Clinical Outcomes and Evaluation of Laparoscopic Proximal Gastrectomy with Double-Flap Technique for Early Gastric Cancer in the Upper Third of the Stomach

Masaru Hayami, MD, PhD, Naoki Hiki, MD, PhD, Souya Nunobe, MD, PhD, Shinji Mine, MD, Manabu Ohashi, MD, PhD, Koshi Kumagai, MD, PhD, Satoshi Ida, MD, PhD, Masayuki Watanabe, MD, PhD, Takeshi Sano, MD, PhD, and Toshiharu Yamaguchi, MD, PhD

Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

ABSTRACT

Background. A novel double-flap esophagogastrostomy technique developed to prevent reflux after proximal gastrectomy was applied to laparoscopic proximal gastrectomy (LPG), and the clinical outcomes of this technique (LPG-DFT) were evaluated and compared to those of laparoscopic total gastrectomy (LTG).

Methods. This retrospective study of 90 patients with early gastric cancer (EGC) in the upper third of the stomach compared surgical outcomes, postoperative endoscopic findings, and nutritional status between two procedure groups, LPG-DFT (n = 43) and LTG (n = 47). The association between morbidity and surgical procedure was analyzed by controlling for body mass index (BMI).

Results. Mean operation time was significantly higher for LPG-DFT than LTG (386.5 vs. 316.3 min, P < 0.001). The morbidity and the frequency of anastomotic complications were lower, although not significantly, for LPG-DFT (7.0 vs. 21.3%, P = 0.073; and 4.7 vs. 17.2%, P = 0.093). Median postoperative hospital stay was significantly shorter for LPG-DFT than LTG (10 vs. 13 days, P = 0.002). The LPG-DFT procedure was identified as the most significant independent predictor of low morbidity after adjustment for BMI (P = 0.028, OR = 0.232, 95% CI 0.047–0.862). LTG induced more severe reflux esophagitis than LPG-DFT (14.9% vs. 2.3%, P = 0.06). The mean baseline weight, total protein, and hemoglobin were significantly higher with LPG-DFT than with LTG (P < 0.05).

Conclusions. LPG-DFT is a better surgical procedure for treating upper-third EGC than LTG in terms of morbidity, postoperative hospital stay, and postoperative nutritional status.

Recent studies have reported an increasing trend in the incidence of upper-third gastric cancers, including early gastric cancers (EGC), in Korea, China, and Japan.1–6 Although total gastrectomy (TG) is considered the standard operation for such cases, proximal gastrectomy (PG) has been performed for selected patients with upper-third EGC as a function-preserving procedure. However, PG is associated with some postoperative functional disorders such as reflux esophagitis and difficulty in swallowing due to anastomotic stenosis, both of which lead to poor dietary intake and weight loss.1,7 Thus, many surgeons do not consider PG superior to TG in terms of function, such as a lower risk of regurgitation, and thus choose to perform TG for upper-third EGC. Several reconstruction methods can be adopted for use after PG, such as esophagogastros- tomy,7–10 jejunal interposition,10,11 and double-tract reconstruction.11,12 Esophagogastrosurgery is the simplest reconstruction method, but it carries a high risk of reflux esophagitis and gastrooesophageal anastomotic steno- sis.7,9,10 Jejunal interposition also has some problems, such as the technically complicated nature of the procedure, associated functional disorders indicating delayed emptying, esophago-jejunal anastomotic stenosis,13 and difficulty in endoscopic surveillance, particularly in patients with longer interposed segments.10 Double-tract reconstruction is a complicated procedure and remains unproven in terms of functional advantages.12
In 2001, Kamikawa et al.¹ invented a novel esophagogastrostomy with double-flap technique (DFT) to prevent reflux. Several studies have applied this reconstruction method to laparoscopic proximal gastrectomy (LPG)¹⁴,¹⁵; however, there is no report of clinical outcomes after LPG with DFT (LPG-DFT) for treating upper-third EGC. This study thus sought to demonstrate the short- and long-term clinical outcomes of LPG-DFT for EGC in terms of postoperative complications, nutritional status, and endoscopic findings and to evaluate and compare these results with those of laparoscopic total gastrectomy (LTG).

**PATIENTS AND METHODS**

**Patients**

From June 2011 to December 2014, laparoscopy-assisted gastrectomy was performed in 901 patients with preoperatively diagnosed EGC at the Cancer Institute Hospital, Tokyo, Japan. The diagnoses of tumor depth and lymph node involvement were based on the results of gastric endoscopy, barium radiography, computed tomography (CT), or endoscopic ultrasonography (EUS). The staging of the tumor was classified according to the Japanese Classification of Gastric Carcinoma, 3rd English edition.¹⁶

From January 2013 to December 2014, LPG-DFT was performed in 43 patients for clinically diagnosed cT1N0 EGC located in the upper third of the stomach, and it was considered that at least two-thirds of the stomach could be preserved preoperatively in all cases. For patients to undergo LPG-DFT, additional endoscopy was performed preoperatively to mark with clips the distal margins (approximately 2 cm from the tumor), confirmed by biopsy to be negative for cancer. The proximal margins were also marked in cases where the lesions had spread to the esophageal side.

From June 2011 to December 2012, LTG was performed in 47 patients with T1N0 EGC located in or involving the upper third of the stomach. The outcome of LTG in this period was compared with that of LPG-DFT. From January 2013 to December 2014, LTG was also performed in 42 patients with EGC with the same indications as in the previous period. However, the latter period was not selected, because the number of LPG-DFTs had gradually increased during the period by the increasing number of operators who could perform LPG-DFT, and it was important to avoid selection bias, including the surgeon’s preference in relation to adopting the procedure for upper-third EGC.

This was a retrospective study using clinicopathological, surgical, and follow-up data, approved by the institutional review board at Cancer Institute Hospital, Tokyo, Japan.

**Surgical Procedure of LPG**

LPG and D1+ lymphadenectomy (nodes no. 1, 2, 3a, 4a, 4sb, 7, 8a, 9, and 11p) were performed according to the 2010 Japanese Gastric Cancer Treatment Guidelines, version 3.¹⁷ Lymph flow along the posterior gastric artery is considered particularly important in upper-third gastric cancer; therefore, node 11p should be properly dissected along the splenic artery up to the periphery of the posterior gastric arterial root. The hepatic branch and peripheral pyloric branches of the anterior branch of the vagus nerve were always preserved, and if possible, so was the celiac branch, which is the main branch of the posterior vagal trunk. The right gastric artery and right gastroepiploic artery were also preserved. After mobilization of the stomach and lymph node dissection, intraoperative gastroscopy was performed to confirm the location of the tumor and the preoperatively placed clips. The locations of clips and the esophagogastric junction were marked by suturing in the outer wall, and a safe gastric resection line was marked with dye. The stomach was transected with endoscopic linear staplers. It is important to create a wide gastric remnant, because a narrow remnant might cause insufficient blood flow at its tip after creating the seromuscular flaps.

Before cutting the proximal end of the esophagus, the point 5 cm above the planned cut end must be marked due to esophageal shrinkage after resection. The esophagus was resected using ultrasonically activated laparoscopic coagulating shears.

**Reconstruction by LPG-DFT**

The detailed surgical procedure of esophagogastrostomy with valvuloplasty by DFT was described in a previous report.¹⁴,¹⁵,¹⁸ The double seromuscular flaps (2.5 cm wide × 3.5 cm high) were created at the anterior wall of the gastric remnant using electric cautery to cautiously detach the submucosal layer and expose the mucosa, resulting in creation of the seromuscular flap (Fig. 1a). After creation of the double flap, the inferior end of the mucosal window was opened, and the posterior wall of the esophagus was fixed to the superior edge of the mucosal window using four stitches at the previously marked point 5 cm above the cut end. Continuous suturing was performed between the posterior wall of the esophagus and the superior opening of the mucosa on the gastric remnant (Fig. 1b). On the anterior wall of the esophagus and gastric wall at the lower end of the flap, released areas were anastomosed layer-by-layer using interrupted sutures. Finally, the anastomosis was fully covered by the seromuscular flaps using continuous suturing (Fig. 1c). After
this anastomotic procedure, intraoperative gastroscopy was always performed to confirm tightening of the anastomosis.

**Reconstruction in LTG**

LTG was performed as previously described. Esophagojejunostomy was performed using a modified lift-up method, which reduces both the difficulty of anvil insertion by lifting up the nasogastric tube connected to the anvil head, and anastomotic complications by using the single-stapling technique for circular-stapled esophagojejunostomy. Then, the antecolic R-Y reconstruction was completed.

**Clinical Analysis and Surgical Outcomes**

The following background characteristics were obtained from medical records: age, sex, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS), history of abdominal surgery, previous treatment with endoscopic submucosal dissection (ESD), staging of patients (clinical T stage, pathological T stage, pathological N stage, and pathological stage), and postoperative adjuvant chemotherapy. Surgical findings such as operation time, estimated blood loss, combined cholecystectomy, conversion to open surgery, extent of lymph node dissection, number of retrieved lymph nodes, and residual tumor (R) were also recorded. The following data were recorded to evaluate early postoperative outcomes: postoperative mortality, postoperative hospital stay, and postoperative complications within 3 months after surgery including anastomotic complications (anastomotic leakage, anastomotic stricture, and anastomotic bleeding) related to esophagogastronomy in LPG-DFT or esophagojejunostomy in LTG, intra-abdominal bleeding, pancreatic fistula, intra-abdominal infection, esophageal perforation, pneumonia, empyema, and abdominal wall abscess. Postoperative complications were classified according to the Clavien-Dindo (CD) classification of surgical complications, and complications of grade III and above were reviewed.

**FIG. 1** Schema of reconstruction with LPG-DFT. a Seromuscular flap, 2.5 cm × 3.5 cm (width × height). b Continuous suturing of the posterior wall. c The anastomosis was fully covered by the seromuscular flaps using continuous suturing.
Follow-up and Postoperative Nutritional Status

The 90 patients were followed-up for a mean period of 38.4 months (range 12–62 months). Postoperative endoscopic findings were recorded within 12 months after surgery to evaluate reflux esophagitis, classified according to the Los Angeles classification, while grade B and above cases were reviewed.

To evaluate postoperative nutritional status, changes in weight and serum concentrations of total protein (TP), albumin (Alb), and hemoglobin (Hb) were evaluated at 1, 3, 6, and 12 months after surgery. In evaluating nutritional status, the case of postoperative adjuvant chemotherapy, 4 cases treated by LPG-DFT, and 3 cases treated by LTG were excluded.

Statistical Analysis

The Mann–Whitney U-test, Student’s t test, and the Chi squared test or Fisher’s exact test were used as appropriate to compare clinicopathological characteristics, surgical outcomes, and endoscopic findings between study groups. Postoperative changes in weight, TP, Alb, and Hb were compared using repeated measures ANOVA (adjusted for preoperative values). Multiple logistic regression analysis and the Mantel–Haenszel test were performed to estimate the association between morbidity and surgical procedure by controlling for BMI, the potential confounding factor.

Statistical analyses were performed with JMP 10 (SAS Institute, Cary, NC, USA). All P values cited are two-sided, and significance levels were set at 5%.

RESULTS

Patient Characteristics

Table 1 details the characteristics of patients undergoing LPG-DFT and LTG. No significant differences were observed in age, sex, BMI, ASA-PS, previous abdominal operation, tumor location, staging of patients, histological type, and postoperative adjuvant chemotherapy. The median tumor size was significantly larger for LTG patients (25.0 mm) than for LPG-DFT patients (34.5 mm). The number of previous treatments with ESD was larger for LPG-DFT than for LTG patients, but the difference was not significant (P = 0.069). There was also heterogeneity with respect to pathological N stage, but again the difference was not significant (P = 0.053).

Operative and Early Postoperative Outcomes

Table 2 details operative and early postoperative outcomes of patients undergoing LPG-DFT and LTG. In terms of operative outcomes, the mean operation time was significantly higher in the LPG-DFT group (386.5 min) than in the LTG group (316.3 min), whereas no significant differences were observed in estimated blood loss, combined cholecystectomy, and extent of lymph node dissection between the groups. No patients needed conversion to open surgery. R0 resection was performed in all patients. There were significantly fewer retrieved lymph nodes in the LPG-DFT group (30) than in the LTG group (48), and no mortality was recorded across all patients.

The overall postoperative complication rate (morbidity) was lower in the LPG-DFT group (7.0%) than in the LTG group (21.3%), and the frequency of anastomotic complications was lower in the LPG-DFT group (4.7%) than in the LTG group (17.2%), but not significantly (P = 0.073 and P = 0.093, respectively). There were no significant differences between the groups in complication rates for intra-abdominal bleeding, pancreatic fistula, intra-abdominal infection, pneumonia, perforation of the digestive tract, and empyema. The mean postoperative hospital stay was significantly shorter in the LPG-DFT group (10 days) than in the LTG group (13 days).

Table 3 details the association between the risk of morbidity and the surgical procedure by controlling for BMI, the potential confounding factor, using multivariable logistic regression analysis and the Mantel–Haenszel test. The procedure of LPG-DFT was identified as the most significant independent predictor of lower morbidity after adjustment for BMI (P = 0.028, odds ratio = 0.232, 95% confidence interval = 0.047–0.862). The Mantel–Haenszel test also showed a difference between LPG-DFT and LTG (P = 0.035).

Follow-Up and Postoperative Nutritional Status

The median follow-up times of the 43 patients undergoing LPG-DFT and 47 patients undergoing LTG were 25 months (range 12–40 months) and 49 month (range 18–62 months), respectively. None of them developed cancer recurrence in distant organs, remnant stomach, or lymph nodes. For the incidence of reflux esophagitis within 12 months after LPG-DFT and LTG, Los Angeles Grade B or more severe reflux esophagitis was observed in 7 of the LTG group patients (14.9%), compared to 1 case for the LPG-DFT group (2.3%), but the difference was not significant (P = 0.06).

Figure 2 shows the pre and postoperative mean weight, TP, Alb, and Hb in patients undergoing LPG-DFT and LTG. The mean baseline weight, TP, and Hb were significantly higher in the LPG-DFT group than in the LTG group. The mean baseline Alb was also higher in the LPG-DFT group than in the LTG group, but not significantly (P = 0.06).
DISCUSSION

In this patient series, the total postoperative complication rate adjusted for BMI was significantly lower in the group of patients treated by LPG-DFT than in those treated by LTG, and we conclude that anastomotic complications most strongly influenced this result. The frequency of anastomotic complications such as leakage and stricture was lower in the LPG-DFT group than in the LTG group, despite the difference not being significant, and this trend could be explained by the tight anastomosis reinforced by covering with the seromuscular flap. Furthermore, the flexibility of anastomosis with LPG-DFT could be attributed to the softness of the posterior side of anastomotic sites, which comprised only mucosa, resulting in a lower risk of anastomotic stenosis. These results might in turn explain the shorter postoperative hospital stay in the LPG-DFT group compared to the LTG group.

The mean operation time was significantly longer in the LPG-DFT group than in the LTG group, probably because of the time-consuming nature of the complex valvuloplasty used in the LPG-DFT. This procedure demands masterful intracorporeal suturing, although standardization of the procedure could shorten the operation time for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LPG-DFT (n = 43)</th>
<th>LTG (n = 47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72 (37–90)</td>
<td>69 (41–84)</td>
<td>0.329</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>31 (72.1)/12 (27.9)</td>
<td>34 (72.3)/13 (27.7)</td>
<td>0.979</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 (18.2–36.2)</td>
<td>22.4 (16.4–30.6)</td>
<td>0.293</td>
</tr>
<tr>
<td>ASA-PS (1/2/3)</td>
<td>22 (51.2)/20 (46.5)/1 (2.3)</td>
<td>15 (31.9)/31 (66.0)/1 (2.1)</td>
<td>0.205</td>
</tr>
<tr>
<td>Previous abdominal operation, n (%)</td>
<td>9 (20.9)</td>
<td>11 (23.4)</td>
<td>0.805</td>
</tr>
<tr>
<td>Previous treatment with ESD, n (%)</td>
<td>17 (39.5)</td>
<td>10 (21.3)</td>
<td>0.069</td>
</tr>
<tr>
<td>Tumor location (U/M/L)</td>
<td>42 (97.7)/1 (2.3)/0</td>
<td>42 (89.4)/5 (10.6)/0</td>
<td>0.206</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>25.0 (8–70)</td>
<td>34.5 (7–105)</td>
<td>0.016</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
<td>0.459</td>
</tr>
<tr>
<td>T1a (M)</td>
<td>8 (18.6)</td>
<td>12 (25.5)</td>
<td></td>
</tr>
<tr>
<td>T1b (SM)</td>
<td>35 (81.4)</td>
<td>35 (74.5)</td>
<td>0.128</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated</td>
<td>27 (62.8)</td>
<td>22 (46.8)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>16 (37.2)</td>
<td>25 (53.2)</td>
<td></td>
</tr>
<tr>
<td>Pathological T stagea</td>
<td></td>
<td></td>
<td>0.834</td>
</tr>
<tr>
<td>T1</td>
<td>35 (81.4)</td>
<td>42 (89.4)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>5 (11.6)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>2 (4.7)</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>1 (2.3)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Pathological N stagea</td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>N0</td>
<td>37 (86.1)</td>
<td>44 (93.6)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>6 (14)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>0</td>
<td>3 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Pathological stagea</td>
<td></td>
<td></td>
<td>0.521</td>
</tr>
<tr>
<td>IA</td>
<td>32 (74.4)</td>
<td>42 (89.4)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>7 (16.3)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>2 (4.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>2 (4.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>0</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>0</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Postoperative adjuvant chemotherapy</td>
<td>4 (9.3)</td>
<td>3 (6.4)</td>
<td>0.705</td>
</tr>
</tbody>
</table>

LPG-DFT laparoscopic proximal gastrectomy with valvuloplasty by double-flap technique, LTG laparoscopic total gastrectomy, BMI body mass index, ASA-PS American Society of Anesthesiologists physical status, ESD endoscopic submucosal dissection

Values are expressed as n (%), median (range), or n

a According to the Japanese Classification of Gastric Carcinoma, 3rd English edition
treatments involving DFT. Recently, barbed sutures (V-Loc™) have been used to eliminate the time consumption of continuous suturing. The V-Loc™ is composed of a unidirectional barbed and absorbable thread, with a surgical needle at one end and a loop at the other end, which allows for tissue closure without the need to tie knots at the end of suturing.

In terms of long-term nutritional status, LPG-DFT also showed a significant advantage over LTG because the postoperative mean weight, TP, and Hb were significantly higher in the LPG-DFT group than in the LTG group. These results could reflect the presence of the gastric remnant because, with preservation of the gastric fundic gland region in PG, gastric-acid secretion, and production of Castle intrinsic factor and ghrelin, there is less loss of iron and vitamin B12 and increased appetite postoperatively. Additionally, the lower incidence of dumping symptoms and regurgitation associated with LPG-DFT might contribute to a lower incidence of anorexia and improved quality of life.

Severe reflux esophagitis was not observed on endoscopy in LPG-DFT, possibly due to minimal regurgitation with addition of the valvuloplasty, which preserves the backflow prevention valve embedded between the submucosal layer and the seromuscular flap of the stomach. We consider that the flexibility of this valve and the change in pressure between the esophageal lumen and the remnant gastric lumen might contribute to the unidirectional valve function.

The present study has some limitations. First, this was a retrospective study with a small sample size at a single institution. Second, quality of life was not evaluated in these patients because it was not fully followed-up using a validated questionnaire. Third, the comparison of outcomes did not include other reconstructions, including esophagogastrectomy, jejunal interposition, and double-tract reconstruction, after LPG. A randomized clinical trial with equivalent background characteristics among the reconstructions after LPG is required to further analyze the advantages of LPG-DFT.

CONCLUSION

In conclusion, LPG-DFT is a better surgical procedure for upper-third EGC than LTG in terms of morbidity, postoperative hospital stay, and postoperative nutritional status. Further randomized clinical trials with a large sample size will be required to fully investigate the comparative benefits of LPG-DFT.
TABLE 3 Association between morbidity and surgical technique adjusted for BMI using multivariable logistic regression and the Mantel–Haenszel test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (&lt;25 kg/m²)</td>
<td>0.306</td>
<td>0.083–1.110</td>
<td>0.071</td>
</tr>
<tr>
<td>BMI (≥25 kg/m²)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPG-DFT</td>
<td>0.232</td>
<td>0.047–0.862</td>
<td>0.028</td>
</tr>
<tr>
<td>LTG</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complications No complications Total

BMI < 25 (kg/m²)

- Procedure
  - LPG-DFT: 2 (6.9) 27 (93.1) 29 (100)
  - LTG: 5 (13.9) 31 (86.1) 36 (100)
  - Total: 7 (10.8) 58 (89.2) 65 (100)

BMI ≥ 25 (kg/m²)

- Procedure
  - LPG-DFT: 1 (7.1) 13 (92.9) 14 (100)
  - LTG: 5 (45.4) 6 (54.6) 11 (100)
  - Total: 6 (24.0) 19 (76.0) 25 (100)

Values are expressed as n (%)

FIG. 2 Comparison of changes in nutritional parameters between LPG-DFT and LTG. **TP** total protein, **Alb** Albumin, **Hb** hemoglobin
ACKNOWLEDGEMENT The authors would like to thank Dr. Naoki Ishizuka for his statistical advice and for always taking the time to read this manuscript and respond rapidly with valuable suggestions for improvements.

REFERENCES
