

Laparoscopic proximal gastrectomy with double tract reconstruction is superior to laparoscopic total gastrectomy for proximal early gastric cancer

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Abstract

Background Laparoscopic proximal gastrectomy (LPG) with double tract reconstruction (DTR) is known to reduce reflux symptoms, which is a major concern after proximal gastrectomy. The aim of this study is to compare retrospectively the clinical outcomes of patients undergoing LPG with DTR with those treated by laparoscopic total gastrectomy (LTG).

Methods Ninety-two and 156 patients undergoing LPG with DTR and LTG for proximal stage I gastric cancer were retrospectively analyzed for short- and long-term clinical outcomes.

Results There were no significant differences in the demographics, T-stage, N-stage, and complications between the groups. The LPG with DTR group had a shorter operative time and lower estimated blood loss than the LTG group (198.3 vs. 225.4 min, $p < 0.001$; and 84.7 vs. 128.3 mL $p = 0.001$). The incidence of reflux symptoms \geq Visick grade II did not significantly differ between the groups during a mean follow-up period of 37.2 months (1.1 vs. 1.9%, $p = 0.999$). The hemoglobin change was significantly lower in the LPG with DTR group compared to in the LTG group in the first and second postoperative years (5.03 vs. 9.18% $p = 0.004$; and 3.45 vs. 8.30%, $p = 0.002$, respectively), as was the mean amount of vitamin B₁₂ supplements 2 years

after operation (0.1 vs. 3.1 mg, $p < 0.001$). The overall survival rate was similar between the groups.

Conclusions LPG with DTR maintained comparable oncological safety and anastomosis-related late complications compared to LTG and is preferred over LTG in terms of preventing postoperative anemia and vitamin B₁₂ deficiency.

Keywords Laparoscopic proximal gastrectomy · Double tract reconstruction · Proximal early gastric cancer · Anemia

Gastric cancer is the most common malignancy in Korea. The epidemiological characteristics of gastric cancer have changed over the last several decades, with the incidence of early gastric cancer (EGC) in Korea having increased from 24.8 to 48.9% as a result of improved surveillance through the National Cancer Screening Program of Korea. Similarly, the incidence of proximal gastric cancer has also gradually increased from 5.3 to 14.0% in recent years [1].

The Korean Laparoscopic Gastrointestinal Surgery Study Group recently reported that the long-term oncologic outcomes of laparoscopic gastrectomy for patients with gastric cancer were comparable to those of open gastrectomy [2]. Moreover, many other groups have also reported the oncological safety of laparoscopic gastrectomy [3, 4]; accordingly, various extents of laparoscopic gastrectomy and various reconstruction methods according to the different kinds of gastrectomy have been attempted.

On the other hand, laparoscopic proximal gastrectomy (LPG) is generally not considered as a suitable operation for proximal EGC in Korea. In fact, in 2009, in spite of the increased incidence of proximal EGC, proximal gastrectomy (PG) comprised only 1% (141 cases) of all gastric

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operations in Korea, including open cases [5]. In several previous studies, the oncological safety of PG for proximal EGC has been demonstrated to be comparable to that of total gastrectomy (TG) [6–9]; however, the unpopularity of PG is largely due to the high incidences of reflux symptoms and anastomotic stenosis associated with this method, with approximately 21.4–56.2% of patients experiencing reflux symptoms or anastomotic stenosis after PG [9–12]. In addition, LPG is considered a relatively technically demanding procedure.

We have previously compared the clinical outcomes between LPG with esophagogastrostomy (EG) and laparoscopic TG (LTG) for proximal EGC and concluded that EG after LPG was associated with an increased risk of reflux symptoms (32.0%) [9]. Based on this previous study, we have been attempting double tract reconstruction (DTR) after LPG for reducing reflux symptoms since 2009. Our initial case series of LPG with DTR demonstrated that it is a feasible, simple, and useful reconstruction method with excellent postoperative outcomes in terms of preventing reflux symptoms [13]. However, no comparison of the late clinical outcomes of LPG with DTR and LTG has yet been conducted.

Therefore, the aim of this study was to compare the long-term outcomes in terms of late complications and nutritional status between patients who underwent DTR after LPG and those treated by LTG.

Methods

Patients

Between June 2003 and April 2015, 256 patients with confirmed pathological stage I gastric cancer (pT1N0, T1N1, and T2N0) treated with curative LPG with DTR or LTG at the Seoul National University Bundang Hospital, were enrolled in the present study. The gastric cancer stage was classified according to the seventh edition of the American Joint Committee on Cancer and the Union for International Cancer Control guidelines.

Because other treatments and malignancies may affect the nutritional status, patients with adjuvant chemotherapy for pathological more than stage II gastric cancer, combined splenectomy, other malignancy, or recurrent gastric cancer were excluded from our analyses. Moreover, patients with an incomplete follow-up of less than 1 year were also excluded since their long-term nutritional status could not be evaluated.

The surgical procedure, namely LPG with DTR or LTG, was chosen at the discretion of the surgeons and patients. The 2010 Japanese gastric cancer treatment guidelines suggested the preservation of more than half of the distal

stomach in the PG. Therefore, if the remnant stomach was too small for some functional benefit to be gained from preserving the stomach, the surgeons would perform LTG. There were 92 and 156 patients in the LPG with DTR and LTG groups, respectively.

Evaluation of clinical parameters

The clinical, operative, and pathological variables were compared between the LPG with DTR and LTG groups based on the information obtained from our prospectively collected surgical database. Early postoperative complications (occurring on postoperative days 0–30) were graded using the Clavien–Dindo classification [14]. Early postoperative complications requiring medical, radiological, or surgical interventions (grade 2 or higher) were regarded as an event. Morbidity was classified as follows: (i) local complications, including wound infection, fluid collection/abscess, anastomosis leakage, stenosis, intestinal obstruction, ileus, intraluminal bleeding, intra-abdominal bleeding, and pancreatitis and (ii) systemic complications, including pulmonary, renal, urinary, cardiac, and neurologic problems, as defined in our previous study [15].

Late postoperative complications (after postoperative day 30) requiring radiological or surgical interventions were regarded as an event; these included ileus, internal hernia, cholecystitis, reflux symptoms, and anastomotic stenosis. Reflux symptoms and anastomotic stenosis were diagnosed according to the symptoms and endoscopic findings, and the reflux symptoms were classified using the modified Visick score [16]. If a 9-mm diameter endoscope could not pass through an anastomosis of a patient complaining of dysphagia, anastomotic stenosis was diagnosed. Nutritional status and anemia were evaluated by the changes in body weight and laboratory data (total protein, albumin, cholesterol, and hemoglobin) in the first and second postoperative year. The amount of vitamin B₁₂ supplements was also calculated.

Techniques

LPG with DTR

The lymph node (LN) stations were numbered according to the Japanese classification of gastric cancer (3rd English Edition) [17]. Our LPG with DTR technique has been previously described in detail [13]. Briefly, LN stations 1, 2, 3a, 4sa, 4sb, 7, 8a, 9, and 11p were dissected, and the left gastroepiploic and left gastric vessels were subsequently ligated. The right gastroepiploic vessels, right gastric vessels, and the hepatic and pyloric branches of the vagus nerves were routinely preserved. Intracorporeal Roux-en-Y end-to-side

esophagojejunostomy (EJ) was performed using an endoscopic purse-string instrument, after the left lower port was extended to a length of approximately 3 cm in order to remove the specimen and to insert a circular stapler. Next, side-to-side GJ, 10 cm below the EJ was performed in an extracorporeal fashion using 2 laparoscopic linear staplers. Finally, end-to-side jejunojunostomy (JJ), 20 cm below the GJ, was performed using an extracorporeal hand-sewing suture.

LTG

Our LTG technique has been previously described [18]. Briefly, in addition to the LPG with DTR procedures, the following procedures were added for LTG: the right gastric and gastroepiploic vessels were divided at their origins, and LN stations 3b, 4d, 5, and 6 were dissected. In some cases, such as clinically equivocal EGC, D2 LN dissection was attempted, in which LN stations 10, 11d, and 12a were dissected. The duodenum was transected 2 cm distal to the pylorus, using a laparoscopic linear stapler. Most cases of intracorporeal Roux-en-Y EJ with JJ were performed using the same procedures as for LPG with DTR.

Ethics statement

This study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B1502-286-115).

Statistical analysis

Statistical analyses were performed using Student's *t* test for continuous variables. The χ^2 test was used for analysis of categorical variables. All statistical analyses were performed with PASW statistics 18 software (SPSS, New York, NY, USA), and $p < 0.05$ was considered statistically significant.

Results

Patient demographic, operative, and pathological characteristics

The patient demographic, operative, and pathological characteristics are provided in Table 1. The two groups were comparable in terms of age, sex, comorbidities, and body mass index.

Table 1 Demographic, operative, and pathological characteristics of patients undergoing laparoscopic proximal gastrectomy (LPG) with double tract reconstruction (DTR) and laparoscopic total gastrectomy (LTG)

	LPG with DTR ($n=92$)	LTG ($n=156$)	<i>p</i> value
Age (year)	59.8 ± 11.4	58.7 ± 10.8	0.447
Sex (M:F)	77:15	120:36	0.266
Comorbidity	45 (48.9%)	77 (49.4%)	1.000
BMI (kg/m ²)	23.5 ± 2.7	23.9 ± 3.3	0.441
Operative time (min)	198.3 ± 38.8	225.4 ± 51.6	<0.001
Estimated blood loss (mL)	84.7 ± 81.7	128.3 ± 112.5	0.001
Combined cholecystectomy	2 (2.2%)	5 (3.2%)	0.939
Lymph node dissection			<0.001
D1+	92	86	
D2	0	70	
Size (cm)	2.4 ± 1.3	3.2 ± 1.9	<0.001
Proximal resection margin (cm)	2.8 ± 2.1	2.9 ± 2.2	0.691
Distal resection margin (cm)	2.9 ± 2.3	12.2 ± 4.0	<0.001
Number of retrieved LNs	46.1 ± 19.6	60.0 ± 25.7	<0.001
T-stage			0.858
T1	84 (91.3%)	140 (89.7%)	
T2	8 (8.7%)	16 (10.3%)	
N-stage			0.999
N0	87 (94.6%)	148 (94.9%)	
N1	5 (5.4%)	8 (5.1%)	

Values are presented as *n* (%) or mean ± SD, as appropriate

LPG Laparoscopic proximal gastrectomy, DTR double tract reconstruction, LTG laparoscopic total gastrectomy, M male, F female, BMI body mass index, LNs lymph nodes

In terms of the operative characteristics, the mean operative time was shorter (198.3 ± 38.8 vs. 225.4 ± 51.6 min, $p < 0.001$) and the estimated blood loss was lower in the LPG with DTR group compared to in the LTG group (84.7 ± 81.7 vs. 128.3 ± 112.5 mL, $p = 0.001$). D1+ LN dissection was performed in all 92 cases of LPG with DTR, whereas there were 86 and 70 cases of D1+ LN and D2 LN dissection, respectively, in the LTG group.

In terms of the pathological characteristics, there were no significant differences in the T-stage, N-stage, and proximal resection margins between the groups. The mean tumor size was larger (2.4 ± 1.3 vs. 3.2 ± 1.9 cm, $p < 0.001$), the distal resection margin was longer (2.9 ± 2.3 vs. 12.2 ± 4.0 cm, $p < 0.001$), and the number of retrieved LNs was higher (46.1 ± 19.6 vs. 60.0 ± 25.7 , $p < 0.001$) in the LTG group compared to in the LPG with DTR group.

Postoperative course and early complications

The postoperative course and early complications are summarized in Table 2. The time of gas-passing and postoperative hospital stay were similar between the two groups, and the time of solid food initiation was also similar in the LPG with DTR group. The early complication rates were 10.9 and 18.6% in the LPG with DTR and LTG groups, respectively, and there was no statistically significant difference in the early complications between the 2 groups. Anastomotic leakage occurred in 2 patient (2.2%) in the LPG with DTR group and 3 patients (1.9%) in the LTG group ($p = 0.999$). There were 6 re-operations ($p = 0.999$) for bleeding (LPG with DTR, $n = 1$; LTG, $n = 2$) and mechanical ileus (LTG, $n = 3$). There was no case of mortality in the early stage (until postoperative day 30).

Late complications

Late complications occurred in 8 patients (8.7%) in the LPG with DTR group and 22 patients (14.1%) in the LTG group, with no statistically significant difference observed between the 2 groups (Table 2). In the LPG with DTR group, only one patient underwent re-operation for internal hernia at postoperative month 7. Conversely, in the LTG group, 11 patients underwent re-operations ($p = 0.284$) for mechanical ileus ($n = 1$), internal hernia ($n = 7$), and cholecystitis ($n = 3$). Four patients (LPG with DTR, $n = 1$; LTG, $n = 3$) showed reflux symptoms, all of which were classified as Visick grade II ($p = 0.999$). Five patients (LPG with DTR, $n = 3$; LTG, $n = 2$) with stenosis upon EJ were treated completely by balloon dilatation ($p = 0.175$).

Table 2 Postoperative course of patients undergoing laparoscopic proximal gastrectomy (LPG) with double tract reconstruction (DTR) and laparoscopic total gastrectomy (LTG)

	LPG with DTR ($n = 92$)	LTG ($n = 156$)	<i>p</i> value
Gas-passing (days)	4.0 ± 1.0	3.7 ± 1.1	0.070
Start of diet (days)	4.6 ± 5.3	5.1 ± 4.8	0.467
Postoperative hospital stay (days)	8.5 ± 11.3	8.6 ± 5.7	0.983
Mean follow-up (months)	26.6 ± 10.3	43.5 ± 23.2	<0.001
Early complications (C–D \geq II) ^a	10 (10.9%)	29 (18.6%)	0.152
Fluid collection	2	10	
Pulmonary	3	6	
Ileus	1	6	
Leakage	2	3	
Bleeding	1	2	
Wound	1	2	
Postoperative mortality ^a	0	0	0.999
Late complications ^b	8 (8.7%)	22 (14.1%)	0.289
Ileus	1	6	
Internal hernia	1	7	
Cholecystitis	2	4	
Reflux symptoms	1	3	
EJ stenosis	3	2	

Values are presented as n (%) or mean \pm SD, as appropriate

LPG Laparoscopic proximal gastrectomy, DTR double tract reconstruction, LTG laparoscopic total gastrectomy, C–D Clavien–Dindo classification, EJ esophagojejunostomy

^aUntil postoperative day 30

^bAfter postoperative day 30

Nutritional status and anemia

The decrease rates of body weight and laboratory data were used as indicators of postoperative nutritional status and anemia (Fig. 1). The decrease rates of the serum total protein, albumin, and total cholesterol levels (%) did not significantly differ in either the first or second postoperative year between the 2 groups (Fig. 1A–C). The rate of body weight change (%) was significantly lower in the LPG with DTR group than in the LTG group in the first and second postoperative year (Fig. 1D). Further, the decrease rate of hemoglobin (%) was significantly lower in the LPG with DTR group than in the LTG group in both the first and second postoperative years (Fig. 1E).

The serum vitamin B₁₂ levels were significantly higher in the LPG with DTR group than in the LTG group in both the first and second postoperative years (Fig. 2). Five patients (5.4%) in the LPG with DTR group and 138 patients (88.5%) in the LTG group were supplemented with vitamin B₁₂ (actinamide 1 mg; Shin Poong Pharm., Seoul,

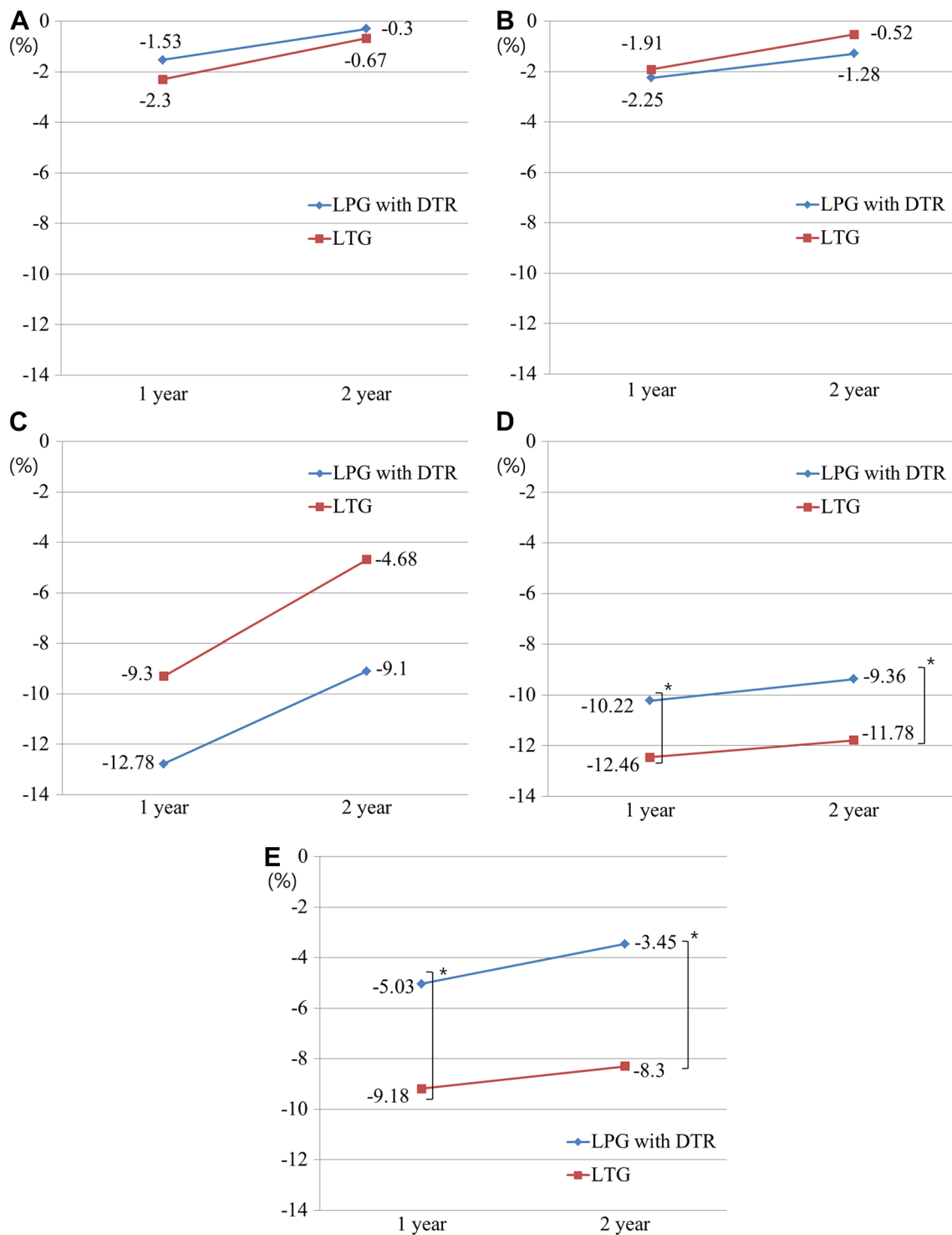


Fig. 1 Comparison of nutritional status and anemia in the first and second postoperative years (decrease rate, %) between laparoscopic proximal gastrectomy with double tract reconstruction and laparoscopic total gastrectomy. *LPG* Laparoscopic proximal gastrectomy,

DTR double tract reconstruction, *LTG* laparoscopic total gastrectomy. **A** Total protein, **B** albumin, **C** total cholesterol, **D** body weight 1 year, $p=0.036$; 2 year, $p=0.049$, **E** hemoglobin, 1 year, $p=0.004$; 2 year, $p=0.002$

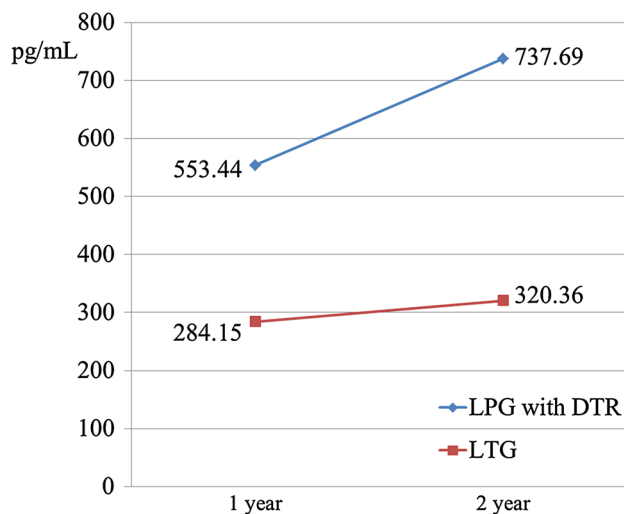


Fig. 2 Comparison of serum vitamin B₁₂ levels in the first and second postoperative years between laparoscopic proximal gastrectomy with double tract reconstruction and laparoscopic total gastrectomy. *LPG* Laparoscopic proximal gastrectomy, *DTR* double tract reconstruction, *LTG* laparoscopic total gastrectomy

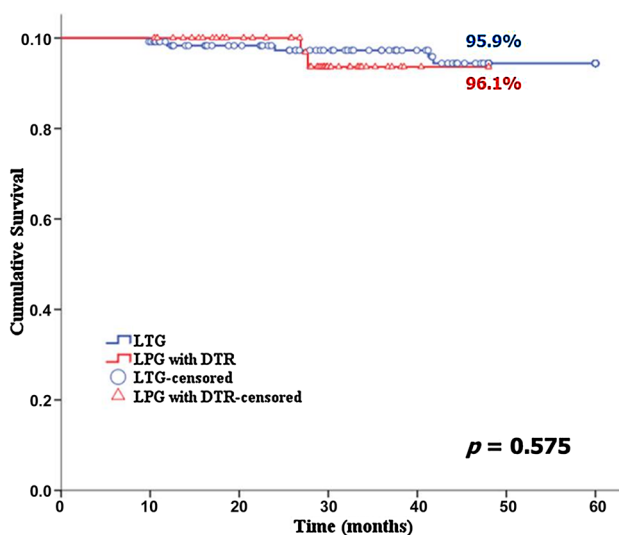


Fig. 3 Comparison of overall survival rates between laparoscopic proximal gastrectomy with double tract reconstruction and laparoscopic total gastrectomy. *LPG* Laparoscopic proximal gastrectomy, *DTR* double tract reconstruction, *LTG* laparoscopic total gastrectomy

Korea) for 2 years after the operation. Accordingly, the mean amount of vitamin B₁₂ supplements was lower in the LPG with DTR group than in the LTG group 2 years after the operation (0.1 ± 0.4 vs. 3.1 ± 2.2 mg, $p < 0.001$).

Recurrence and survival

There was no recurrence in the patients with confirmed stage I gastric cancer after LPG with DTR. However, there

were three recurrent cases (1.9%) with stage I gastric cancer pathologically confirmed after LTG, and these three recurrent cases were excluded in the present study. The overall survival rates were similar between the 2 groups (Fig. 3): the 5-year survival rates were 96.1 and 95.9% for the LPG with DTR and LTG groups, respectively ($p = 0.575$).

Discussion

The epidemiological characteristics of gastric cancer have changed over the last several decades in Korea, with the incidences of EGC and proximal gastric cancer having increased continuously during the past 20 years [1]. Accordingly, the use of laparoscopic gastrectomy has also increased in recent years, owing largely to reports of its superior short-term and comparable long-term oncological outcomes [2–4]. However, LPG is not considered a suitable operation for proximal EGC. In addition, open proximal gastrectomy (OPG) has also recently lost popularity [5]. This unpopularity of OPG and LPG can be attributed to three main concerns, namely their oncological safety, functional benefits, and anastomosis-related late complications [19, 20].

In terms of OPG, these three concerns have been evaluated in numerous studies. In several recent studies, it was demonstrated that OPG and open total gastrectomy had similar 5-year overall and disease-specific survival rates for proximal gastric cancer [6–8]. The functional benefits of OPG have been also reported in terms of preventing post-operative anemia and subjective symptoms [6, 7, 21, 22]. However, although many different types of reconstruction have been attempted to solve the issues of reflux symptoms and anastomotic stenosis, two well-established complications, none has yet been successful. To date, modification of EG after OPG has shown disappointing results in the rates of both reflux symptoms and anastomotic stenosis [10–12], and hence, various types of EJ after OPG have been recently studied to prevent reflux symptoms, including jejunal interposition and jejunal pouch interposition [12, 23]. While the incidence of reflux symptoms after OPG with EJ is reportedly similar to that after open total gastrectomy with Roux-en-Y anastomosis, these procedures for reconstruction are thought to be technically complex under laparoscopy.

Because of these unsolved late complications associated with OPG and the technical demanding procedure of reconstruction by LPG, there are relatively few cases of LPG, and the reports comparing LPG with LTG are therefore scarce. At our institution, LPG with EG has also been performed since May 2003, and we have previously reported that the 5-year overall survival rate was similar between patients treated with LPG with EG

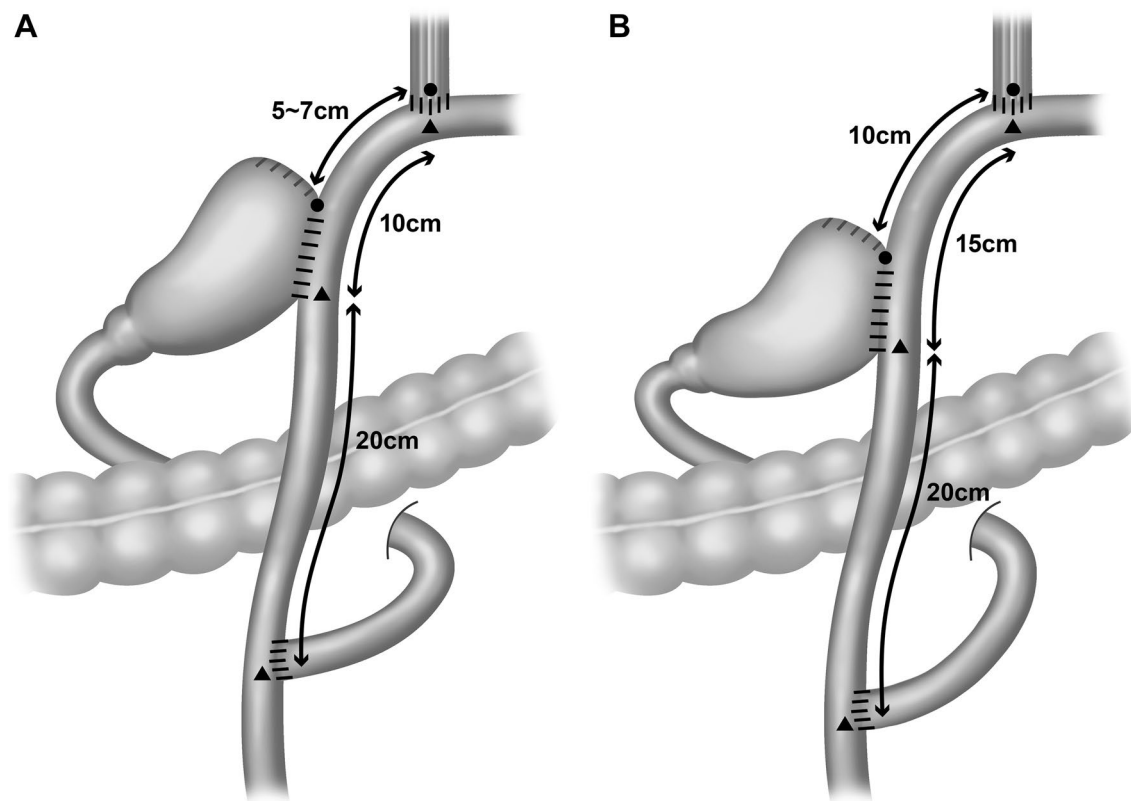


Fig. 4 The distance of anastomosis between gastrojejunostomy (GJ) and esophagojejunostomy (EJ) was changed **A** from 10 cm before the closure of common entry hole **B** to 10 cm after the closure for reducing the anastomosis-related late complications

and LTG [9]. In the present study, there was no recurrent case in patients confirmed with stage I gastric cancer after LPG with DTR, whereas there were three recurrent cases (1.9%) among the 189 patients with pathologically confirmed stage I gastric cancer after LTG. However, we excluded patients treated with adjuvant chemotherapy for pathological more than stage II gastric cancer from this analysis, including 8 cases (8.0%) in the LPG with DTR group and 30 cases (16.1%) in the LTG group, as the addition of chemotherapy may affect the nutritional status and laboratory results. In addition, the overall survival and disease-specific survival rates were also similar between the two groups, including in the excluded cases undergoing adjuvant chemotherapy; however, the mean follow-up period was relatively short (26.6 ± 10.3 months) in the LPG with DTR group. Moreover, tumor recurrence was found in 2 out of 8 patients with adjuvant chemotherapy in the LPG with DTR group; hepatic metastasis was found in one patient with pathologically confirmed stage IIIb at 30 months after LPG with DTR; and peritoneal carcinomatosis was found in the other patient with confirmed stage IIb disease at 24 months after LPG with DTR. Importantly, among the 8 patients with adjuvant chemotherapy, only one recurrent patient diagnosed with

hepatic metastasis expired; therefore, further studies with longer follow-up periods are required for evaluating the long-term survival rates.

The present study showed that LPG with DTR is a feasible and safe technique in terms of the operative time, estimated blood loss, and early and late complications. In our previous report, in which we found that LPG with EG stomy is also a feasible and safe technique, the late complication rates, especially for reflux symptoms and anastomotic stenosis, were substantially high [9], and therefore, we could not conclude that LPG with EG was a good alternative to LTG. However, in the present study, the late complication rates were similar in the LPG with DTR and LTG groups, and there were no patients with a Visick score of III or IV in either group. All anastomosis-related late complications of LTG and LPG with DTR occurred before May 2009 and October 2011, respectively, indicating that the anastomosis-related complication rates decreased significantly after the learning curve of LTG was overcome [24]. In terms of LPG with DTR, we have changed the distance from the EJ to GJ; in the early period, the GJ was made at 10 cm below the EJ. Using this previous approach, after we closed the common entry hole using a linear stapler, we found that the distance from the EJ to the GJ was only

about 5–7 cm. Previous studies have reported that there is a close relationship between the distance of anastomosis and anastomosis-related late complications in the jejunal interposition after OPG. Therefore, we changed the distance of anastomosis from 10 cm before the closure of common entry hole to 10 cm after the closure (Fig. 4). Thus, we now create the GJ at approximately 15 cm below the EJ at the late phase. After changing the distance of the anastomosis, we have not encountered any anastomosis-related late complications among the 76 cases of LPG with DTR.

In the present study, functional benefits of LPG with DTR were observed in terms of preventing postoperative anemia. We supplemented vitamin B₁₂ to the patients whose serum vitamin B₁₂ levels were less than 200 pg/mL or continuously decreasing, and the serum vitamin B₁₂ level of the LPG with DTR group was found to be significantly higher than that of the LTG group. Furthermore, while 138 (88.5%) patients in the LTG group were supplemented with intravenous injection of vitamin B₁₂ for 2 years postoperatively, only 5 (5.4%) patients in the LPG with DTR group were supplemented. However, nonetheless, the hemoglobin level of the LTG group was significantly lower than that of LPG with DTR in spite of the vitamin B₁₂ supplementation in the second postoperative year.

The regular endoscopic evaluations of patients undergoing LPG with DTR have been reported to lead to earlier detection and curative resection of remnant gastric cancer. It has been reported that the rate of remnant gastric cancer is 5–5.4% after OPG [6, 25], and we have previously reported that 3 intubation failures occurred among 43 patients undergoing LPG with DTR during the examination for remnant distal stomach cancer [13]. However, the endoscopists were able to evaluate the distal remnant stomach of these 3 patients at the next endoscopic follow-up, after the surgeons had explained to the endoscopists how to re-make the double tract reconstruction. In our institution, the distal remnant stomach of all patients undergoing LPG with DTR is evaluated by endoscopists, and, to date, tumor recurrence has not been found in the remnant stomach of any patient undergoing LPG with DTR (mean follow-up period, 26.6 months). Thus, regular and repeated communication between surgeons and endoscopists is recommended for the early detection of remnant gastric cancer after LPG with DTR.

The present study has some limitations, including its retrospective design. Moreover, we did not assess the quality of life of the patients, as we do not routinely use a validated questionnaire in the out-patient clinic. However, to our knowledge, this is the first study to report the superiority of LPG with DTR over LTG, and this observed superiority has lead us to plan a phase III multicenter prospective randomized clinical trial comparing LPG with DTR with

LTG (Korean Laparoscopic Gastrointestinal Surgery Study Group (KLASS)—05).

In conclusion, we here found that LPG with DTR maintains comparable oncological safety and anastomosis-related late complications to LTG and is preferred over LTG in terms of preventing postoperative anemia and vitamin B₁₂ deficiency.

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Compliance with ethical standards

Disclosure Do Hyun Jung, Yoontaek Lee, Dong Wook Kim, Young Suk Park, Sang-Hoon Ahn, Do Joong Park and Hyung-Ho Kim have no conflicts of interest or financial ties to disclose.

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