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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

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ABSTRACT

Purpose: Laparoscopic proximal gastrectomy with double-tract reconstruction (LPG-DTR) is a function-preserving procedure performed for treating upper early gastric cancer (EGC). However, few studies have compared the outcomes of LPG-DTR with those of laparoscopic total gastrectomy (LTG). This study aimed at comparing the short-term outcomes of LPG-DTR between LTG and upper EGC.

Materials and Methods: For upper-third EGC, a multicenter, prospective, randomized trial was performed to compare those who underwent LPG-DTR with those who underwent LTG. Short-term outcomes, including clinicopathologic results, morbidity, mortality, and postoperative courses, were evaluated using a full analysis set based on the intention-to-treat principle and the per-protocol set.

Results: Of the patients, 138 who fulfilled the criteria were randomized to each group. One patient in the LPG-DTR group withdrew consent. Sixty-eight patients underwent LPG-DTR and 69 underwent LTG. The operative time (LPG-DTR=219.4 minutes; LTG=201.8 minutes; P=0.085), estimated blood loss (LPG-DTR=76.0 mL; LTG=66.1 mL; P=0.413), and the morbidity rate (LPG-DTR=23.5%; LTG=17.4%; P=0.373) between the groups were not

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significantly different. No mortality occurred in either of the study groups. Two weeks post operation, the Visick scores for postprandial symptoms, including reflux symptoms, were not significantly different between the groups (P=0.749). Laboratory findings on postoperative day 5 were not significantly different between the groups.

Conclusions: The short-term outcomes of LPG-DTR for upper EGC were comparable to those of LTG.

Trial Registration: ClinicalTrials.gov Identifier: NCT02892643

Keywords: Surgery; Treatment; Laparoscopy; Diagnosis

INTRODUCTION

The incidence of gastric cancer is decreasing worldwide, owing to advances in diagnostic technology and regular check-up programs; however, that of upper early gastric cancer (EGC) in the Republic of Korea and Japan is steadily increasing [1,2]. There have been many advances in EGC treatment and diagnostic technologies. A representative example is endoscopic submucosal dissection, which is effective for EGC treatment without worsening quality of life. However, a surgery should be performed if the absolute indications for endoscopic submucosal dissection are unsatisfactory. There are 2 surgical methods for proximal EGC: total and proximal gastrectomy. Total gastrectomy is advantageous in cancer treatment in a radical way; however, this procedure is associated with postoperative problems such as poor quality of life and nutritional problems. Proximal gastrectomy can preserve the distal stomach and provide better nutritional results. Nevertheless, serious complications (e.g., reflux esophagitis or anastomotic stricture) may occur when esophagogastrostomy is performed [3]. In the present era, laparoscopic gastrectomy has been widely used for EGC. Laparoscopic proximal gastrectomy with double-tract reconstruction (LPG-DTR) for distal stomach preservation without any complications, has emerged as a treatment for upper EGC [4]. Certain retrospective studies have shown that LPG-DTR has oncological safety comparable to that of laparoscopic total gastrectomy with Roux-en-Y reconstruction (LTG), with fewer postoperative complications [5,6]. However, only a few prospective randomized studies have been conducted concerning this topic. Thus, the current study represents the first prospective randomized controlled study comparing the outcomes in LPG-DTR with those in LTG.

Based on this background, the Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) group planned and designed a phase III multicenter randomized controlled trial (RCT; KLASS-05) to compare LPG-DTR and LTG for upper-third EGC by evaluating the changes in hemoglobin (Hb) levels and amount of vitamin B12 supplementation. This paper is an early report focusing on short-term morbidity, mortality, and postoperative course before the final long-term results.

MATERIALS AND METHODS

Study design

The KLASS-05 trial was an investigator-initiated, prospective, phase III multicenter RCT conducted by 19 surgeons from 10 institutions. The trial protocol was approved by the Institutional Review Board (IRB) of each participating institution (approval No. B-1609-361-001). The primary endpoint of this study was the comparison of changes in Hb levels and

quantity of vitamin B12 supplementation between the LPG-DTR and LTG groups, 2 years post operation. A secondary endpoint was the comparison of the quality of life, frequency of reflux esophagitis, postoperative complications, and survival between the 2 groups.

Patient population

All participating patients were screened for eligibility. The eligibility criteria were patients 1) diagnosed with gastric adenocarcinoma by tissue biopsy; 2) who are 20–80 years old; 3) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 4) with an American Society of Anesthesiology (ASA) classification of I–III; 5) who agree to voluntarily participate by signing the written informed consent approved by the IRB before study participation following sufficient explanation of the trial's purpose and protocol; 6) who could undergo proximal gastrectomy with the following preoperative test results having the following oncologic characteristics: tumor located in the proximal third of the stomach, tumor size ≤5 cm, clinically diagnosed with T1 (T: tumor) stage, and all lymph nodes (LNs) did not exceed 8 mm on preoperative tests (especially, LNs 4d, 5, 6, and 10); and 7) who could undergo radical resection or were eligible for curative intent surgical resection.

The exclusion criteria included patients 1) with a preoperative diagnosis of anemia (Hb level <13 g/dL for men and 12 g/dL for women); 2) for whom total gastrectomy was the only appropriate treatment because of the presence of other malignant gastric lesions in the distal stomach); 3) who underwent chemotherapy or radiotherapy for gastric cancer before surgery; 4) who required combined resection due to other diseases (except cholecystectomy); 5) with concurrent malignancies that might affect gastric function preservation (i.e., history of malignancy or concurrent malignancy in other organs); 6) with a history of treatment or currently undergoing treatment for a systemic inflammatory disease; 7) with a history of gastrectomy; and 8) vulnerable (e.g., pregnant women, women planning pregnancy, or lack of decision-making capacity).

After obtaining signed informed consent from the patients, the participant eligibility checklist form was sent via fax or e-mail to the principal investigator for patient enrollment. Each patient was assigned a serial number. The serial numbers were assigned sequentially in the order the principal investigator received the subject eligibility checklist form. Eligible patients who fulfilled all the criteria for enrollment were randomly assigned in a 1:1 ratio to the LPG-DTR or LTG groups.

Sample size power calculation

The mean Hb reduction rates 2 years post operation were 8.3% and 3.4% in the LTG and LPG-DTR groups, respectively, in a retrospective study performed at Seoul National University Bundang Hospital [5]. Moreover, the mean amounts of vitamin B12 supplementation 2 years post operation were 3.1 and 0.1 mg in the LTG and LPG-DTR groups, respectively [5]. The 2 primary endpoints, the type 1 errors (α) for Hb reduction rate and amount of vitamin B12 supplementation, were set at 4% and 1%, respectively. The number of patients required to analyze Hb reduction rates and quantity of vitamin B12 supplementation with 80% statistical power were 62 and 10, respectively. Of these patients, 138 (69 patients per group) patients consider a 10% dropout rate.

Randomization

Once the IRB approved the study protocol, the investigator commenced patient enrollment after obtaining eligible patients' consent to participate in this trial. Patient registration

and management were performed using REDCAP, a web-based electronic case report form provided by the Seoul National University Bundang Hospital Medical Research Collaborating Center (SNUBH MRCC). The investigator confirmed eligibility of each patient based on the inclusion and exclusion criteria, using an enrollment eligibility checklist, and accessing the web-based random assignment program provided by the SNUBH MRCC pre-enrollment. All the patients provided written informed consent to participate in the study.

Randomization to the LPG-DTR or LTG groups commenced after surgery. The operator contacted the data center to request randomization if any other organ abnormality was not found, tumor advanced stage was undetected in the preoperative study, or if peritoneal seeding was not identified via laparoscopic exploration. The results were sent to the operating room in real time, after randomization at the data center. Random assignment was performed with a 1:1 allocation ratio using confidential block size and web-based random assignment at SNUBH MRCC. The operator proceeded with the operation after confirming the randomization results. Following the operation, the operators immediately informed the patient of the type of operation performed to fulfill the patient's right to know.

Eligibility criteria of surgeons and quality control

Institutions, that annually performed 80 cases of gastrectomy and having surgeons who had experience with >50 cases of laparoscopic and open gastrectomy, with at least 3 cases of LPG-DTR, were eligible to participate in this trial for standardization and quality control of surgery. The authors designed and conducted a strict evaluation process for interested surgeons. After evaluating unedited video clips, the steering committee accredited all the participating surgeons. The individual selected operator were notified and registered as an investigator after the screening process.

Surgical procedures

Surgical procedures were performed laparoscopically. The surgery was performed as LTG with Roux-en-Y anastomosis or as LPG-DTR. The LN dissection scope was D1+, according to the Korean Gastric Cancer Association and Japanese Gastric Cancer Association guidelines [7,8].

Trocar insertion and placement
The number and placement of trocars varied depending on the investigator's choice. Partial omentectomy was initiated from the hepatic to the splenic flexures. The left gastroepiploic vessels were ligated proximally without disturbing the splenic vessels.

Total gastrectomy with Roux-en Y anastomosis
Short gastric vessel ligation was performed, and the LN stations around the right gastroepiploic artery were dissected by ligating the vessels after omentectomy. The right gastric vessels were ligated and the duodenum was separated using a linear stapler. LN stations 7, 8, 9, and 11p were dissected and the left gastric vessels were ligated depending on the tumor location and stage. LN stations 11p and 11d were dissected along the splenic artery, up to the splenic hilum. The anastomosis method used for esophagojejunostomy (EJ) was intracorporeal anastomosis using a linear stapler, or extracorporeal anastomosis using a circular stapler, depending on the surgeon's preference. Anastomosis was performed using the Roux-en-Y method, and jejunojejunostomy (JJ) was performed 45–50 cm below the EJ site following total gastrectomy.

Proximal gastrectomy with double-tract reconstruction

The procedure and extent of LN dissection for proximal gastrectomy were similar to those for total gastrectomy, except for LN dissection around stations 5 and 6. The methods for EJ in LPG-DTR were the same as those in LTG. Gastrojejunostomy (GJ) and JJ were performed 10–15 cm and 20 cm below the EJ and GJ sites, respectively.

Perioperative care

Patients were managed according to the guidelines of the critical pathway set by each institution. All institutions were audited regularly. Patients received pre- and postoperative thromboprophylaxis at the discretion of the investigator. Prophylactic antibiotics were administered postoperatively for an appropriate period. Moreover, contrast-enhanced imaging was performed at the discretion of the investigator, to check for leakage at the EJ site. The patient had access to water after fasting and progressed to a liquid diet. Diet progression was modified at the discretion of the investigator. Appropriate pain management was implemented, including patient-controlled analgesics. Adjuvant chemotherapy was administered based on the results of the final pathological report. For stage II and III cancers, 5-fluorouracil-based chemotherapy was commenced 5–6 weeks post operation. Laboratory findings, including radiography, were followed up regularly.

Data collection

Pre- and intraoperative data were collected to measure outcomes. Preoperative data were examined for gender, age, body mass index, ASA score, and ECOG performance status. Preoperative staging was performed using endoscopy, abdominopelvic computed tomography (CT) scans, and abdominal ultrasound. Data regarding the operation time, estimated blood loss, extent of lymphadenectomy, presence or absence of combined resection, length of anastomosis (LPG-DTR: distance from EJ to GJ and distance from GJ to JJ; LTG: distance from EJ to JJ), and EJ type were also collected. CT, blood tests, or X-rays were performed to immediately identify complications, if any abnormal findings occurred during the postoperative period.

Morbidity and mortality

Early morbidity was defined as surgery-related complications that occurred within 30 days of surgery. Complications were categorized as either local or systemic. Local complications included wound complications, fluid collection/abscess, intra-abdominal bleeding, intraluminal bleeding, ileus, anastomotic stricture, leakage, and/or pancreatitis/pancreatic fistula. Systemic complications included pulmonary, urinary, renal, hepatic, cardiac, endocrine, and/or miscellaneous complications. Complication severity was classified according to the Clavien-Dindo classification system [9].

Statistical analyses

Two different groups were defined for analysis: the intention-to-treat (ITT) group, which included all patients based on their initial treatment assignment, except those who did not undergo surgery or who voluntarily withdrew their consent for surgery, and the per-protocol (PP) group, which included patients who completed the study without major protocol deviations.

Fisher's exact test was used to investigate differences in the proportions of patients between the groups. Continuous variables were evaluated using Student's t-test. Statistical significance was set at P<0.05. Statistical analyses were conducted using SPSS software (v. 23.0; IBM Corp., Armonk, NY, USA).

Fig. 1. Flow diagram.
LPG-DTR = laparoscopic proximal gastrectomy with double-tract reconstruction; LTG = laparoscopic total gastrectomy with Roux-en-Y reconstruction.

RESULTS

Patient demographics

Fig. 1 presents a flow diagram of the 138 patients enrolled from October 2016 to September 2018 (69 patients assigned to each group). One patient in the LPG-DTR group withdrew consent; therefore, 68 and 69 patients in the LPG-DTR and LTG groups, respectively, underwent surgery and were included in the ITT analysis.

PP analysis was conducted after excluding 9 patients. In the LPG-DTR group, one case of open conversion due to a technical problem, one splenectomy due to bleeding from the splenic parenchyma, and 3 conversions to LTG were excluded. The reasons for LTG conversion were as follows: one case of the possibility of 4d LN metastasis during surgery, one case of a large tumor size based on the investigator's judgment, and one case of the resection margin being reported as positive on frozen biopsy. In the LTG group, one case was converted to open surgery due to a technical problem, and one was converted to distal gastrectomy based on the investigator's judgment during surgery. Two other patients were converted to LPG-DTR. One case was canceled because of unstable vitals after anesthesia, although LPG-DTR was performed a week later, at the investigator's discretion. One other patient agreed to participate in the study and randomization, but chose to undergo LPG-DTR, regardless of the result that turned out to be LTG. **Table 1** shows patient demographics and characteristics. Both ITT groups were randomized according to the study protocol.

Table 1. Patient characteristics

Variable	ITT group			PP group		
	LPG-DTR (n=68)	LTG (n=69)	P-value	LPG-DTR (n=63)	LTG (n=65)	P-value
Sex			0.138			0.048
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 (yr)	56.7±10.4	61.4±11.3	0.152	58.6±10.2	61.3±11.5	0.161
Preoperative BMI (kg/m²)	24.5±2.8	24.2±3.0	0.550	24.5±2.9	24.5±2.9	0.934
ASA classification			0.944			0.767
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 (6.1)	
ECOG performance status			0.429			0.284
1	62 (91.2)	60 (87.0)		58 (92.1)	56 (86.1)	
2	6 (8.8)	9 (13.0)		5 (8.0)	9 (13.8)	
Previous abdominal operation	0	2 (2.9)	0.157	0	1 (1.5)	0.323
Preoperative endoscopic treatment	8 (11.8)	6 (8.7)	0.553	8 (12.7)	6 (9.2)	0.530
Preoperative TNM staging			0.146			0.156
cT1aN0M0	29 (42.7)	38 (55.1)		27 (42.9)	36 (55.4)	
cT1bN0M0	39 (57.3)	31 (44.9)		36 (57.1)	29 (44.6)	
Smoking status			0.489			0.369
Never	44 (64.7)	38 (55.1)		41 (65.1)	35 (53.8)	
Past	6 (8.8)	9 (13.0)		5 (8.0)	9 (13.8)	
Current	18 (26.5)	22 (31.9)		17 (27.0)	21 (32.3)	

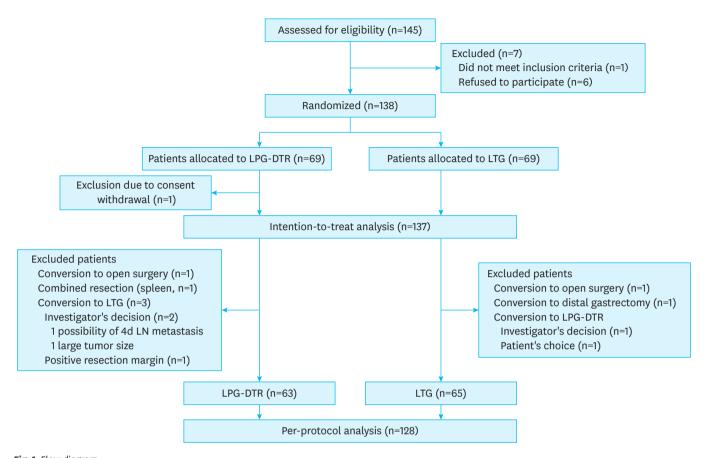Data are shown as mean±SD or number (%).
ITT = intention-to-treat; PP = per-protocol; LPG-DTR = laparoscopic proximal gastrectomy with double-tract reconstruction; LTG = laparoscopic total gastrectomy with Roux-en-Y reconstruction; BMI = body mass index; ASA = American Society of Anesthesiology; ECOG = Eastern Cooperative Oncology Group; TNM = tumor-node-metastasis.

Surgical outcomes

Surgical outcomes, including operation time, estimated blood loss, conversion to open surgery, the extent of lymphadenectomy, combined resection, and omentectomy, did not differ between the ITT and PP treatment groups (**Table 2**). Tumor size, proximal margin length, histologic type, pathologic stage, and tumor (T)-node (N)-metastasis (M; TNM) stage according to the AJCC 7th edition were not significantly different between the groups in the ITT analysis (P=0.919, P=0.232, P=0.592, P=0.233, respectively). However, the number of retrieved LNs, positive LNs, and pathological N stage were higher in the LTG group than in the LPG-DTR group (P=0.002, P=0.008, and P=0.027, respectively). The number of positive LNs and pathological N stage were also higher in the LTG group than in the LPG-DTR group (P=0.009 and P=0.028, respectively; **Table 2**) in the PP analysis.

Operative morbidity and mortality

There were no cases of mortality in either of the study groups. In the ITT analysis, the overall morbidity was not significantly different between the LPG-DTR and LTG groups (23.5% and 17.4%, respectively; P=0.373). Local and systemic complications were not different between the LPG-DTR (13.2% and 5.9%, respectively; P=0.395) and LTG (11.6% and 8.7%, respectively; P=0.747) groups. Moreover, anastomosis-related complications did not occur in either of the study groups. Two cases of intraluminal bleeding were noted in the LPG-DTR group, although the difference was not statistically significant (P=0.319). One case each of conversion to open surgery occurred in both groups. Moreover, 3 reoperations were included in the ITT analysis. Adhesiolysis was performed in one patient belonging to the LPG-DTR group because of mechanical obstruction. Furthermore, 2 reoperations were performed for the LTG group. Due to narrowing of the JJ site, mechanical obstruction occurred in one patient; therefore, JJ was revised. One more patient underwent a reoperation because of wound dehiscence. Distal gastrectomy was performed because the operator had determined

Table 2. Surgical outcomes

	ITT group			PP group		
	LPG-DTR (n=68)	LTG (n=69)	P-value	LPG-DTR (n=63)	LTG (n=65)	P-value
Operation time (min)	219.4±66.4	201.8±51.2	0.085	217.1±67.5	200.8±51.9	0.117
Estimated blood loss (mL)	76.0±76.9	66.1±63.6	0.413	75.5±74.7	65.5±62.7	0.415
Conversion to open surgery	1 (1.5)	1 (1.4)	0.992	0	0	N/A
Combined resection			0.346			N/A
Gall bladder	2 (2.9)	5 (7.2)		0	0	
Liver	0	0		0	0	
Spleen	1 (1.5)	0		0	0	
Omentectomy			0.177			0.182
Complete	1 (1.5)	4 (5.8)		1 (1.6)	4 (6.1)	
Partial	67 (98.5)	65 (94.2)		62 (98.4)	61 (93.8)	
Distance from EJ to GJ (cm)	16.1±5.5	N/A	N/A	16.1±5.6	N/A	N/A
Distance from GJ to JJ (cm)	22.3±5.8	N/A	N/A	22.2±5.6	N/A	N/A
Distance from EJ to JJ (cm)	N/A	41.4±10.5	N/A	N/A	40.9±10.2	N/A
Type of anastomosis in EJ			0.531			0.841
Extracorporeal using a circular stapler	41 (60.3)	38 (55.1)		36 (57.1)	36 (55.4)	
Intracorporeal using a linear	27 (39.7)	30 (43.5)		27 (42.9)	29 (44.6)	
Unknown	0	1 (1.4)				
No. of retrieved lymph nodes	42.3±21.6	56.4±26.0	0.002	40.8±18.3	55.1±24.9	0.000
No. of positive lymph nodes	0.0±0.1	0.4±1.2	0.008	0.0±0.1	0.5±1.3	0.009
Tumor size (cm)	2.6±1.2	2.6±1.5	0.919	2.5±1.1	2.5±1.4	0.914
Proximal RM (cm)	2.1±1.7	2.6±2.9	0.232	2.1±1.7	2.7±3.0	0.229
Distal RM (cm)	3.3±2.5	13.8±4.1	0.000	2.9±1.9	14.1±3.7	0.000
Histologic type			0.592			0.791
Intestinal	36 (52.9)	34 (49.3)		33 (52.4)	33 (50.8)	
Diffuse	29 (42.6)	29 (42.0)		27 (42.9)	27 (41.5)	
Mixed	3 (4.4)	6 (8.7)		3 (4.8)	5 (7.7)	
pT stage			0.233			0.311
Tis	1 (1.5)	1 (1.4)		1 (1.6)	1 (1.5)	
T1a	37 (54.4)	26 (37.7)		35 (55.5)	25 (38.5)	
T1b	20 (29.4)	34 (49.3)		19 (30.2)	32 (49.2)	
T2	8 (11.8)	6 (8.7)		6 (9.5)	6 (9.2)	
T3	1 (1.5)	1 (1.4)		1 (1.6)	1 (1.5)	
T4a	1 (1.5)	0		1 (1.6)	0	
pN stage			0.027			0.028
N0	67 (98.5)	58 (85.1)		62 (98.4)	54 (83.1)	
N1	1 (1.5)	6 (8.7)		1 (1.6)	6 (9.2)	
N2	0	4 (5.8)		0	4 (6.1)	
N3a	0	1 (1.4)		0	1 (1.5)	
TNM stage[*]			0.40			0.33
Ia	59 (86.8)	53 (76.8)		55 (87.3)	49 (75.4)	
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)	

Data are shown as mean±SD or number (%).
ITT = intention-to-treat; PP = per-protocol; LPG-DTR = laparoscopic proximal gastrectomy with double-tract reconstruction; LTG = laparoscopic total gastrectomy with Roux-en-Y reconstruction; EJ = esophagojejunostomy; GJ = gastrojejunostomy; JJ = jejunojejunostomy; N/A = not available; RM = resection margin; TNM = tumor-node-metastasis.
[*]TNM staging was performed according to the AJCC 7th edition.

its availability during the first surgery. Therefore, this patient was excluded from PP analysis (**Table 3**).

There was no significant difference in the severity of morbidity according to the Clavien-Dindo classification between the groups (P=0.405). Operative morbidity was not significantly different between the groups in PP analysis (**Table 3**).

Table 3. Operative morbidity and mortality

	ITT group			PP group		
	LPG-DTR (n=68)	LTG (n=69)	P-value	LPG-DTR (n=63)	LTG (n=65)	P-value
Overall morbidity	16 (23.5)	12 (17.4)	0.373	15 (23.8)	10 (15.4)	0.229
Local complication	9 (13.2)	6 (11.6)	0.395	9 (14.3)	5 (7.7)	0.232
Wound infection	3 (4.4)	1 (1.4)	0.303	3 (4.8)	0	0.075
Intra-abdominal abscess	3 (4.4)	1 (1.4)	0.303	3 (4.8)	1 (1.5)	0.295
Intra-abdominal bleeding	0	1 (1.4)	0.319	0	1 (1.5)	0.323
Intraluminal bleeding	2 (2.9)	0	0.151	2 (3.2)	0	0.148
Intestinal obstruction	1 (1.5)	2 (2.9)	0.568	1 (1.6)	2 (3.1)	0.578
Paralytic ileus	0	1 (1.4)	0.319	0	1 (1.5)	0.323
Anastomosis stenosis	0	0	N/A	0	0	N/A
Anastomotic leakage	0	0	N/A	0	0	N/A
Pancreatic fistula	0	0	N/A	0	0	N/A
Systemic complication	4 (5.9)	5 (8.7)	0.747	3 (4.8)	4 (6.1)	0.729
Pulmonary	4 (5.9)	5 (8.7)	0.747	3 (4.8)	4 (6.1)	0.729
Others	3[*] (4.4)	1[†] (1.4)	0.303	3[*] (4.8)	1[†] (1.5)	0.302
Conversion to open surgery	1 (1.5)	1 (1.4)	0.983	0	0	N/A
C-D grade			0.405			0.179
I	5 (7.3)	3 (4.3)	0.453	4 (6.3)	3 (4.6)	0.666
II	8 (11.8)	6 (8.7)	0.553	8 (12.7)	5 (7.7)	0.349
III	3 (4.4)	1 (1.4)	0.303	3 (4.8)	0	0.075
IV	0	2 (2.9)	0.157	0	2 (3.1)	0.161
Reoperation	1[‡] (1.5)	2[§] (2.9)	0.568	1[‡] (1.6)	1[∥] (1.5)	0.982
Mortality	0	0		0	0	N/A

Data are shown as number (%).
ITT = intention-to-treat; PP = per-protocol; LPG-DTR, laparoscopic proximal gastrectomy with double-tract reconstruction; LTG, laparoscopic total gastrectomy with Roux-en Y reconstruction; C-D grade, Clavien-Dindo grade; N/A, not available; POD = postoperative day.
[*]1 acute cholecystitis treated with percutaneous transhepatic gall bladder drainage on POD 18, 2 fever of unknown origin treated with antibiotics on POD 3; [†]1 acute colitis treated with intravenous antibiotics on POD 3; [‡]Adhesiolysis due to ileus; [§]1 wound closure due to surgical site dehiscence after distal gastrectomy (excluded in PP analysis), 1 neo jejunojejunostomy; [∥]Neo jejunojejunostomy.

Postoperative course and laboratory findings

In the ITT analysis, the time to the first flatus and diet did not differ between the LPG-DTR and LTG groups (3.5 and 3.7 days, respectively, P=0.326). Postoperative hospital stay was not significantly different between the groups (7.4 and 7.8 days, respectively; P=0.567; **Table 4**). Moreover, no significant difference was noted in the preoperative and 2 weeks postoperative Visick scores between the groups (P=0.749 and P=0.793, respectively). The Hb levels, white blood cell counts, along with the albumin and C-reactive protein levels pre operation and on days 2 and 5 post operation were not significantly different between the groups (P=0.150, P=0.563, P=0.976, P=0.321, P=0.504, P=0.325, P=0.759, and P=0.879, respectively).

The PP analysis showed results similar to those of the ITT analysis in terms of laboratory results and postoperative course (**Table 4**).

DISCUSSION

KLASS-05 was the first RCT to compare LPG-DTR with LTG. This study focused on the short-term results of this RCT. There were no significant differences in postoperative complications or course between the LPG-DTR and LTG groups. In general, LPG-DTR has more anastomoses than LTG and is structurally complex, and estimated to have high complications. Contrastingly, the current study revealed that the operative time and number of anastomosis-related complications were not high in the LPG-DTR cohort. The postoperative course, including Visick scores, which indicate the quality of life and

Table 4. Postoperative course and laboratory findings

	ITT group			PP group		
	LPG-DTR (n=68)	LTG (n=69)	P-value	LPG-DTR (n=63)	LTG (n=65)	P-value
First flatus (day)	3.5±1.1	3.7±1.2	0.326	3.5±1.1	3.7±1.0	0.476
First soft diet (day)	4.8±2.1	4.7±2.2	0.820	4.8±2.2	4.6±1.7	0.504
Hospital stay (day)	7.4±3.1	7.8±4.1	0.567	7.4±3.2	7.3±2.9	0.922
Body weight (kg)						
Preoperative	65.5±9.6	65.8±11.5	0.840	65.2±9.7	66.5±11.3	0.493
POD 2 weeks	61.8±9.1	61.5±11.1	0.873	61.6±9.21	62.1±10.9	0.759
Visick score						
Preoperative			0.749			0.576
I	49 (72.1)	52 (75.4)	0.660	44 (69.8)	49 (75.4)	0.482
II	7 (10.3)	8 (11.6)	0.807	7 (11.1)	8 (12.3)	0.833
Unknown	12 (17.6)	9 (13.0)	0.455	12 (19.0)	8 (12.3)	0.294
POD 2 weeks			0.793			0.700
I	48 (70.6)	50 (72.5)	0.915	44 (69.8)	48 (73.8)	0.717
II	9 (13.2)	9 (13.0)	0.973	8 (12.7)	9 (9.2)	0.848
III	1 (1.5)	0	0.312	1 (1.6)	0	0.308
Unknown	10 (14.7)	10 (14.5)	0.972	10 (15.9)	8 (12.3)	0.562
WBC (× 10³)						
Preop	6.2±1.6	6.2±1.4	0.992	6.2±1.7	6.2±1.4	0.971
POD 2	10.5±3.4	10.5±2.3	0.976	10.4±3.5	10.5±2.3	0.914
POD 5	6.9±1.6	6.6±1.6	0.321	6.8±1.6	6.7±1.6	0.725
Hb (g/dL)						
Preoperative	14.1±1.2	14.2±1.4	0.827	14.1±1.2	14.3±1.3	0.583
POD 2	12.4±1.4	12.7±1.4	0.150	12.4±1.3	12.8±1.3	0.840
POD 5	12.0±1.3	12.2±1.3	0.563	12.0±1.3	12.3±1.2	0.272
Albumin (g/dL)						
Preoperative	4.5±0.5	4.4±0.5	0.265	4.6±0.6	4.5±0.5	0.315
POD 2	3.5±0.4	3.5±0.4	0.504	3.5±0.4	3.5±0.3	0.542
POD 5	3.4±0.4	3.4±0.3	0.325	3.4±0.4	3.4±0.3	0.344
CRP						
Preoperative	0.2±0.4	0.3±1.0	0.420	0.2±0.5	0.3±1.1	0.435
POD 2	12.2±11.7	12.9±14.7	0.759	12.0±11.9	13.3±15.2	0.591
POD 5	10.6±12.6	10.3±7.3	0.879	10.5±12.9	10.7±7.6	0.953

Data are shown as mean±SD or number (%).
ITT = intention-to-treat; PP = per-protocol; LPG-DTR = laparoscopic proximal gastrectomy with double-tract reconstruction; LTG = laparoscopic total gastrectomy with Roux-en-Y reconstruction; POD = postoperative day; WBC = white blood cell count; Hb = hemoglobin; CRP = C-reactive protein.

postprandial symptoms, did not differ between the groups, although this was a short-term result. Mortality and major complications, defined as a grade higher than Clavien-Dindo grade III, did not differ between the groups.

In a recently published retrospective study [10-12], the short-term complication rates of LPG-DTR and LTG were 12%–17% and 17%–20%, respectively. This was not significantly different from the results of the current study. There is a possibility of leakage due to the presence of a duodenal stump; however, no duodenal stump leakage was noted in the current study in the case of LTG. Although 1 more GJ was added in the case of LPG-DTR, anastomosis-related complications (e.g., bleeding at the anastomosis or dehiscence of anastomosis) did not occur more frequently compared to LTG. In addition, in the case of LTG, the LN dissection range is further expanded, which may lead to more complications; however, the current study did not show a difference compared to other retrospective studies. Therefore, there was no technical difference between performing LPG-DTR for proximal EGC in the current study.

Laparoscopic EJ is one of the most challenging LTG or LPG-DTR procedures, and surgeons are typically reluctant to perform it. Although 2 cases of open conversion due to an EJ-related problem were noted, EJ-related complications did not occur in either of the study groups.

According to a prospective study by Yang et al. [13], the incidence of EJ-related complications was approximately 1.8%, which is not significantly different from that in the current study. However, other studies have reported high complication rates [14]. This is because the anastomosis is anatomically located deeply, laparoscopic repair becomes difficult when technical failure occurs. To overcome this, various methods have been proposed; however, to the best of our knowledge, there is no research result reporting an ideal method. In our study, 3 methods (extracorporeal, intracorporeal circular, and linear stapling) were used. The reason for the low observed complication rate is believed to be the participation of surgeons who overcame the learning curve of each method.

With regard to the treatment of gastric cancer, the accuracy of preoperative examinations is very important in determining the scope, type, and method of surgery. In particular, total gastrectomy must be performed if LN metastasis to LN stations 5 or 6 is present. Therefore, screening of these high-risk patients through preoperative screening for upper EGC is important. Thus, methods using sentinel node navigation or fluorescence imaging with indocyanine green are being studied [15,16]; however, there is still no standardized method for efficient preoperative screening. Ichikawa et al. [17] and Nanishi et al. [18] reported that clinical staging might be underestimated compared to pathological staging in upper gastric cancer. In the current study, the N staging and number of positive LNs were high in the LTG patient group post-surgery, although the patient registration criteria were strictly applied during preoperative examinations. Distinguishing whether this was a result of wide LN dissection in the LTG group or a coincidence remains difficult. Therefore, this imbalance between the groups might require long-term observations, and additional well-designed studies are essential to address these problems.

Based on the aforementioned results, the authors confirm no significant clinical differences in the short-term implementation of LPG-DTR and LTG. Therefore, LPG-DTR is considered a possible treatment option for proximal EGC.

The current study, however, has certain limitations. Firstly, the male-to-female ratio in the PP group did not match despite randomization. This was appropriately randomized in the ITT group, but was thought to be a bias caused by the switch between the LPG-DTR and LTG groups during surgery. Secondly, as previously mentioned, a difference in pathological N staging was noted between the 2 groups, although no differences in TNM staging were noted. Thus, a research design is needed to collect and analyze LNs for each LN station in surgical specimens during or after surgery; however, this could not be implemented in the present study. In this regard, close follow-up and review are necessary.

In conclusion, the KLASS-05 study is the first prospective, randomized, and multicenter trial to compare LPG-DTR and LTG outcomes. In the current report, there were no significant differences in morbidity or mortality between the LPG-DTR and LTG groups. Therefore, the short-term outcomes of LPG-DTR for upper EGC were comparable to those of LTG, and the KLASS-05 study will hopefully address concerns regarding the long-term results.

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