and LTG groups did not show a significant difference in Hb change.

In the LPG-DTR group, 85.3% of patients did not require vitamin B_{12} supplementation, while 14.7% of patients received vitamin B_{12} supplementation. The patients who received supplementation presumably required it because the volume in their remnant stomachs was small or less food passed into the stomach. In the LTG group, 58.0% of patients received vitamin B_{12} supplementation for 2 years, while 42.0% did not. If these patients were followed up for more than 2 years, we would expect that more patients would need supplementation.

There was no difference between the 2 groups in the rates of complications within 30 days and during 2 years of follow-up, demonstrating that LPG-DTR was technically feasible and as safe as LTG. In particular, the LPG-DTR group was expected to have longer operative time or more anastomosis-related complications due to 3 anastomoses. However, no difference in operative time or anastomosis-related complications was found in comparison with the LTG group. The incidence of reflux esophagitis and anastomosis after direct esophagogastrostomy has been reported to be approximately 30%.[5,7] However, in the current study, the incidence of both reflux esophagitis and anastomosis decreased significantly to 2.9% after LPG-DTR, and these values were not significantly different than those observed after LTG. Therefore, the reason for not performing PG due to reflux could be eliminated by reducing the occurrence of reflux esophagitis to the TG level. The longer the physical distance between the esophagojejunostomy and the gastrojejunostomy, the less likely reflux esophagitis will occur. However, if the distance is longer than 30 cm, gastroscopic surveillance becomes difficult, which has the disadvantage of being detected as advanced GC later.[16] In this study, the distance between the esophagojejunostomy and gastrojejunostomy was set to be 10 to 15 cm. Because the reflux frequency in the LPG-DTR group was the same as that of the LTG group (2.9% in both groups), this length was deemed appropriate.

According to the gastric emptying time, the ratio of food entering the remnant stomach to food going directly to the small intestine at 3 months after LPG-DTR was 49.8% to 50.3%. However, over time, the amount of food entering the remnant stomach increased, and the ratio of food entering the remnant stomach to food entering the small intestine became 58.3% to 41.7% after 2 years. The fact that 60% of the food went into the remnant stomach after LPG-DTR might be 1 reason patient weight was not better after LPG-DTR compared with LTG. A procedure that blocks the jejunum below the gastrojejunostomyhas been proposed to increase the rate of entry into the remnant stomach.[17] However, if the function of the pylorus and remnant stomach is not good, food stagnation becomes severe and causes reflux esophagitis. This ratio seems to vary depending on the location of the gastrojejunostomy, such as the posterior wall, anterior wall, or greater curvature, which requires additional research. Delayed gastric emptying after gastrectomy is not uncommon, but the cause of delayed gastric emptying after PG may be a decrease in pyloric function. However, most patients in the current study did not have any specific symptoms. It is not recommended that

pyloromyotomy or pyloroplasty be performed during PG because these procedures promote bile reflux. If there is obvious pyloric stenosis, interventions such as balloon dilatation can be performed.

The results of this RCT revealed a general likelihood that QOL scores would deteriorate sharply at postoperative 3 months, regardless of the type of procedure the patient received, and gradually improved over time. We measured the *P* values of the interactions between type of procedure and time for each parameter of QOL. The LPG-DTR group had better physical and social functioning scores than the LTG group. The categories of nausea and vomiting on the EORTC QLQ-C30 and reflux symptoms on the EORTC QLQ-STO22, which may be associated with reflux esophagitis, showed no difference between the 2 groups.

Many studies[5,10,18] have reported no difference in survival between PG and TG among patients with upper early GC, and several studies[19,20] have found no difference in survival between PG and TG, even among patients with some advanced GCs. In our study, there was no difference in recurrence and survival between those who received LPG-DTR vs LTG. Many studies[5,10,18] have reported that PG could be performed in patients with upper early GC because there was almost no metastasis to the distal LNs. In the case of gastroesophageal junction cancer, especially Siewert type II cancer, there is almost no metastasis to distal LNs if the tumor size is less than 4 cm, even if it is category T3 or T4. Thus, PG can also be performed.[3] Furthermore, studies to identify a subgroup capable of undergoing PG for the treatment of upper advanced GC are being actively conducted,[21,22] and there are many suggestions that PG can be performed in patients with T2 and small-sized T3 GCs. Cases of upper GC have recently increased worldwide, and the incidence of early GC has increased in East Asia[1,2]; therefore, the number of PGs is expected to increase in the future. This study's findings may contribute to the implementation of LPG for the treatment of upper GC in the future by demonstrating that LPG-DTR was superior to LTG because it required less vitamin B_{12} supplementation, and there was no increase in surgical complications and no difference in recurrence or survival rates compared with LTG.

Limitations

This study has some limitations. First, the follow-up period was 2 years. Therefore, long-term outcomes at 5 years or more could not be shown. Second, it would have been ideal to have QOL as an original primary end point. However, because there is no objective measure that can be used to calculate the optimal sample size for assessing QOL, other specific parameters, such as change in Hb level and amount of vitamin B_{12} supplementation, were used. Third, when measuring Hb change, which is a co–primary end point, the effect of iron supplementation during the follow-up period was not assessed.

Conclusions

This multicenter RCT showed that patients with upper-third early GC who received LPG-DTR required less vitamin B_{12} supplementation than those who received LTG, with no increase in complication rates and no difference in overall and disease-free survival rates. There was no difference in change in hemoglobin levels between the groups. In addition, the LPG-DTR group had better scores on physical and social functioning scales than the LTG group. These findings suggest that LPG-DTR may be as safe as LTG and a function-preserving procedure for the treatment of patients with upper-third early GC.

ARTICLE INFORMATION

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660

2. Information Committee of the Korean Gastric Cancer Association. Korean Gastric Cancer Association–led nationwide survey on surgically treated gastric cancers in 2019. *J Gastric Cancer*. 2021;21(3):221-235. doi:10.5230/jgc.2021.21.e27

3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. 2021;24(1):1-21. doi:10.1007/s10120-020-01042-y

4. Kong SH, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. Reverse double-stapling end-to-end esophagogastrostomy in proximal gastrectomy. *Dig Surg*. 2010;27(3):170-174. doi:10.1159/000264658

5. Ahn SH, Lee JH, Park DJ, Kim HH. Comparative study of clinical outcomes between laparoscopy-assisted proximal gastrectomy (LAPG) and laparoscopy-assisted total gastrectomy (LATG) for proximal gastric cancer. *Gastric Cancer*. 2013;16(3):282-289. doi:10.1007/s10120-012-0178-x

6. Ronellenfitsch U, Najmeh S, Andalib A, et al. Functional outcomes and quality of life after proximal gastrectomy with esophagogastrostomy using a narrow gastric conduit. *Ann Surg Oncol*. 2015;22(3):772-779. doi:10.1245/s10434-014-4078-7

7. Tokunaga M, Ohyama S, Hiki N, et al. Endoscopic evaluation of reflux esophagitis after proximal gastrectomy: comparison between esophagogastric anastomosis and jejunal interposition. *World J Surg*. 2008;32(7):1473-1477. doi:10.1007/s00268-007-9459-7

8. Ahn SH, Jung DH, Son SY, Lee CM, Park DJ, Kim HH. Laparoscopic double-tract proximal gastrectomy for proximal early gastric cancer. *Gastric Cancer*. 2014;17(3):562-570. doi:10.1007/s10120-013-0303-5

9. Jung DH, Lee Y, Kim DW, et al. Laparoscopic proximal gastrectomy with double tract reconstruction is superior to laparoscopic total gastrectomy for proximal early gastric cancer. *Surg Endosc*. 2017;31(10):3961-3969. doi:10.1007/s00464-017-5429-9

10. Masuzawa T, Takiguchi S, Hirao M, et al. Comparison of perioperative and long-term outcomes of total and proximal gastrectomy for early gastric cancer: a multi-institutional retrospective study. *World J Surg*. 2014;38(5):1100-1106. doi:10.1007/s00268-013-2370-5

11. Takiguchi N, Takahashi M, Ikeda M, et al. Long-term quality-of-life comparison of total gastrectomy and proximal gastrectomy by postgastrectomy syndrome assessment scale (PGSAS-45): a nationwide multi-institutional study. *Gastric Cancer*. 2015;18(2):407-416. doi:10.1007/s10120-014-0377-8

12. Yoo CH, Sohn BH, Han WK, Pae WK. Long-term results of proximal and total gastrectomy for adenocarcinoma of the upper third of the stomach. *Cancer Res Treat*. 2004;36(1):50-55. doi:10.4143/crt.2004.36.1.50

13. Hwang SH, Park DJ, Kim HH, et al. Short-term outcomes of laparoscopic proximal gastrectomy with double-tract reconstruction versus laparoscopic total gastrectomy for upper early gastric cancer: a KLASS 05 randomized clinical trial. *J Gastric Cancer*. 2022;22(2):94-106. doi:10.5230/jgc.2022.22.e8

14. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an evidence-based, multi-disciplinary approach. *J Gastric Cancer*. 2019;19(1):1-48. doi:10.5230/jgc.2019.19.e8

15. Schijns W, Homan J, van der Meer L, et al. Efficacy of oral compared with intramuscular vitamin B-12 supplementation after Roux-en-Y gastric bypass: a randomized controlled trial. *Am J Clin Nutr*. 2018;108(1):6-12. doi:10.1093/ajcn/nqy072

16. Ohyama S, Tokunaga M, Hiki N, et al. A clinicopathological study of gastric stump carcinoma following proximal gastrectomy. *Gastric Cancer*. 2009;12(2):88-94. doi:10.1007/s10120-009-0502-2

17. Nomura E, Lee SW, Kawai M, et al. Functional outcomes by reconstruction technique following laparoscopic proximal gastrectomy for gastric cancer: double tract versus jejunal interposition. *World J Surg Oncol*. 2014;12:20. doi:10.1186/1477-7819-12-20

18. Yamasaki M, Takiguchi S, Omori T, et al. Multicenter prospective trial of total gastrectomy versus proximal gastrectomy for upper third cT1 gastric cancer. *Gastric Cancer*. 2021;24(2):535-543. doi:10.1007/s10120-020-01129-6

19. Rosa F, Quero G, Fiorillo C, et al. Total vs proximal gastrectomy for adenocarcinoma of the upper third of the stomach: a propensity-score–matched analysis of a multicenter Western experience (on behalf of the Italian Research Group for Gastric Cancer–GIRCG). *Gastric Cancer*. 2018;21(5):845-852. doi:10.1007/s10120-018-0804-3

20. Sugoor P, Shah S, Dusane R, Desouza A, Goel M, Shrikhande SV. Proximal gastrectomy versus total gastrectomy for proximal third gastric cancer: total gastrectomy is not always necessary. *Langenbecks Arch Surg*. 2016;401(5):687-697. doi:10.1007/s00423-016-1422-3

21. Yun WG, Lim MH, Kim S, et al. Oncologic feasibility of proximal gastrectomy in upper third advanced gastric and esophagogastric junctional cancer. *J Gastric Cancer*. 2021;21(2):169-178. doi:10.5230/jgc.2021.21.e15

22. Yura M, Yoshikawa T, Otsuki S, et al. Oncological safety of proximal gastrectomy for T2/T3 proximal gastric cancer. *Gastric Cancer*. 2019;22(5):1029-1035. doi:10.1007/s10120-019-00938-8

SUPPLEMENT 1.

Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.

eFigure 1. Diagram for Proximal Gastrectomy With Double-Tract Reconstruction

eFigure 2. Quality of Life After Laparoscopic Proximal Gastrectomy With Double-Tract Reconstruction vs Laparoscopic Total Gastrectomy Measured by the EORTC QLQ-C30 and EORTC QLQ-STO22

SUPPLEMENT 3.

Data Sharing Statement