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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Feasibility and Nutritional Benefits of Laparoscopic Proximal Gastrectomy for Early Gastric Cancer in the Upper Stomach

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ABSTRACT

Background. Laparoscopic proximal gastrectomy (LPG) has recently been applied for early gastric cancer (EGC) in the upper stomach as a minimally invasive and function-preserving surgery. This study aimed to clarify the feasibility and nutritional benefits of LPG over laparoscopic total gastrectomy (LTG).

Methods. This was a retrospective study of 77 patients with clinical stage I gastric cancer in the upper stomach. Of these patients, 25 underwent LPG, while 52 underwent LTG. Surgical outcomes and postoperative nutritional status such as changes in body weight and blood chemistries were compared between LPG and LTG.

Results. Intraoperative blood loss and C-reactive protein levels at 3 and 7 days after surgery were significantly lower in LPG than in LTG ($p = 0.018$, 0.036, and 0.042, respectively). No significant differences were observed in postoperative early or late complication rates between LPG and LTG. The incidence of Los Angeles Grade B or more severe reflux esophagitis after LPG was 9.1 %, which was similar to that after LTG (9.3 %). Postoperative changes in body weight at 6 months and 1 and 2 years after surgery were consistently less in LPG than in LTG ($p = 0.001$, 0.022, and 0.001, respectively). Moreover, postoperative levels of hemoglobin and serum albumin and total lymphocyte count were also higher in LPG than in LTG.

Conclusion. LPG may be a better choice for EGC in the upper stomach than LTG because it has distinct advantages in terms of surgical invasiveness and postoperative nutritional status.

The incidence of gastric cancer in the upper stomach has been increasing in both Western and Asian countries.[1,2] Although total gastrectomy (TG) has been widely performed as standard surgery for proximal gastric cancer, postoperative nutritional status is not satisfactory. Therefore, proximal gastrectomy (PG) has recently been applied as a minimally invasive and function-preserving surgery for selected patients with proximal early gastric cancer (EGC). PG has potential advantages in terms of postoperative nutritional status and anemia because the gastric reservoir is preserved, and gastric-acid secretion and Castle intrinsic factor are maintained. Previous studies, including ours, reported that the long-term oncological outcomes of PG were similar to those of TG in patients with EGC.[3–5]

The incidence of EGC in Asian countries has continued to increase, and laparoscopic gastrectomy is widely used as a less invasive surgery.[6] Therefore, laparoscopic proximal gastrectomy (LPG) may be an ideal surgical approach for selected cases of proximal EGC; however, this has not yet been confirmed because of the technical difficulties associated with laparoscopic reconstructions.[7] Following LPG, esophagogastrostomy (EG) is considered the most useful reconstruction technique because of its simplicity and ease. However, several studies found that the risk of postoperative reflux esophagitis with EG was high, but failed to show the nutritional benefits of PG even in open procedures.[7,8]

We herein compared surgical outcomes and postoperative nutritional statuses between patients undergoing LPG with EG and laparoscopic total gastrectomy (LTG).

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The aim of this study was to examine the feasibility and nutritional benefits of LPG for EGC in the upper stomach.

PATIENTS AND METHODS

Patients

Between January 2009 and August 2014, a total of 77 patients underwent LPG with EG or LTG with Roux-en-Y (R-Y) reconstruction for clinical stage I gastric cancer in the upper stomach at Kyoto Prefectural University of Medicine. LPG was performed in 25 cases that essentially fulfilled the following criteria:[4,9,10] (1) EGC diagnosed as cT1N0M0 stage IA; (2) tumor located in the upper third of the stomach; and (3) a resection line in the stomach at least 5 cm apart from the gastric angle. On the other hand, LTG was performed in 52 cases of clinical stage IA (T1N0M0) and IB (T1N1M0, T2N0M0) gastric cancer that were beyond our indication for LPG. Each tumor was histologically diagnosed as gastric adenocarcinoma, and was classified according to the Japanese classification of gastric carcinoma.[11]

Surgical Procedure of Laparoscopic Proximal Gastrectomy with Esophagogastrostomy Reconstruction

The detailed surgical procedure of LPG with EG was described in our previous study,[9] and is shown in electronic supplementary Fig. 1. Briefly, after PG (one-third of the stomach) with D1+ lymph node dissection based on the Japanese gastric cancer treatment guidelines (JGCTG),[12] intracorporeal circular-stapled EG was performed in an end-to-side manner at the anterior wall of the remnant stomach. This technique allowed the greater curvature near the top of the remnant stomach to function as the new fundus. Seromuscular anchoring sutures were made between the top of the remnant stomach and the lower esophagus on both sides, which allowed the top of the remnant stomach to wrap around the lower esophagus in a semicircular fashion and established an acute angle at EG to prevent gastroesophageal regurgitation.

Surgical Procedure of Laparoscopic Total Gastrectomy with Roux-en-Y Reconstruction

LTG was performed as previously reported.[13] Briefly, after TG with D1+ or D2 lymph node dissection based on the JGCTG,[12] extracorporeal jejunojejunostomy was performed through a 4-cm left upper transverse incision. Intracorporeal circular-stapled esophagojejunostomy (EJ) was subsequently performed in an end-to-side manner, and antecolic R-Y reconstruction was completed.

Clinical Analyses and Surgical Outcomes

The clinical and surgical findings were obtained from medical records. The following data were recorded to evaluate surgical outcomes: morbidity (both early and late complications), mortality, and postoperative hospital stay. Early complications (0–30 days) consisted of anastomotic leakage, anastomotic bleeding, pancreatic fistula, intra-abdominal abscess, ileus, and pneumonia. Late complications (30 days onward) included anastomotic stricture, ileus, and pneumonia. Early complications were classified according to the Clavien–Dindo classification of surgical complications,[14,15] and complications greater than or equal to grade II were reviewed. Among the late complications encountered, anastomotic stricture was diagnosed if patients developed dysphasia during the postoperative follow-up and a 9.8-mm-diameter endoscope could not pass through the anastomotic site of EG or EJ.

Acute Inflammatory Response After Surgery

The white blood cell (WBC) count and C-reactive protein (CRP) levels at 1, 3, and 7 days after surgery were measured to evaluate acute inflammatory responses after LPG or LTG.

Postoperative Nutritional Status and Endoscopic Gastroesophageal Reflux

Postoperative body weight and the following laboratory findings were recorded at 6 months and 1 and 2 years after surgery to evaluate postoperative nutritional status: hemoglobin, serum total protein, serum albumin, serum total cholesterol, and total lymphocyte count. Endoscopic gastroesophageal reflux was generally evaluated 1 year after surgery according to the Los Angeles classification.

Statistical Analysis

To compare surgical outcomes and nutritional statuses between LPG and LTG, the χ^2 test and Student's t test were used for categorical variables and continuous variables, respectively. Statistical analyses were performed using JMP 10 (SAS Institute, Cary, NC, USA). All p values quoted were two-sided and significant levels were set at 5 %.

RESULTS

Patient Characteristics

Table 1 details the characteristics of patients undergoing LPG and LTG. No significant differences were observed in

TABLE 1 Characteristics of patients undergoing LPG and LTG

Characteristics	LPG ($n = 25$)	LTG ($n = 52$)	p Value
Age [years; median (range)]	66 (41–80)	67 (40–89)	0.474
Sex (male/female) [n]	17/8	45/7	0.054
BMI [kg/m^2; median (range)]	22.3 (17.7–28.0)	23.6 (19.0–42.8)	0.086
Co-morbidities [n (%)]	9 (36.0)	31 (59.6)	0.052
Previous abdominal operation [n (%)]	12 (48.0)	16 (30.8)	0.141
Clinical stage [n]			0.276
T1N0M0 stage IA	24	45	
T1N1M0 stage IB	0	5	
T2N0M0 stage IB	1	2	

LPG laparoscopic proximal gastrectomy, *LTG* laparoscopic total gastrectomy, *BMI* body mass index

age, sex, body mass index (BMI), co-morbidities, previous abdominal operation, or clinical stage between the two groups, even though the LPG group contained more females and patients with lower BMI or co-morbidities. One patient with a small cT2 tumor that was beyond our indication for PG was included in the LPG group.

Surgical Outcomes

The surgical outcomes of patients undergoing LPG and LTG are summarized in Table 2. No significant differences were observed in the extent of lymph node dissection or frequencies of combined organ resection and conversion to open surgery between the two groups. One patient in the LTG group needed conversion to the open procedure followed by simultaneous splenectomy because of bleeding from the spleen. However, no patient in either the LPG or LTG group needed conversion to open surgery because of difficulties encountered during the reconstructions. Although no significant differences were observed in the operation time between the groups, estimated blood loss was significantly less in the LPG group. There were significantly fewer retrieved lymph nodes in the LPG group than in the LTG group, whereas R0 resection was performed in all patients. The overall early complication rate was 8.0 % in the LPG group and 15.4 % in the LTG group. No significant differences were noted in the early complication rates regarding anastomotic leakage, anastomotic bleeding, pancreatic fistula, intra-abdominal abscess, ileus, and pneumonia between the groups. The overall late complication rate was 16.0 % in the LPG group and 21.2 % in the LTG group. The incidence of anastomotic stricture was 4 (16.0 %) in the LPG group and 5 (9.6 %) in the LTG group, respectively; all of these cases were treated by endoscopic treatments. Three patients in the LTG group had ileus (internal hernia in two patients, and blind loop syndrome in one patient), all of which resulted from R-Y reconstruction. No mortality was recorded in either the LPG or LTG group, and no significant differences were noted in postoperative hospital stays between the groups.

Perioperative Levels of White Blood Cell and C-Reactive Protein

Figure 1 shows the pre- and postoperative levels of CRP in patients undergoing LPG and LTG. Although the postoperative levels of WBC were not significantly different between the two groups (electronic supplementary Fig. 2), the mean CRP levels at 1, 3, and 7 days after surgery were lower in the LPG group than in the LTG group ($p = 0.090$, 0.036, and 0.042, respectively).

Postoperative Nutritional Status and Reflux Esophagitis

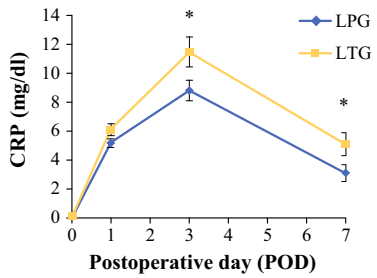
The mean follow-up times of the 25 patients undergoing LPG and 52 patients undergoing LTG were 36.1 months (range 5.2–71.3 months) and 37.6 months (range 3.5–71.3), respectively. In the LPG group, none of the patients developed cancer recurrence but one patient died of acute myocardial infarction. In the LTG group, one patient with pathological T4aN2M0 stage IIIB developed peritoneal recurrence but is currently alive, while one patient died of pneumonia without gastric cancer recurrence.

Figure 2 shows comparisons of postoperative nutritional statuses between LPG and LTG: hemoglobin, serum albumin, total lymphocyte count, and body weight. Hemoglobin levels at 2 years after surgery were significantly higher in the LPG group than in the LTG group ($p < 0.001$). Although the postoperative levels of serum total protein and total cholesterol were not significantly different between the two groups (electronic supplementary Fig. 3), the levels of serum albumin and total lymphocyte count 1 year after surgery were significantly higher in the LPG group than in the LTG group ($p = 0.042$ and 0.030, respectively). Moreover, body weights at 6 months and 1 and 2 years after surgery were significantly

TABLE 2 Surgical outcomes of patients undergoing LPG and LTG

Variables	LPG ($n = 25$)	LTG ($n = 52$)	p Value
Lymph node dissection (n)			
D1+/D2	25/0	50/2	0.320
Combined resection [n (%)]			0.738
Gall bladder	1	3	
Spleen	0	1	
Conversion to open surgery [n (%)]	0 (0)	1 (1.9)	0.485
Operation time [min; median (range)]	373 (278–566)	411 (269–656)	0.115
Estimated blood loss [ml; median (range)]	40 (0–204)	88 (0–565)	0.018
No. of lymph nodes retrieved [median (range)]	20 (9–53)	34 (10–112)	0.002
R0 resection [n (%)]	25 (100)	52 (100)	–
Early complications [n (%)]	2 (8.0)	8 (15.4)	0.367
Anastomotic leakage	0 (0)	0 (0)	–
Anastomotic bleeding	0 (0)	0 (0)	–
Pancreatic fistula	1 (4.0)	2 (3.8)	0.974
Intra-abdominal abscess	1 (4.0)	3 (5.8)	0.743
Ileus	0 (0)	2 (3.8)	0.320
Pneumonia	0 (0)	1 (1.9)	0.485
Late complications [n (%)]	4 (16.0)	11 (21.2)	0.593
Anastomotic stricture	4 (16.0)	5 (9.6)	0.414
Ileus	0 (0)	3 (5.8)	0.221
Pneumonia	0 (0)	3 (5.8)	0.221
Mortality [n (%)]	0 (0)	0 (0)	–
Postoperative hospital stay [days; median (range)]	13 (10–150)	13 (8–96)	0.541

LPG laparoscopic proximal gastrectomy, *LTG* laparoscopic total gastrectomy



	Baseline	1POD	3POD	7POD
LPG	0.181 ± 0.172	5.201 ± 0.432	8.819 ± 1.029	3.105 ± 0.796
LTG	0.256 ± 0.119	6.105 ± 0.300	11.49 ± 0.714	5.111 ± 0.557
P-value	0.720	0.090	0.036	0.042

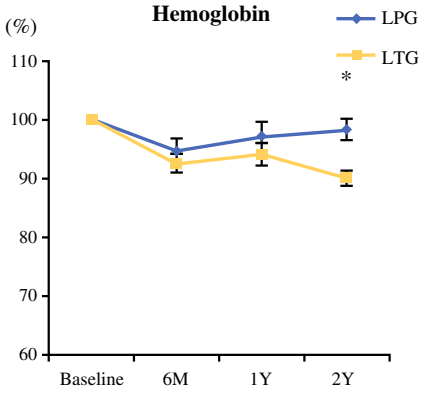
FIG. 1 Mean CRP levels at baseline and 1, 3, and 7 days after surgery in patients undergoing LPG and LTG. Data are expressed as the mean ± SE. * $p < 0.05$, significant

higher in the LPG group than in the LTG group ($p = 0.001$, 0.022 and 0.001, respectively).

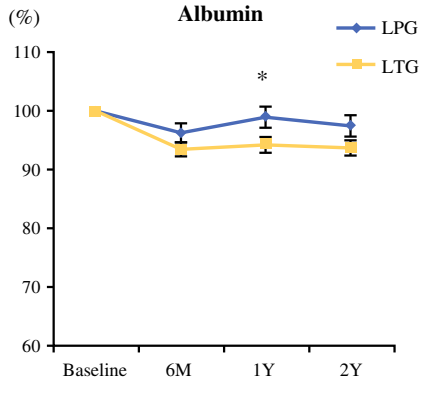
Postoperative reflux symptoms that required proton pump inhibitors or camostat mesilate for symptom relief were observed in three patients (12.0 %) in the LPG group and four patients (7.7 %) in the LTG group ($p = 0.538$); however, none of these required reoperations owing to severe reflux symptoms that were medically intractable. Twenty-two of the 25 patients in the LPG group and 43 of the 52 patients in the LTG group underwent postoperative endoscopy at or within 1 year after surgery to evaluate gastroesophageal reflux. The incidence of endoscopic gastroesophageal reflux after LPG and LTG are summarized in Table 3. Los Angeles Grade B or more severe reflux esophagitis was observed in two patients (9.1 %) in the LPG group and four patients (9.3 %) in the LTG group, respectively ($p = 0.978$).

DISCUSSION

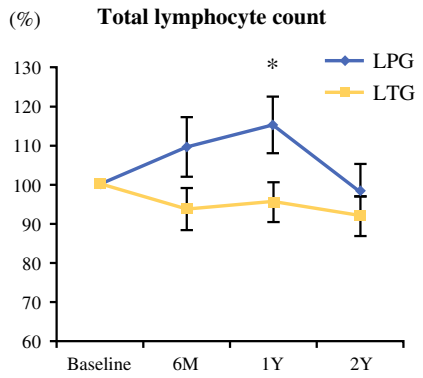
EGC has a low recurrence rate and good long-term survival; thus, current interest has been focused on improvements in postoperative quality of life (QOL). A Japanese nationwide multi-institutional comparative study of postoperative QOL between PG and TG recently showed that body weight loss, diarrhea, dumping, and the necessity for additional meals were significantly lower with PG.[16] In the current era of minimally invasive surgery, laparoscopic gastrectomy is widely used in the treatment of EGC.[6] Therefore, LPG, instead of LTG, may be an ideal surgical approach for proximal EGC as a less invasive and



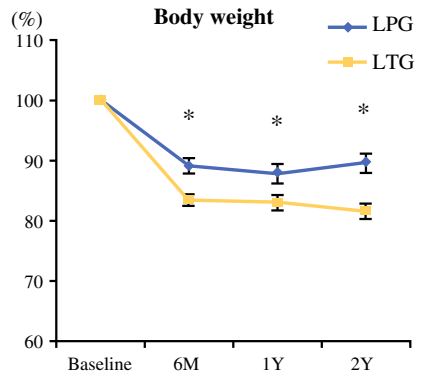
	Baseline	6M	1Y	2Y
LPG	100 (n=25)	94.7 ± 2.1 (n=23)	97.0 ± 2.7 (n=19)	98.3 ± 1.8 (n=15)
LTG	100 (n=52)	92.5 ± 1.6 (n=44)	94.7 ± 2.0 (n=36)	89.9 ± 1.3 (n=28)
P-value	-	0.420	0.397	< 0.001



	Baseline	6M	1Y	2Y
LPG	100 (n=25)	96.3 ± 1.8 (n=23)	99.0 ± 1.8 (n=19)	97.5 ± 1.7 (n=15)
LTG	100 (n=52)	93.5 ± 1.3 (n=44)	94.3 ± 1.3 (n=36)	93.8 ± 1.3 (n=28)
P-value	-	0.221	0.042	0.100



	Baseline	6M	1Y	2Y
LPG	100 (n=25)	109.6 ± 7.6 (n=22)	115.3 ± 7.2 (n=18)	98.2 ± 7.1 (n=15)
LTG	100 (n=52)	93.8 ± 5.3 (n=44)	95.5 ± 5.2 (n=35)	92.0 ± 5.2 (n=28)
P-value	-	0.092	0.030	0.485



	Baseline	6M	1Y	2Y
LPG	100 (n=25)	89.0 ± 1.3 (n=23)	87.8 ± 1.6 (n=19)	89.5 ± 1.7 (n=16)
LTG	100 (n=52)	83.4 ± 1.0 (n=42)	83.0 ± 1.2 (n=33)	81.6 ± 1.3 (n=28)
P-value	-	0.001	0.022	0.001

FIG. 2 Comparisons of postoperative nutritional statuses between LPG and LTG: hemoglobin, serum albumin, total lymphocyte count, and body weight. All postoperative data were represented as values (mean ± SE) relative to preoperative data. * $p < 0.05$, significant. M: month after surgery, Y: year after surgery

TABLE 3 Incidence of endoscopic gastroesophageal reflux after LPG and LTG

	LPG ($n = 22$)	LTG ($n = 43$)	p Value
Reflux esophagitis (n)[a]			
Grade A	2	1	
Grade B	1	3	
Grade C	1	0	
Grade D	0	1	
≥Grade B [n (%)]	2 (9.1)	4 (9.3)	0.978

LPG laparoscopic proximal gastrectomy, *LTG* laparoscopic total gastrectomy

[a] Reflux esophagitis according to the Los Angeles classification

function-preserving surgery. In the present study, intraoperative blood loss and postoperative CRP levels in LPG were significantly lower than those in LTG, suggesting that LPG was more advantageous than LTG in terms of surgical invasiveness.

Previous studies did not report the nutritional benefits of LPG over LTG, possibly because of the lack of a secure method for anastomosis with an appropriate anti-reflux procedure. Ahn et al. found that LPG with EG was associated with a markedly higher rate of reflux symptoms (32.0 %) but failed to show the nutritional advantages of LPG over LTG;[7] however, they also demonstrated that the rate of reflux symptoms after LPG decreased slightly with

more surgical experience. In that regard, we have gained considerable experience in PG with EG, and reported its favorable outcomes with acceptable incidences of postoperative reflux esophagitis in both open and laparoscopic surgery.[4,9,10,17]

Our procedures of PG with EG consist of the preservation of as much of the abdominal esophagus as possible and at least two-thirds of the stomach, creation of end-to-side EG at the anterior wall 2 cm from the lesser curvature and 3 cm from the top of the remnant stomach, and seromuscular anchoring sutures between the top of the remnant stomach and the lower esophagus on both sides, which allowed the top of the remnant stomach to wrap around the lower esophagus in a semicircular fashion to establish an acute angle at EG.[4,9,10,17] With respect to the fundoplication in PG with EG, Nakamura et al. recently reported that the incidence of reflux esophagitis was significantly lower in patients with a >180° wrap of the remnant stomach around the esophagus than in patients with a smaller wrap.[18] Accordingly, our dorsal semicircular wrap (>180°) may also have contributed to preventing postoperative reflux esophagitis.

Several previous studies reported high rates of anastomotic stricture after PG due to inflammation at the anastomotic site caused by reflux.[7,8] In this series, LPG was not significantly associated with an increased risk of anastomotic stricture compared with LTG, suggesting that prevention of reflux contributed to a decrease of anastomotic stricture. Meanwhile, four patients who experienced anastomotic stricture after LPG had not complained of reflux symptoms prior to the diagnosis of stenosis. Therefore, technical matters in intracorporeal circular-stapled EG (e.g. involvement of excessive gastric wall into the anastomotic site) might be the reasons other than reflux. In fact, the incidence of anastomotic stricture decreased with an accumulation of surgical experience (data not shown).

The gastric fundic gland region is preserved in PG; therefore, the secretion of gastric acid and Castle intrinsic factor are maintained. In this series, none of the patients undergoing LPG needed vitamin B_{12} replacement, whereas more than 1 year after LTG all of the patients had been treated with intramuscular injection of cyanocobalamin or oral administration of mecobalamin (data not shown). Meanwhile, the duodenal passage is preserved in PG with EG, which is very important for the absorption of dietary iron.[19] According to these mechanisms, PG has potential advantages over TG in terms of both postoperative iron deficiency and vitamin B_{12} deficiency anemia.[19,20] In the present study, LPG was superior to LTG in terms of postoperative anemia.

Pronounced body weight loss and nutritional deficiencies are frequently observed in patients with LTG.[21] In the present study, LPG had a significant advantage over LTG in terms of postoperative body weight loss. Moreover, the postoperative levels of serum albumin and total lymphocyte count, which are also useful indicators of nutritional status,[22,23] were significantly higher in patients with LPG than in those with LTG. Although the detailed mechanisms underlying the nutritional advantage of LPG over LTG were not examined in this study, a larger food intake, well-preserved digestive and absorptive functions, and acceptable incidence of reflux esophagitis may have contributed to the improved nutritional status of LPG.

The major limitations of this study were that there might be some biases because of a retrospective study, and the sample size may not have been large enough to identify real differences in patient characteristics and surgical outcomes between the two groups. However, in this study period, we exclusively performed LPG, instead of LTG, for any EGCs that met our criteria of selecting LPG based solely on tumor location and clinical stage. Another limitation was the lack of data on patient's subjective symptoms or QOL scored by validated questionnaires in a prospective fashion. Nevertheless, to the best of our knowledge this is the first study to demonstrate nutritional advantages of LPG over LTG for EGC in the upper stomach. The results of the present study should be validated by prospective studies with large sample sizes, and oncological safety should be verified by long-term follow-up.

CONCLUSION

LPG may be a valuable procedure for proximal EGC because it has distinct advantages over LTG in terms of the surgical invasiveness and postoperative nutritional status.

DISCLOSURE Toshiyuki Kosuga, Daisuke Ichikawa, Shuhei Komatsu, Kazuma Okamoto, Hirotaka Konishi, Atsushi Shiozaki, Hitoshi Fujiwara, and Eigo Otsuji declare that they have no conflicts of interest.

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